Appendix 2: Methodology for Assessment of Vaccines for Endemic Disease Prevention

Vaccine Investment Strategy
Programme and Policy Committee Meeting
2-3 May 2018

Gavi
The Vaccine Alliance

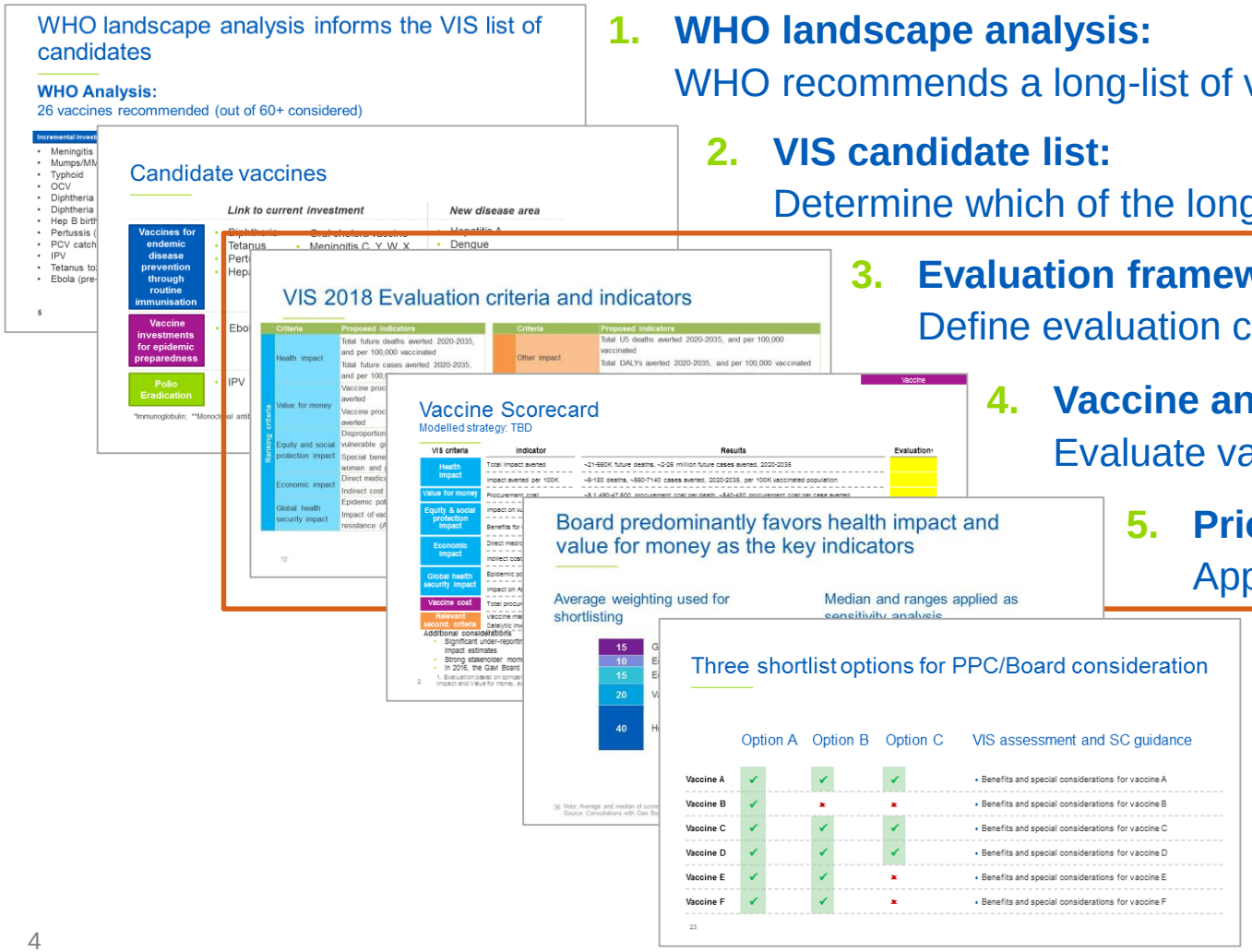
Topics

1. Introduction and general considerations
2. Evaluation framework
3. Vaccine analyses: Modelling approach and comparison of different models
4. Prioritisation methodology

1

Introduction and general considerations

VIS Shortlisting follows a six step process



1. **WHO landscape analysis:**
   WHO recommends a long-list of vaccines for consideration in the VIS

2. **VIS candidate list:**
   Determine which of the long-list vaccines are appropriate to evaluate

Focus of document

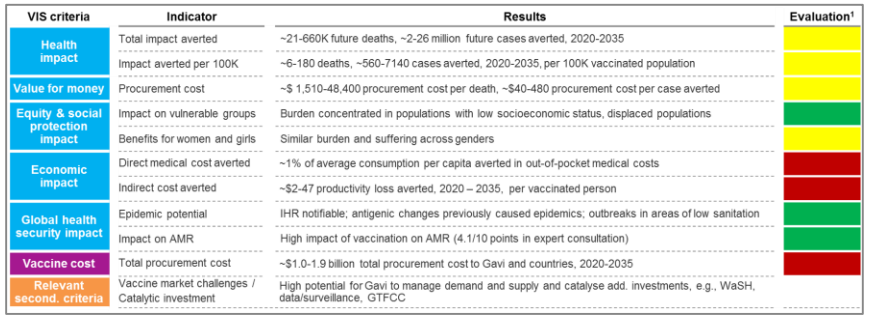
3. **Evaluation framework:**
   Define evaluation criteria, indicators and thresholds

4. **Vaccine analyses:**
   Evaluate vaccines along the indicators

5. **Prioritisation methodology:**
   Apply criteria towards shortlisting based on board priorities

6. **Shortlist options:**
   Derive several shortlists based on prioritisation

Vaccine scorecards are populated based on both quantitative and qualitative analyses



VIS criteria	Indicator	Results	Evaluation[1]
Health impact	Total impact averted	~21-660K future deaths, ~2-26 million future cases averted, 2020-2035	
	Impact averted per 100K	~6-180 deaths, ~560-7140 cases averted, 2020-2035, per 100K vaccinated population	
Value for money	Procurement cost	~$ 1,510-48,400 procurement cost per death, ~$40-480 procurement cost per case averted	
Equity & social protection impact	Impact on vulnerable groups	Burden concentrated in populations with low socioeconomic status, displaced populations	
	Benefits for women and girls	Similar burden and suffering across genders	
Economic impact	Direct medical cost averted	~1% of average consumption per capita averted in out-of-pocket medical costs	
	Indirect cost averted	~$2-47 productivity loss averted, 2020 – 2035, per vaccinated person	
Global health security impact	Epidemic potential	IHR notifiable; antigenic changes previously caused epidemics; outbreaks in areas of low sanitation	
	Impact on AMR	High impact of vaccination on AMR (4.1/10 points in expert consultation)	
Vaccine cost	Total procurement cost	~$1.0-1.9 billion total procurement cost to Gavi and countries, 2020-2035	
Relevant second. criteria	Vaccine market challenges / Catalytic investment	High potential for Gavi to manage demand and supply and catalyse add. investments, e.g., WaSH, data/surveillance, GTFCC	

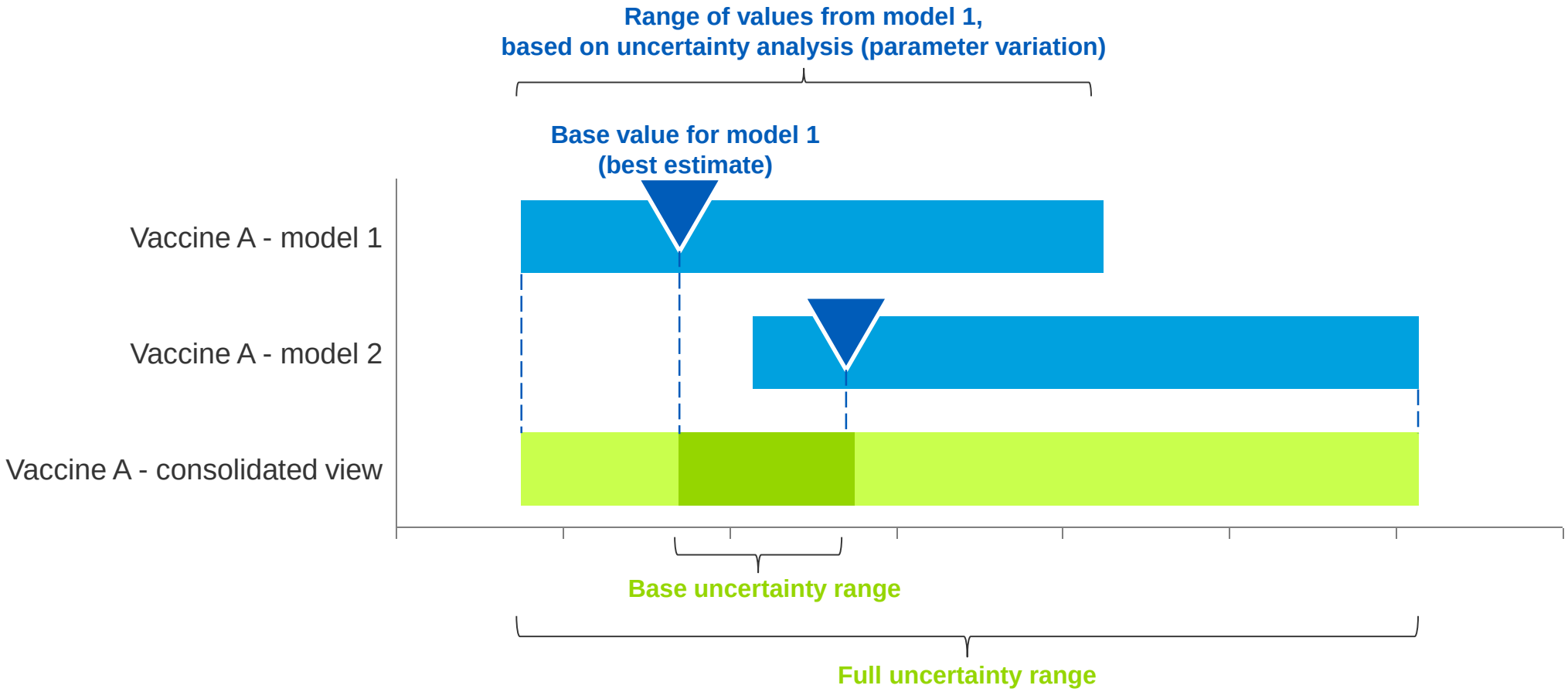
Quantitative analyses

- Several analytical activities drive assessment of health, economic and cost indicators
- Projections based not on point estimates, but assessment of uncertainty and leveraging multiple modellers
- Assumptions informed by disease experts
- Ranked outcomes across vaccines to determine relative score

Qualitative analyses

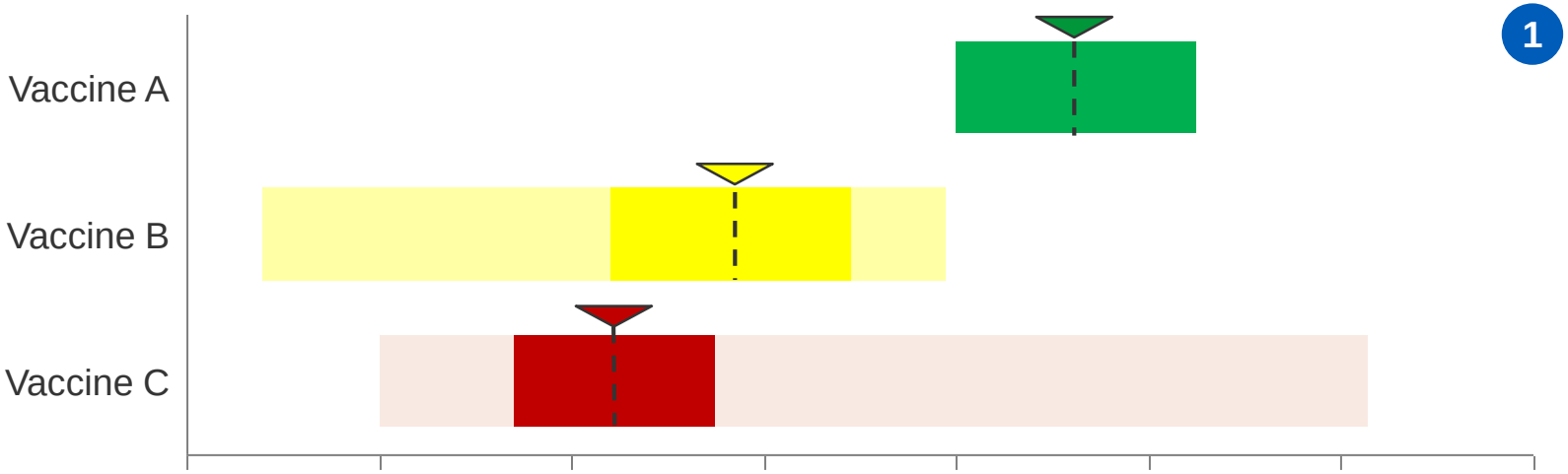
- Transparent scoring method for each qualitative criterion
- Informed by disease experts

Uncertainty ranges incorporate variation across models and parameters



Note: Vaccines for which only one model is provided only show a full uncertainty range

Scoring method for quantitative indicators (1/2)



1 Calculate range average for each vaccine:

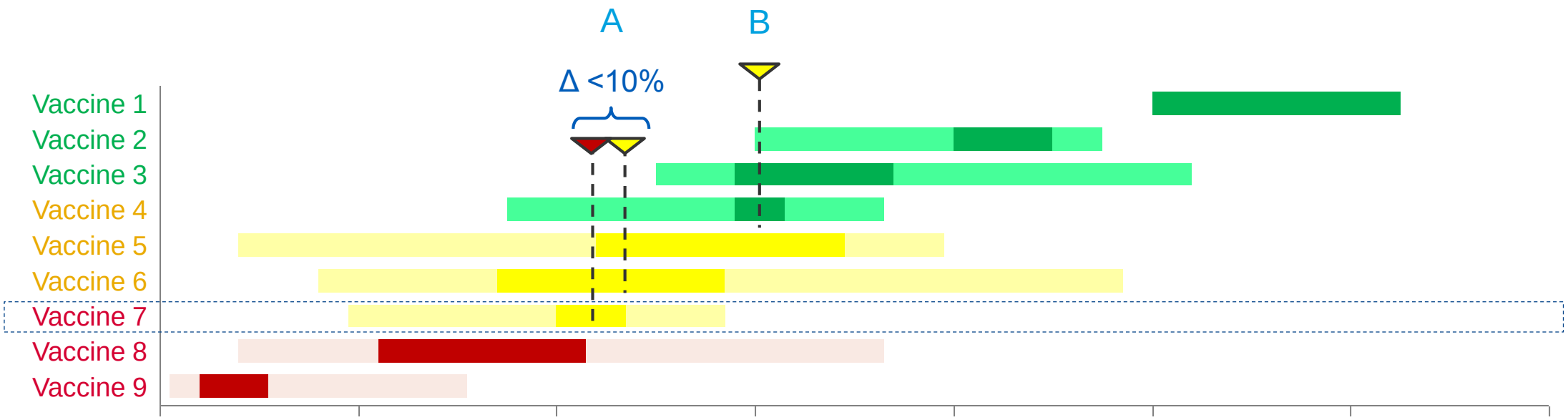
- Average of base range is used for vaccines for which 2 or more models are provided *(Vaccines B and C here)*
- Average of full uncertainty range is used for vaccines for which only one model is provided *(Vaccine A above)*

2 Rank vaccines based on range averages. Considering 9 VIS candidates (excluding Malaria), colours were assigned as below:

- First three vaccines: Green
- Vaccines ranked 4, 5 and 6: Yellow
- Last 3 vaccines: Red

Range averages

Scoring method for quantitative indicators (2/2)



3 "Round up" to next colour if[1] :

A. Range average is less than 10% smaller than the range average of the upper colour
E.g. Vaccine 7 here has a range average less than 10% below vaccine 6. Colour is changed from red to yellow.

B. Range average is included in the base range of a vaccine with the upper colour
E.g. The range average of Vaccine 4 falls into the range for Vaccine 3. Colour is changed from yellow to green.

Range averages

Note: Additional sensitivity analyses performed showed that colour changes to vaccines did not have strong impact on overall ranking (except: total deaths averted)

1. Rounding up only considered for the original colours (those after step 2)

Vaccine assessments were conducted in close cooperation with technical partners

Demand Forecasting

- Vaccine products
- Vaccination strategy
- Schedule/dosing
- Delivery strategy
- Target population
- Country introduction
- Coverage

Impact Modelling

- Burden of disease
- Case fatality rate
- Efficacy
- Duration of protection

Price Forecasting

- Products
- Supplier projections
- Price projections

Other quant. analyses

- Procurement cost
- Operational costs
- Value for money
- Economic Impact: cost of illness
- Global burden of disease

Qualitative analyses

- Epidemic potential
- Impact on AMR
- Disease specifics
- Vaccination policy
- Other qualitative input

Bill & Melinda Gates foundation
University of Glasgow
Johns Hopkins University
London School of Hygiene & Tropical Medicine
Clinton Health Access Initiative
WHO
University of Cambridge
PATH
CDA Center for Disease Analysis
Imperial College London
University of Antwerp
Vaccine Impact Modelling Consortium
CDC Centers for Disease Control and Prevention
IHME Institute for Health Metrics and Evaluation
Swiss TPH

Note: Non exhaustive. Many other institutions and individuals were consulted as part of the VIS 2018

2

Evaluation framework

VIS 2018 Evaluation criteria and indicators

	Criteria	Proposed indicators
Ranking criteria:	Health impact	Total future deaths averted 2020-2035, and per 100,000 vaccinated Total future cases averted 2020-2035, and per 100,000 vaccinated
	Value for money	Vaccine procurement cost per death averted Vaccine procurement cost per case averted
	Equity and social protection impact	Disproportionate impact of disease on vulnerable groups Special benefits of vaccination for women and girls
	Economic impact	Direct medical cost averted Indirect cost averted
	Global health security impact	Epidemic potential of disease Impact of vaccination on antimicrobial resistance (AMR)

	Criteria	Proposed indicators
Secondary criteria:	Other impact	Total U5 deaths averted 2020-2035, and per 100,000 vaccinated Total DALYs averted 2020-2035, and per 100,000 vaccinated Vaccine procurement cost per DALY averted
	Gavi comparative advantage	Degree of vaccine market challenges Potential for Gavi support to catalyse additional investment
	Implementation feasibility	Ease of supply chain integration Need for health care worker behaviour change Feasibility of vaccination time point Acceptability in target population Long-term financial implications
	Alternate interventions	Optimal use of current and future alternative interventions (prevention and treatment)
	Broader health system benefits	*No specific indicator – evaluated case-by-case*
Financial implications:	Vaccine cost	Total procurement cost to Gavi and countries, 2020-2035
	Operational cost	Incremental in-country operational costs per vaccinated person
	Additional implementation costs	Additional costs for introduction

Health impact & Value for Money indicators

Based on quantitative modelling and comparison with VIS 2018 candidates

Health Impact	Value for money
Total future deaths averted from vaccinations delivered from 2020 to 2035, over the lifetime of vaccinated individuals[1]	Vaccine procurement cost per death averted from vaccinations delivered from 2020 to 2035, over the lifetime of vaccinated individuals[1]
Total future deaths averted from 2020 to 2035 per 100,000 vaccinated	
Total future cases averted from vaccinations delivered from 2020 to 2035, over the lifetime of vaccinated individuals[1]	Vaccine procurement cost per case averted from vaccinations delivered from 2020 to 2035, over the lifetime of vaccinated individuals[1]
Total future cases averted from 2020 to 2035 per 100,000 vaccinated	

Thresholds[2]

Lowest tier candidates, *the ones with the lowest impact or the highest cost per impact*	Medium tier candidates	Top tier candidates, *the ones with the highest impact or the lowest cost per impact*

1. I.e. including deaths / cases averted that would have occurred after 2035 2. Detailed methodology described previously
Values include deaths and cases averted in Gavi-supported countries (direct impact) and in countries within 5 years post transition (catalytic impact)

Equity and social protection impact

Based on expert evaluation and pre-determined thresholds

Indicator	Thresholds		
Disproportionate impact of disease on vulnerable groups	n/a	Relatively even distribution of disease burden across groups	Disease burden concentrated to vulnerable groups[1]: • Low socioeconomic status • Rural poor • Urban slum residents • Refugees • Displaced populations • Indigenous persons • Elderly • LGBTQ+ • Injecting drug users • Sex workers
Special benefits of vaccination for women and girls	n/a	No increased burden or suffering in women/ girls	Women/ girls experience higher disease burden or suffering (or vaccine confers additional benefits to women/ girls)

1. Draws from: WHO vulnerable groups as identified by the Environmental Health in Emergencies programme and UN Rights of vulnerable groups with disabilities standards

Economic impact

Based on quantitative modelling and comparison with VIS 2018 candidates

Direct medical cost averted

Financial burden averted

- Accounts for financial burden of **direct medical costs** incurred by individuals affected by the disease

Thresholds

Low financial burden of disease

High financial burden of disease

Indirect cost averted

Productivity loss averted

- Accounts for the **economic output lost** to disease and death

Thresholds

Low impact on economic output

High impact on economic output

Note: If the average of the base range for a vaccine in one threshold falls inside the range of a vaccine in the next threshold, the vaccine was adjusted up into that grouping

Direct medical cost averted

Quantitative ratio of out of pocket costs to income – financial burden averted

$$\text{Ratio} = \frac{\text{Out of pocket medical costs}}{\text{Average annual consumption}}$$

Out of pocket medical costs

1. Average direct medical costs per case *(USD)*
X
2. Share of medical costs that are out of pocket *(%)*

Average annual consumption

3. National average household consumption per capita in the countries in scope *(annual, USD)*

Sources

1. Treatment and hospitalization costs from literature and WHO-CHOICE; averaged across relevant countries taking into account cases in each country
2. Country-level data from World Bank[1]; averaged across relevant countries taking into account cases in each country
3. Country-level data from World Bank[2]; averaged across relevant countries taking into account cases in each country

1. World Bank indicator: Out-of-pocket health expenditure (% of private expenditure on health), from 2014
2. Latest year available for each country

Direct medical cost averted: approach

- Approach for calculating average medical costs per case developed with BMGF Integrated Portfolio Management (IPM) team, drawing upon methodology used in the Decade of Vaccine Economics Cost of Illness modelling approach

- Treatment costs averted follow decision tree based on:
  - Cases averted estimates (generated by health impact modeling)
  - Model care-seeking by disease severity (when appropriate from disease-specific burden studies)
  - Location (rural vs. urban) and facility level (outpatient, health center, or hospital care)
  - Facility costs adjusted (25% higher) from standard WHO CHOICE values to account for medication and diagnostic costs

  - Treatment costs are not discounted and are provided in US$2016 (consistent with health impact models)

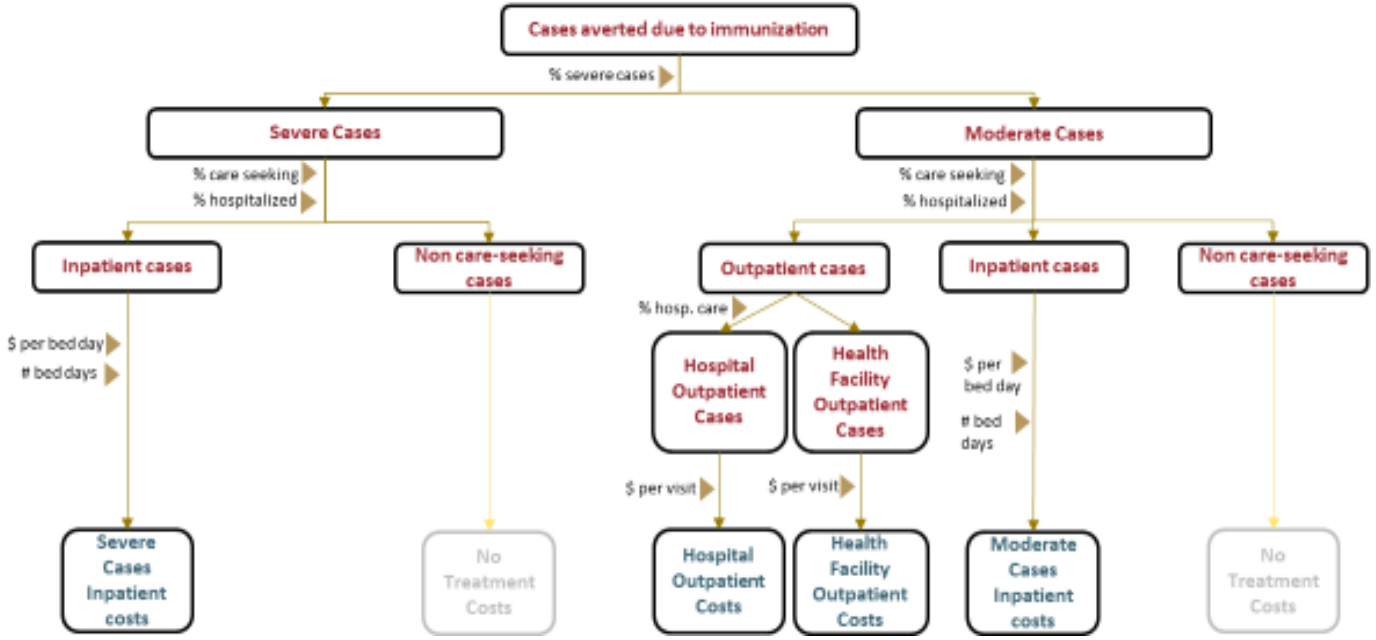
Source: IPM documentation

Direct medical cost averted: details

Applying methodologies similar to the DOVE[1] Cost of Illness modelling approach, treatment costs averted in the IPM analyses:

- Primary inputs are cases averted estimates generated by health impact modeling
- Model care-seeking by disease severity (when appropriate from disease-specific burden studies)
- Based on location (rural vs. urban) and facility level (outpatient, health center, or hospital care)
- Facility costs adjusted (25% higher) from standard WHO CHOICE values to account for medication and diagnostic costs

Example Treatment Costs Averted Decision Tree:



1. Ozawa et al. 2017. Estimated economic impact of vaccinations in 73 low-and middle-income countries, 2001–2020. Bulletin of the World Health Organization, 95(9), 629.

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Direct medical cost averted: data inputs

Principles

- Where available, disease- and country-specific severity and care-seeking values used
- When possible, alignment with other economic analyses that have been previously performed in collaboration with Gavi

Prioritized data sources

- Collected based on input from disease experts
- Rapid literature review for published and grey research on care-seeking
- Proxy values to approximate care-seeking behavior

Source: IPM documentation

Indirect cost averted

Quantitative measure of economic output loss averted per vaccinated person

$$\text{Indicator (\$)} = \frac{\text{(4) \# DALY averted 2020-2035} \times \text{(5) GDP per capita in the countries in scope (\textit{annual, USD})}}{\text{(6) Number of fully vaccinated persons 2020-2035}}$$

Calculated on a per-country basis and consolidated as a total measure for all countries in scope

Sources

Methodology: adapted from Ozawa, Clark & Portnoy 2017 – "Estimated economic impact of vaccinations in 73 low- and middle-income countries, 2001-2020"
Bull World Health Organ 2017

4 VIS impact modelling

5 Country-level data from World Bank

6 VIS impact modelling

Global health security impact

Based on expert evaluation and pre-determined thresholds

Indicator	Thresholds		
Epidemic potential of disease	Low epidemic potential	Intermediate epidemic potential	High epidemic potential
Impact of vaccination on antimicrobial resistance (AMR)*	Low impact of vaccination on AMR (mortality, morbidity, antibiotic use, inequality, societal impact): Expert score <2	Moderate impact of vaccination on AMR (mortality, morbidity, antibiotic use, inequality, societal impact): Expert score 2-4	High impact of vaccination on AMR (mortality, morbidity, antibiotic use, inequality, societal impact): Expert score >4

Epidemic potential of disease

		Thresholds		
Factors	**Methodology**			
IHR notifiable	*Check against list in the IHR 2005 & WHO subsequent reports*	• Not listed in IHR and no outbreaks reported by WHO	• Not listed in IHR but some outbreaks reported by WHO	• Disease listed in IHR or having high number of reported outbreaks by WHO
Potential for biological and/or epidemiological shifts	*Expert input*	• Low or little evidence of evolutionary potential and geographic spread (due to population movements, changes in sanitation or vector range)	• There is some evidence of rapid pathogen evolution • There is a potential trend towards increasing severity of the disease • There is a potential trend towards the increasing transmissibility of the pathogen • There is a potential trend towards changing geographic spread (due to population movements, changes in sanitation or vector range)	• There is much evidence of rapid pathogen evolution • There is a strong trend towards increasing severity of the disease • There is a strong trend towards the increasing transmissibility of the pathogen • There is a strong trend towards changing geographic spread (due to population movements, changes in sanitation or vector range)
Impact of vaccination strategy on epidemic potential of disease	*Expert input*	• Little or no ability to prevent future epidemics/ outbreaks	• Reduce frequency/ size/ other impact of epidemics/ outbreaks	• Preventing future epidemics/ outbreaks

Impact of vaccination on AMR

Factor	Evaluation (1=low, 10=high)
Actual mortality due to resistant pathogens that will be prevented by the vaccine through a direct effect (resistance within the vaccine-targeted organism)	1 ⟷ 10
Actual morbidity due to resistant pathogens that will be prevented by the vaccine through a direct effect (resistance within the vaccine-targeted organism)	1 ⟷ 10
Antibiotic use prevented by the vaccine	1 ⟷ 10
Time trend and sense of urgency related to AMR threat due to vaccine-targeted pathogen (considering therapeutic options in coming 10 years, general transmissibility)	1 ⟷ 10
Societal impact from vaccine-targeted resistant pathogens	1 ⟷ 10
Ethical importance: the importance of vaccine-targeted resistant pathogens as sources of inequity and social exclusion	1 ⟷ 10

Each factor **weighted** and assessed based on expert input to arrive at a **score 1-10** for each vaccine

Gavi comparative advantage

Based on Gavi Secretariat evaluation, expert review and pre-determined thresholds

	Thresholds		
Indicator			
Degree of vaccine market challenges	Low degree of market challenges for Gavi to address	Moderate degree of market challenges for Gavi to address	High degree of market challenges for Gavi to address
Potential for Gavi support to catalyse additional investments	n/a	Limited or moderate potential for Gavi investment to directly catalyse longer-term financial investments in vaccination or complimentary interventions/activities by countries or other development organisations	High potential for Gavi investment to directly catalyse longer-term financial investments in vaccination or complimentary interventions/activities by countries or other development organisations

Degree of vaccine market challenges

Factor	Proposed Methodology	Thresholds		
Long-term competition	Manufacturer and expert input	3+ manufacturers by 2025[1]	2 manufacturers by 2025[1]	1 manufacturer by 2025[1]
Individual supplier risk	Gavi Secretariat analysis, based on current Gavi experience	Manufacturers in market by 2025 have significant prior experience supplying to Gavi	Manufacturers in market by 2025 have some prior experience supplying to Gavi	Manufacturers in market by 2025 have no prior PQ vaccines
Suitability of products to Gavi-supported countries	Gavi Secretariat analysis, based on manufacturer and expert input	Current / planned presentations do not pose programmatic challenges[2]	Current / planned presentations pose some programmatic challenges[2]	Current / planned presentations not programmatically suitable[2]
Availability of supply for Gavi-supported countries relative to demand	Based on manufacturer and expert input and demand forecast	Current / planned capacity to meet Gavi demand	Current / planned capacity to meet most of Gavi demand	Current / planned capacity to meet some Gavi demand
Volatility of demand	Based on assumed vaccination strategy and demand forecast	Predictable demand (e.g., routine immunisation)	Fluctuating demand (e.g., routine immunisation and preventive campaigns)	Uncertain demand (e.g., risk-based campaigns)

All factors to be considered to arrive at a **colour score** for each vaccine. Thresholds and "weighting" of factors vary and take into account unique market characteristics.

1. Draws from: WHO vulnerable groups as identified by the Environmental Health in Emergencies programme and UN Rights of vulnerable groups with disabilities standards

Implementation feasibility

Based on Gavi Secretariat evaluation, expert review and pre-determined thresholds

Indicator	Thresholds		
Ease of supply chain integration	High packed volume, short shelf life, low stability	Moderate packed volume, shelf life, and stability	Low packed volume, long shelf life, high stability
Need for healthcare worker behaviour change	Vaccine introduction requires one of: • Training of new HCW group • Use of complex new present./ method of administration/ schedule of dosing • Complex follow-up procedure	Vaccine introduction requires one of: • Outreach to patients • Use of new presentations/ method of administration/ schedule of dosing • Specific follow-up procedure	No significant healthcare worker behavior change required
Feasibility of vaccination time-point	*Other:* Adults/ elderly, ad hoc	*Existing access points:* School-entry, newborns, pregnant women	*Established vacc. time-point:* EPI, second year of life, adolescent
Acceptability in target population[1]	Low acceptability, decision-maker understanding of burden, and priority for countries	Moderate acceptability, decision-maker understanding of burden, and priority for countries	High acceptability, decision-maker understanding of burden, and priority for countries
Long-term financial implications	Price per course >5 USD	Price per course 2-5 USD	Price per course < 2 USD

1. Informed by input from VIS in-country stakeholder consultations conducted in February 2018

Ease of supply chain integration

Semi-quantitative approach to assessing ease of supply chain integration, using manufacturer data as the source

Factor	Proposed Methodology	Thresholds		
Packed volume (cm3)[1]	• Average packed volume of licensed and under-development products using WHO Vaccine Volume Calculator • Thresholds established based on range of average packed volume/antigen	>18cm^3	6cm^3-18cm^3	<6cm^3
Shelf life	• Average shelf life of licensed and under-development products • Thresholds established based on range of average shelf life/antigen	<18 months	18-30 months	>30 months
Stability	• Average VVM of licensed and under-development products • Thresholds established based on range of average VVM/antigen	<VVM5	VVM5 – VVM8	>VVM8

Factors **weighted** based on expert input to arrive at a **colour score** for each vaccine

1. Includes wastage data

Alternate interventions

Based on Gavi Secretariat evaluation, expert review and pre-determined thresholds

	Thresholds		
Indicator			
Optimal use of current and future alternative interventions (prevention and treatment)	n/a	Yes, alternative interventions for effective disease control (prevention and treatment) are used and can be scaled up, or will be available in the near future	No, alternative interventions are not available now or in the near future for effective disease control and / or do not have potential for scale up

Operational cost

Based on quantitative modelling and comparison with VIS 2018 candidates

Indicator	Thresholds		
Incremental in-country operational costs per dose • Logistician costs • Cold chain costs • Transportation costs • Human resource costs for administration (routine/facility) • Operational costs (campaign/outreach) • Other non-labor costs (training, social mobilization, disease surveillance, program management) **X** **Number of doses per fully vaccinated person**	Last 3 candidates in ranking order, *the ones with the **highest operational cost** per vaccinated person*	Middle 3 candidates in ranking order	Top 3 candidates in ranking order, *the ones with the **lowest operational cost** per vaccinated person*

Source: IPM for all vaccines except malaria & dengue; Malaria estimated based on mening proxy; Dengue estimated based on DTP proxy

Operational cost: principles

Analyses led by BMGF Integrated Portfolio Management (IPM) team

Principles

1. Costs must be incremental to estimate the addition of a vaccine to a vaccination system
2. The highest degree of specificity based on vaccine characteristics and country-level structure was sought
3. When possible, alignment with other economic analyses that have been previously performed in collaboration with Gavi

PATH collaboration

The IPM team engaged in a collaboration with PATH's Vaccine Technology Impact Assessment (V-TIA) model to explore country-specific incremental delivery costs that take into account vaccine characteristics (e.g. packed volume per dose, delivery platform).

The VTIA model is an Excel-based tool that provides a comparative economic evaluation of the commodity and system costs and impact for alternative vaccine presentations. Its primary use is to inform decision-making of key stakeholders in the early stages of vaccine development.

The tool estimates the incremental system costs for each alternative target product profile for the vaccine technologies under consideration.

Note: The model calculates the cost of delivering the demanded vaccination doses including wasted doses. Delivery costs are NOT computed for buffer stock doses; Source: IPM documentation

Operational cost: estimation of service delivery costs per dose

Costs area	Estimation methodology
Logistician	Costs per dose of logistician time were estimated by using country-specific logistician salaries and reported doses delivered in the most recent comprehensive multi-year plans (cMYPs). Specific logistician costs per dose were obtained at four levels of the health system (national, regional, district, and health facility) and aggregated to determine the total resource use per dose.
Cold chain	Costs per cm^3 for cold chain were estimated from countries' cMYP-reported equipment, energy use, and energy costs at national, regional, district, and health center and estimated total vaccine volume delivered.
Transportation	Costs per cm^3 for transportation were estimated from countries' cMYP-reported vehicles and cold box type, and related reported carriage capacity, fuel use and mileage. Distance traveled to sites at national, regional, district, and health center levels are determined based on the number of vehicles, number of facilities at each of the noted four levels, and country size.
HR for administration (routine / facility)	Human resource costs for administration (routine/facility). Human resource costs per second for vaccine administration are based on cMYP-reported salaries, multiplied by seconds needed for administration based on product formulation and presentation. Values of seconds per administration are based on time-motion studies of immunization conducted by PATH.
Operations (campaign / outreach)	Operational costs reported in cMYPs by vaccine type are used in lieu of human resources costs for products delivered via campaign or outreach platforms. When exact product operational costs were not available, an indexed vaccine was used matched on similarities in formulation/presentation.
Adjustment for additional non-labor costs	While the PATH VTIA model provides a robust estimate of the incremental resources needed for the delivery of vaccines, a few additional non-labor cost areas are not included for products delivered routinely or at the facility: training, social mobilization, disease surveillance, program management, and other recurrent costs. In a previous cMYP-based costing analyses, these costs added 10.6% above costs analogous to those included in VTIA. Estimates for service delivery costs per dose with this adjustment are included for each relevant product and are the costs ultimately used in the IPM analysis.

Note: Where any country-specific values were not available for the above information from cMYPs, group average values were used based on region or country size. Source: IPM methodology

Additional costs for introduction

Based on Gavi Secretariat evaluation, expert review and comparison with VIS 2018 candidates

Introduction cost categories	Cost score	Aggregate colour score
Technical Assistance	1 ⟷ 5	
Healthcare Worker Training	1 ⟷ 5	
Demand Generation/Education	1 ⟷ 5	
Microplanning	1 ⟷ 5	
Data (surveillance, M&E)	1 ⟷ 5	
Waste Management	1 ⟷ 5	

Low cost ⟷ *High cost*

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High costs	Moderate costs	Low costs
Expert score > 20	Expert score 17 – 20	Expert score < 17

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3

Vaccine analyses

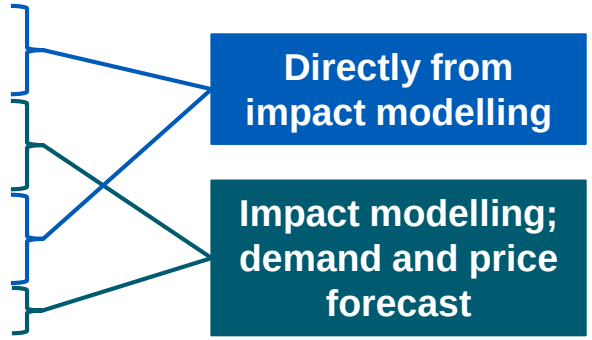
Health impact modelling approach

Comparison of different models

Modelling informs several indicators in the evaluation framework for vaccines for endemic disease

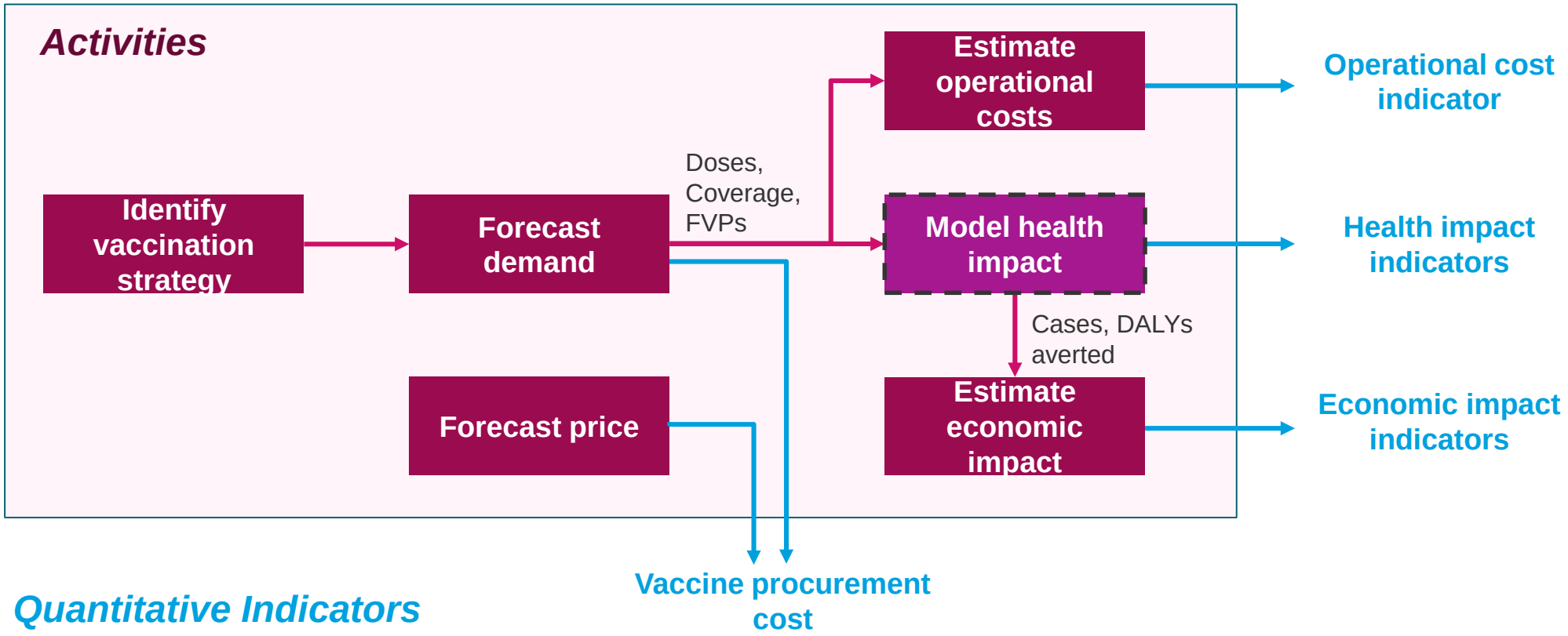
Health impact modelling is necessary to provide estimates for several of the indicators in the evaluation framework, namely deaths/cases/DALYs averted and value for money

	Criteria	Indicators
Ranking criteria:	Health impact	Total future deaths averted 2020-2035, and per 100,000 vaccinated
		Total future cases averted 2020-2035, and per 100,000 vaccinated
	Value for money	Vaccine procurement cost per death averted
		Vaccine procurement cost per case averted
Secondary criteria:	Other impact	Total U5 deaths averted 2020-2035, and per 100,000 vaccinated
		Total DALYs averted 2020-2035, and per 100,000 vaccinated
		Vaccine procurement cost per DALY averted



Where possible, more than one model was used to give a range of outputs in order to capture uncertainty in data and parameter estimates

Several analytical activities drive assessment of health, economic and cost indicators



Impact modelling aims to capture uncertainties across key parameters

A consultative process with disease experts was conducted to identify the critical model inputs and key uncertainties to inform VIS assessments

Key modelling inputs	• Demand forecasts • Disease burden datasets • Vaccine efficacy • Vaccine duration of protection
Uncertainties	• For some parameters significant uncertainty existed • Multiple scenarios were assessed for each vaccine with different assumptions for uncertain parameters • Uncertainties included disease burden, vaccine efficacy and duration of protection
Multiple models	• Where possible multiple models with independent approaches were used to capture uncertainty in estimated impact of vaccine candidates

In most cases, multiple models used to estimate impact

Impact modelling for vaccine shortlisting

- **Integrated Portfolio Management (IPM)** tool was used **for most vaccines** to generate impact estimates from a standard methodology
  - IPM tool developed specifically to compare across different potential investments using standard inputs and approaches (e.g., burden, transmission, model structure, DALY weighting)
  - Provides ability to have impact estimates across nearly all VIS candidates from a consistent methodology
- **Additional disease-specific models** were used where available to capture both the range of uncertainty in Gavi's potential impact and where complex disease dynamics and indirect effects existed
- The **number of models** used to generate impact estimates **varied** for each vaccine depending on availability

3

Vaccine analyses

Health impact modelling approach

Comparison of different models

Summary of models used in VIS shortlisting phase

Vaccine Candidate	Models utilised
Diphtheria	IPM
Tetanus	IPM
Pertussis	IPM
Hepatitis B	Center for Disease Analysis (CDA), Imperial College London, Goldstein
Cholera	IPM, Johns Hopkins University (JHU)
Meningitis	IPM, Cambridge University
Hepatitis A	IPM
Dengue	Imperial College London
RSV	IPM, PATH, London School of Hygiene and Tropical Medicine (LSHTM) / University of Antwerp
RSV mAb	
Rabies vaccine and Ig	IPM, Cambridge University
Malaria (RTS,S)	Results from modelling conducted in 2015 by Swiss Tropical and Public Health Institute & Imperial College London being used
Maternal Influenza	IPM

Cholera: key assumptions

xx: included in model uncertainty range
xx: not included

Models	IPM direct	JHU
Vaccination strategies	2 doses to at risk population ≥ 1 yo Every 3 years; Crisis countries vaccinate every 2 years[1]	2 doses to at risk population ≥ 1 yo Every 5 years
Uncertainty analysis driving ranges	Effectiveness (62%, 76%, 85%) Burden estimated (Low[2], Base, High) Duration of protection (3yr, 5yr)	
Other key assumptions	Fully vaccinated persons: Gavi Strategic Demand Scenarios (S2, S3 and S5) Estimated at risk population decreasing over time based on Ending Cholera Roadmap assumptions	

1. Applies to base and high scenario; three crisis countries currently included in model; 2. Low burden estimates not included for JHU model, as overall cholera burden likely underestimated

Cholera: key model attributes & differences

	Model characteristics	*Model-specific uncertainties and direction of bias*
IPM	**Burden data** • Cases and deaths calculated using data from Ali et al. (the primary data sources for cholera cases and deaths were from WHO 2008-2012) which took into account cholera risk determined using ecological covariate of % population using at least basic improved drinking water sources. • Case definition included suspected (severe dehydration and watery diarrhoea in over 5 year population) and confirmed cases. • **Model structure:** static population-based cohort model • **Modelled impact:** direct effects only	• 5 years duration of protection would call for spacing the campaigns out more (currently modelled based on demand forecast with periodic campaigns every 3 years) • IPM model does not account for herd immunity or waning efficacy of the vaccine
JHU	**Burden data** • Derived from a previously published model estimating average annual cholera incidence from 2010-2016 at the 20x20km grid cell scale or if not included in this study, point estimates used for countries or sub-regions • Cholera risk determined using ecological covariates of % population with access to improved drinking water and sanitation and distance to coastline/ major waterbody. • **Model structure:** Stochastic model based on spatially explicit statistical model, modelling susceptible, infected, recovered and vaccinated • **Modelled impact:** Measured direct effects and indirect effects of vaccine and demographic turnover, with herd effects considered • **Sensitivities:** considers decreasing incidence over time at a rate consistent with global decline in cases reported to WHO	• Same issue with periodic campaigns as IPM • India and Bangladesh have very little data on incidence but large populations, and thus large uncertainty • Uncertainty regarding assumptions on CFR and future trends in incidence • Estimates based on clinical cases and care-seeking are reported, with no adjustment for missed cases

Cholera: parameter sensitivity and key drivers of differences across models

IPM and JHU models

Parameters sensitivity

Parameter sensitivity:

- Modelling is highly sensitive to estimates around burden, approximately 9-10 times more infections in high versus low burden scenarios in IPM model. For JHU, the difference is 50 times greater
- The modelling is less sensitive to variations in the efficacy of the vaccine, with 30-40% more infections in the high versus the low efficacy scenarios for IPM. For JHU, results are almost identical.

Results comparison across models

Comparison of baseline scenarios:

- Lowest impact (deaths averted) in JHU model
- Highest impact in IPM model
- Estimates for IPM model generally higher than those of JHU, with the exception of the high burden scenario

Explicit factors likely to be driving variation in results

- Burden data is highly uncertain and the models are highly sensitive to variations in burden, which leads to differences in estimates
- The models used slightly different approaches to estimate burden, and drew on different sources to estimate case fatality ratios

Dengue: key assumptions

xx: included in model uncertainty range
xx: not included

Models	Imperial		
Vaccination strategies	Routine, 2 doses, 4 year olds	Routine, 1 dose, 2 year olds	Routine, 3 doses, 9 year olds[1]
Uncertainty analysis driving ranges	Variation in demand forecast • # doses (1 or 2) • Inclusion of risk enhancement[2]		
Other key assumptions	Efficacy: Seropositive: 80%-85% Seronegative: 40%-60%	Duration of protection: Seropositive: lifelong Seronegative: ~2 years	Coverage: MCV2 analogue

1. In countries with seroprevalence >50% in target population 2. For both considered product profiles, scenarios with increased risk enhancement for seronegative population were taken into account, where the risk of getting Dengue because of the vaccine is higher in those seronegative population

Dengue: key model attributes

	Model characteristics	*Model-specific uncertainties and direction of bias*	*Parameter sensitivity*
Imperial	• **Disease Burden:** Maps of dengue transmission intensity for different countries were generated from a machine-learning based model, fitted to force of infection estimates • **Model structure and impact:** Four serotype SIR dynamic transmission model that includes cross-protective and/or enhancing immunity between serotypes • **Sensitives:** Both risk enhancing and non-enhancing scenarios were modelled to mimic potential safety concerns	• Uncertainty in: disease severity parameter estimates, spatially-disaggregated transmission intensity estimates and vaccine efficacy estimates **Simplifying assumptions** • All four serotypes have same risk of causing disease • Severity of infections depends on number of past infections, not specific serotypes of those infections and their precise timing • Seasonality of dengue transmission is represented simplistically, and not climate driven, therefore inter-annual variability in incidence may be under-estimated • Transmission model used is non-spatial, i.e. random mixing of entire mosquito and human populations is assumed	• Challenges in disaggregating parameter sensitivity due to different vaccine profiles being compared across scenarios

DTP: key assumptions

xx: included in model uncertainty range
xx: not included

Models	IPM[1]				
Vaccination strategies	EPI/1 yo (DTwP/penta) School entry /5 yo (Td) Adolescent /10 yo (Td)				
Uncertainty analysis driving ranges	*Primary series vaccination*	FVPs as baseline (excl. PVPs)	FVPs as baseline (excl. PVPs)	FVPs and PVPs as baseline	FVPs and PVPs as baseline
	Booster series vaccination	FVPs only (excl. PVPs)	Partial complet° of boosters (PVPs) and FVPs	FVPs only (excl. PVPs)	Partial complet° of booster (PVPs) and FVPs
Other key assumptions	Efficacy (1st/2nd/3rd booster): Diph: 95.5%/95.5%/98.4% Tet: 99%/99%/99% Pert: 96%	Duration of protection (1st/2nd/3rd booster): Diph: 10y/10y/29y Tet: 3 to 5y/20y/20y Pert: 10y		Coverage: MCV2 analogue	

1. Models used in evaluation only measure direct impact
Note: FVP—fully vaccinated persons; PVP—partially vaccinated persons

DTP: key model attributes

	Model characteristics	*Model-specific uncertainties and direction of bias*	*Parameter sensitivity*
IPM	**Diphtheria, Tetanus & Pertussis were all modelled separately** **Burden data:** • IHME primary date source for burden data. Cases estimated by calculating case fatality rate in 2016, by country and age group, using Global Burden of Disease Study (GBD) 2016 historic data • **Modelled structure:** static population-based cohort model for diphtheria, tetanus & pertussis • **Modelled impact:** Direct effect only. **Sensitivities** • Low burden scenarios: countries had incidence 50% of base incidence and CFR 1% • High burden scenarios: countries had 150% of the base incidence and CFR was 3%	• Burden data uncertain and expert opinion indicates an underestimation across all three diseases • Model only considers children vaccinated sequentially with each booster, thus underestimating impact from children who are covered with non-sequential boosters • Limitations to approach due to 'fitting' of waning immunity to a step change approach to account for efficacy	• Difficult to assess individual parameter sensitivity as there is large uncertainty around efficacy acquired through different combinations of primary and booster series for individual antigens. Comparison across scenarios is not consistent, because different populations are captured in each scenario, not able to perform consistent comparison to determine parameter sensitivity • Impact greatest for pertussis (130–135,000 deaths averted), least for diphtheria (5,800–6,900 deaths averted)

Hepatitis A: key assumptions

xx: included in model uncertainty range
xx: not included

Models	IPM[1]
Vaccination strategies	Routine single dose to children at 12 months
Uncertainty analysis driving ranges	Duration of protection • Low: 11 years • Medium: 30 years • High: lifetime
Other key assumptions	Efficacy: 90% Coverage: MCV2 analogue

1. Models used in evaluation only measure direct impact

Hepatitis A: key model attributes

	Model characteristics	*Model-specific uncertainties and direction of bias*	*Parameter sensitivity*
IPM	• **Burden data:** Cases and deaths estimated by calculating CFR 2016, by country and age group, using GBD 2016 historic data; average historical CFR was used • **Model structure:** Static population-based cohort model • **Modelled impact:** direct impact only	• Model not calibrated to country incidence. • Herd immunity not considered*	• Three scenarios considered; low, medium, and high duration of the vaccine, with a base line efficacy. There were approximately 20% fewer infections in the high duration scenario, and approximately 20% more infections in the low duration scenario compared to the baseline scenario

Hepatitis B: key assumptions

xx: included in model uncertainty range
xx: not included

	CDA	Imperial	Goldstein
Models	CDA	Imperial	Goldstein
Vaccination strategies	Routine 1 dose, in facility births (no use of Uniject)	Routine, in facility birth usual vaccine + Out of facility Uniject	Routine, in facility birth usual vaccine + Out of facility Uniject
Uncertainty analysis driving ranges	Variation in parameters • Efficacy (high, medium, low)[2] • Transmission risks (high, medium, low)		
Other key assumptions	Duration of protection: Between administration and 1st dose of Penta	Coverage: Percent of births in a health facility discounted by 7.69%[1]	

1. Average difference between HepB BD coverage and % facility births for Gavi countries with HepB BD already introduced
2. Not included because those uncertainties analysis were modeled with variation of pentavalent vaccine efficacy as well and thus not exploitable

Hepatitis B: key models attributes & differences

	Model characteristics	*Model-specific uncertainties and direction of bias*
Goldstein	• **Burden data:** calculated through risk equations by age, for individual stages of disease • **Model structure:** static, age stratified model • **Modelled impact:** Direct effects only, no herd immunity	• Mortality rates for cirrhosis and liver cancer are adjusted from developed countries' death registries • Probability of vaccination is the same for infants born to HBsAg+ and HBsAg- mothers which may differ were screening exists
Centre for Disease Analysis	• **Burden data:** captured through progression of several disease stages by time, sex and age • **Model structure:** Compartmental deterministic dynamic Markov disease model stratified by disease stage, sex and age • **Modelled impact:** Direct effects and herd immunity.	• Background mortality used in model is not adjusted for co-morbidities present in HBV-infected population
Imperial	• **Burden data:** Burden data captured through progression of several disease stages by time, sex and age • **Model structure:** Compartmental deterministic dynamic transmission model stratified by disease stage, sex and age • **Modelled impact:** Direct effects only, no herd immunity • **Sensitives:** performed on efficacy of birth dose vaccine against chronic infection if mother HBeAg negative or positive, rate of vertical transmission of chronic infection	• Gaps in data on HBsAg/ HBeAg prevalence in certain countries • Limited information on relative contribution of child-to-child transmission routes • Model does not incorporate any immunity benefits children receive from birth dose who do not also receive the infant vaccination (likely to be marginal)

Hepatitis B: parameter sensitivity and key drivers of differences across models

Imperial, CDA, and Goldstein models

Parameters sensitivity

Parameter sensitivity:

- The Goldstein and Imperial models are sensitive to variations in transmission. With scenarios where transmission rates are assumed to be high, averting the largest number of deaths (because the vaccine becomes relatively more "effective" if transmission rate is assumed to be higher).
- The already high vaccine efficacy of Hep B birth-dose (95%) means that varying the efficacy parameter does not result in significant variations in deaths averted; the scenarios varying the efficacy parameter were removed from analysis due to differential modeler interpretation

Results comparison across models

Comparison of baseline scenarios:

- Lowest impact (deaths averted) in CDA model.
- Highest impact in Goldstein Model.
- Goldstein and Imperial Models have most comparable estimates (1.3 and 1.18 million deaths averted versus 0.26 for CDA)

Explicit factors likely to be driving variation in results

- The dynamic models (Imperial and CDA) both verified their prevalence of Hep B against the reported prevalence data for each country, by age. They also validated the number of pregnant women at time points. Adding a greater level of reliability than the results produced by the static model (Goldstein)
- Differences between estimates is most likely to be driven by assumptions around the burden data for Hep B

Malaria: key assumptions

xx: included in model uncertainty range

Models	Swiss TPH	Imperial
Vaccination strategies	Surviving infants, 4 doses[1]	
Uncertainty analysis driving ranges	None, one scenario only	
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: 100-90-80-60[2] % of MCV1 (by order of the dose)

Modelling from Gavi's 2016 decision to inform RTS,S pilot investment

1. All modelling have been done assuming a fully vaccinated child receives 3 doses 2. 20% drop in coverage between dose 3 and 4

Maternal influenza: key assumptions

xx: included in model uncertainty range
xx: not included

Models

IPM direct (direct impact only)

Vaccination strategies

Single dose to pregnant women (24-36 weeks) year round

Uncertainty analysis driving ranges

Source of burden data:
- WHO (low estimate)
- WHO (high estimate)
- IHME GBD 2013
- IHME GBD 2010, extrapolated based on GBD 2013 trajectory

Duration of protection Infants:
- 2 months
- 4 months
- 6 months

Infants efficacy
- 55%
- 46%
- 34%

Other key assumptions

Coverage:
ANC coverage during the vaccination window (24-36 weeks) discounted by number of services received by ANC visitors from DHS

Duration of protection:
Mother: 6 months

Mother efficacy: 48%

Maternal Influenza: key model attributes & differences

	Model characteristics	*Model-specific uncertainties and direction of bias*	*Parameter sensitivity*
IPM	• **Burden data:** GBD (2010 & 2013), WHO systematic review (Fell et al., 2017) • **Model structure:** direct impact only • **Modelled impact:** static cohort model • **Sensitivities:** performed on burden utilizing multiple estimates; infant <6 month efficacy (34-55%) and infant duration of protection (2-6 months)	• Differences in burden data used drive high uncertainty in model outcomes • High uncertainty for estimated case fatality rate in Gavi-support countries • Indirect protection not included in estimate, may reduce impact of vaccination to wider population • Seasonality, outbreak dynamics, and viral match between vaccine and circulating virus not considered	• As expected, the model is very sensitive to burden data estimates

Meningitis: key assumptions

xx: included in model uncertainty range
xx: not included

Models	Cambridge	IPM (direct impact only)		
Vaccination strategies	Routine 1 dose at 15-18mo Campaign 5-14yo	Routine 2 doses at 9mo and 15-18mo Campaign 5-14 yo	Routine 1 dose at 15-18mo Campaign 1-29yo	Routine 2 doses at 9mo and 15-18mo Campaign 1-29yo
Uncertainty analysis driving ranges	None			
Other key assumptions	Efficacy: 90%	Duration of protection: 10 years	Coverage: MCV1 and MCV2	

Meningitis: key model attributes & differences

	Model characteristics	*Model-specific uncertainties and direction of bias*
IPM	**Burden data:** • Countries grouped to high, medium, low incidence categorisation based on previous work by Trotter et al. • Age-specific cases per country were back-calculated from age-specific incidence and 1988 census report for Niger. Number of cases were distributed evenly amongst years in an age group category. • Age-specific CFR estimated from Campagne et al. • **Model structure:** Models susceptible, exposed, symptomatic, recovered, asymptomatic and vaccinated compartments • **Modelled impact:** direct effects only	• Model does not account for partial immunity due to incomplete immunization of multiple doses. • Future burden is based on an assumption of constant incidence and case fatality to UN population projections.
Cambridge	**Burden data:** • Countries grouped to high, medium, low incidence categorisation based on previous work by Trotter et al. • CFR of 10% • **Model structure & impact:** SIRS dynamic transmission model that captures seasonality through variation in force of infection per year, age-specific carriage, and periodic irregular epidemics; herd immunity captured	• Cycles of NmA independent of other serogroups, i.e. no potential for serogroup replacement • CWYX grouped together although may have different transmission cycles and disease potential & uncertainty in the future burden of disease due to non-A serogroups • Disease due to serogroups other than NmA is more uncertain; dealt with by changing FOI parameter

Meningitis: parameter sensitivity and key drivers of differences across models

Cambridge and IPM models

Parameters sensitivity

Parameter sensitivity:

- Model is moderately sensitive to increases in additional doses of the multivalent vaccine (2 doses versus 1), with an additional 5% of deaths averted for routine doses and campaigns in 5–14 year olds, and an additional 2% for routine doses and campaigns in ages 1–29 year olds.
- When the age range for the campaign is extended to reach 1–29 year olds, an additional ~20% of deaths may be averted
- For scenarios in which the multivalent vaccine is offered as routine (1 dose) and campaign (5–14 or 1–29 year olds) versus a scenario in which only MenA is provided as a routine (1 dose at 9 or 18 months), 27–34 times as many deaths, respectively, are estimated to be averted

Results comparison across models

- IPM model has significantly fewer number of cases and deaths averted than Cambridge model, which may partly be explained by the exclusion of indirect effects.

Explicit factors likely to be driving variation in results

- Waning immunity accounted for in Cambridge model but not IPM, leading to likely over-estimate of impact
- Cambridge model captures both direct and indirect (meningococcal carriage), increases reliability of estimates

Rabies: key assumptions

xx: included in model uncertainty range
xx: not included

Models	Cambridge	IPM[1]		
Vaccination strategies	Vaccination as part of Post-exposure prophylaxis in treatment seeking patients (PEP), 2 sites, ID regimen on days 0, 3, 7 (total 6 doses of 0.1ml each)	Addition of RIG for severe cases	Alternative baseline burden (with Dog vaccination, or Dog vaccination + IBCM)	
Uncertainty analysis driving ranges	Maximum share of rabid bite victims seeking treatment (85%, 90%, 95%)	Maximum share of victims receiving treatment (88%, 93%, 98%)	Maximum share of victims completing treatment (50%, 80%, 90%)	• Incremental impact compared to current ongoing programs • Total impact, accounting for all current initiatives[2]
Other key assumptions	Efficacy: 100%			

1. Models used in evaluation only measure direct impact
2. This uncertainty was chosen to reflect the fact that current PEP delivered in countries are mainly OOP costs. Gavi could then envision to take over those programs; Note: IBCM – Integrated Bite Case Management

Rabies: key model attributes & differences

	Model characteristics	*Model-specific uncertainties and direction of bias*
IPM	**Burden data:** • Disease burden estimates are modelled as a function of bite incidence from rabid dogs, ~ 1 in 6 individuals bitten by rabid dogs develop rabies in absence of PEP • Case number per country/year is based on a distribution pattern • DALYs equivalent to YLLs, no short term disability as all cases are fatal • **Model structure & impact:** Static cohort model showing direct impact only	• Estimates of burden are model based.
Cambridge	**Burden data:** • Disease burden estimates are modelled as a function of bite incidence from rabid dogs, ~ 1 in 6 individuals bitten by rabid dogs develop rabies in absence of PEP • Case number per country/year is based on a distribution pattern • DALYs equivalent to YLLs, no short term disability as all cases are fatal • **Model structure & impact:** Dynamic transmission model (SEIV) that captures rabies dynamics in domestic dog populations and impact of dog vaccinations	• Estimates of burden are model based • Uncertainty in decision tree model structure • Transmission model for dogs parameterised only with data from Tanzania, country-specific estimates not generated due to availability of data and practical limitations • Rabies deaths in Cuba, Guyana, and Honduras likely over-estimates in scenario with no dog vaccine, because countries have implemented dog vaccination programmes

Rabies: parameter sensitivity and key drivers of differences across models

IPM and Cambridge Models

Parameters sensitivity

Parameter sensitivity:

- IPM model highly sensitive to assumptions around % of individuals who seek treatment (half as many deaths averted in the low treatment seeking group versus the high treatment seeking group). The Cambridge model is less sensitive to these variations (25% more deaths averted in high versus low scenarios)
- Dog vaccination strategies have a significant impact on averting additional cases and leading to elimination
- The addition of RIG has a negligible incremental impact in the Cambridge model

Results comparison across models

Comparison of baseline scenarios:

- Lowest impact (deaths averted) in IPM model
- Highest impact in Cambridge model
- Estimates from Cambridge model as high as double the number of deaths averted from IPM (in scenario of low % of patients receiving treatment)

Explicit factors likely to be driving variation in results

- Challenges in estimating burden data likely to drive variations in impact estimates.

RSV: key assumptions

xx: included in model uncertainty range
xx: not included

Models	Univ. Antwerp /LSHTM[1]	PATH[1]	IPM (direct impact only)[1]
Vaccination strategies	Single dose RSV vaccine for pregnant women (24-36 weeks)	Single infant birth dose mAb	Mixed (Pregnant women vaccine + Infants mAb)
Uncertainty analysis driving ranges	Efficacy • RSV vaccine (30%[2], 50%, 70%) • mAb (60%, 70%, 80%)	Duration of protection • RSV vaccine (3 mo., 4 mo., 5 mo.) • mAb (4 mo., 5 mo., 6 mo.)	Coverage ANC coverage[3] DTP3 coverage

1. All models used in evaluation only model direct impact
2. Not included because very unlikely that the vaccine would reach the market with an efficacy of 30%
3. ANC coverage during the vaccination window (24-36 weeks) discounted by number of services received by ANC visitors from DHS

RSV: key model attributes & differences (1/2)

	Model characteristics	*Model-specific uncertainties and direction of bias*
IPM	• **Burden data:** Burden data derived from Shi et al. with country-specific CFRs • **Model structure:** Static population-based cohort model • **Modelled impact:** Direct effects only	• Seasonality not accounted for. • Waning immunity not considered, but could have significant implications for impact estimates. • Herd-immunity not considered. • Associated deaths from flu, asthma, pneumonia not considered.
LSTHM/ Antwerp	**Burden data:** • Burden data derived from Shi et al. • **Model structure:** Compartments modelled are: susceptible, vaccinated, symptomatic/ not symptomatic, no healthcare/ death • **Modelled impact:** Static population based cohort model of direct effects • **Sensitivities:** Probabilistic and deterministic sensitivity analyses assesses changes to key parameters including duration of vaccine/ mAb protection, IHME estimates of disease burden and different discounting rates	• Exclusion of herd immunity may underestimate impact • Potential age shift in RSV not captured in model – which could lead to over-estimate of benefits of vaccine/mAbs • Burden of disease data not country-specific • Strategy only captures benefits to infants and not to the mother • Seasonality not accounted for • Long-term chronic illness not accounted for in DALY estimates

RSV: key model attributes & differences (2/2)

	Model characteristics	*Model-specific uncertainties and direction of bias*
PATH	**Burden data** • Burden data derived from Shi et al., aggregate estimates applied because of gaps in data • RSV deaths in line with GBD study • **Model structure:** Compartments modelled are: susceptible, vaccinated/ unvaccinated, RSV associated ALRI/No RSV ALRI, disease/hospitalisation/death • **Modelled impact:** Direct effects only • **Sensitivities:** Deterministic sensitivity analyses by changing key parameters including duration of vaccine/mAb protection; disability weights and disease burden	• Disease burden has unknown community burden • No other effective treatment considered • Seasonality not accounted for

RSV: parameter sensitivity and key drivers of differences across models

UA, PATH, and IPM models

Parameters sensitivity

Parameter sensitivity:

- All models estimate approximately twice as many deaths averted when efficacy is varied from low (30%) to high (70%). This is likely due to the nature of the static model (i.e., change in one parameter and not accounting for a dynamic transmission patterns)
- The impact results are slightly less sensitive to variations in duration of vaccine effectiveness (approximately 30-40% more deaths averted when comparing low with high duration)

Results comparison across models

Comparison of baseline scenarios:

- Lowest impact (deaths averted) in PATH model
- Highest impact in IPM model
- Estimates from IPM model almost double the number of deaths averted seen in LSHTM and PATH models (in base scenario and pessimistic (low efficacy and short duration scenario). For optimistic scenario (high efficacy and high duration), IPM results 2–3 times higher than LSHTM and PATH models

Explicit factors likely to be driving variation in results

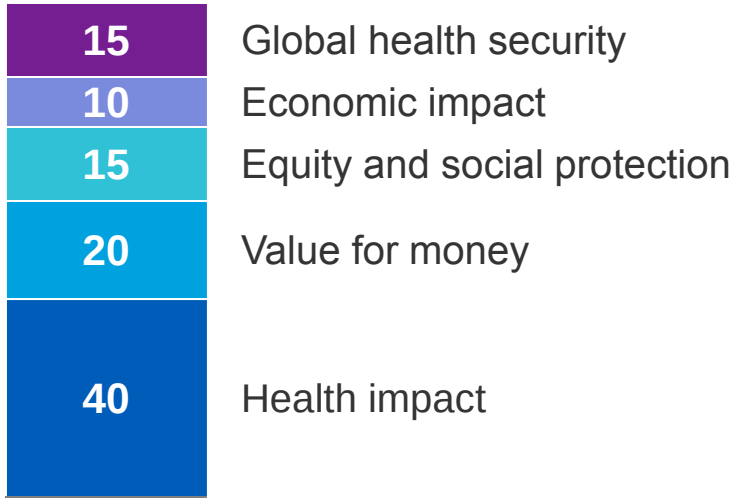
- High levels of uncertainty around burden, particularly levels of burden within the community
- LSHTM model validated estimates with UK data, and cross validated results with PATH modellers, adding an additional level of reliability to these model results
- All models used UN estimates for demographic data although estimates for infant populations calculated slightly differently, which may lead to variations in model outputs

3

Prioritization methodology

Board predominantly favors health impact and value for money as the key indicators

Average weighting used for shortlisting



Median and ranges applied as sensitivity analysis

Criteria	Average	Median	Min - Max
Health impact	**40**	45	[20 - 65]
Value for money	**20**	20	[10 - 40]
Equity and social protection	**15**	15	[5 - 30]
Economic impact	**10**	10	[0 - 25]
Global health security	**15**	10	[0 - 45]

Note: Average and median of scores assigned by Board members, scaled to 100
Source: Consultations with Gavi Board members representing 17 constituencies/seats in February 2018

Ranking criteria colours determine scoring of vaccines

VIS criteria	Indicators	Evaluation	Points
Health impact	Impact on total deaths averted		0.5
	Impact on deaths averted, per 100K vaccinated population		1
Value for money	Vaccine procurement cost per deaths averted		0
Equity and social protection impact	Disproportionate impact on vulnerable groups		1
	Benefits for women and girls		0
Global health security impact	Epidemic potential		1
	Impact of AMR		0.5
Economic impact	Direct medical cost averted		1
	Indirect cost impact		0
Total		Total	49%
Secondary criteria			

1. Assign points to each vaccine based on its color on each of the ranking criteria on scale of 0 to 1
   - Red = 0
   - Yellow = 0-0.5[1]
   - Green = 1

2. Weight the score for each criterion based on weighting[2] from Board consultations and add up point tally of each vaccine

3. Secondary criteria can be used to adjust the ranking of a vaccine

1. Score of 0.5 for criteria that are evaluated as red, yellow or green; Score of 0 for criteria that are evaluated as yellow or green 2. Scores within a criterion are averaged except for Health Impact, were 40% are distributed as 30% for total deaths averted and 10% on deaths averted, per 100K population