06a - Annex C: Oral Cholera Investment Case

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

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Agenda

1. Executive summary
2. Key benefits / challenges and strategic rationale
3. Policy approach
4. Demand, health impact, cost and value for money
5. Impact and value for money compared to VIS candidates
6. Country perspective
7. Implementation requirements
8. Risks and mitigation
9. Investment recommendation
10. Experts and sources

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Executive summary

Oral Cholera Executive Summary (1/2)

Cholera causes ~2.9M cases per year which result in ~95,000 deaths per year, mostly among poor and vulnerable populations in Sub-Saharan Africa, South Asia, and parts of the Americas

- Significant under-reporting of disease burden due to socio-political and economic disincentives
- Cholera has high epidemic potential with associated risks of large-scale societal disruption and political / economic consequences
- Vaccination can have broader impact (beyond health) given its ability to prevent spread of disease and control outbreaks

VIS 2013 decision to support the global cholera stockpile and strengthen evidence base for preventive campaigns has led to strong stakeholder and country momentum as well as:

- Significant increase in use of oral cholera vaccine (OCV) stockpile for outbreak response and preventive vaccination (from 4-5M doses to over 20M doses 2014-2019)
- Improved supplier landscape with new manufacturer (2015), reduced vaccine price, and innovative presentation (2017)
- Insights on questions identified in VIS 2013 regarding duration of protection (at least 3 years) and feasibility of campaigns
- Improved understanding of disease burden and OCV impact in endemic countries

WHO-recommended periodic immunisation would move away from ad hoc emergency requests towards comprehensive planning of OCV campaigns within broader disease control strategies

- Modelled vaccination strategy would be planned, periodic immunisation among high-risk populations in sub-national hotspots to serve as near-medium term response to cholera as a complement to longer-term investments in health interventions such as water, sanitation and hygiene (WASH)
- Supporting preventive campaigns would unlock stronger market-shaping potential by improving the predictability of demand
- Decreasing outbreak occurrence would reduce stockpile use in emergency settings

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Oral Cholera Executive Summary (2/2)

As currently modelled, cholera vaccination strategy could avert ~61,000 – 608,000 deaths and ~3-25M cases between 2021-2035 (~$2-21K per death averted)

- Medium procurement cost per deaths averted relative to other VIS vaccines

OCV use sits within a multisectoral disease control strategy that includes WASH, enhanced surveillance, social mobilisation and case management

- Planned, periodic vaccination would serve as a time-limited near-term response to cholera as a complement to longer-term investments in health interventions such as WASH, which has broader health benefits beyond reduced incidence of cholera
- Could catalyse comprehensive approach to cholera control by use of OCV campaign planning as opportunity to take a broader approach to identifying and implementing additional, sustainable interventions
- Establishment of the Global Task Force for Cholera Control and the development of the Ending Cholera Roadmap provides context and incentive to apply holistic lens to cholera control

Improved vaccines, and optimised schedule and campaign frequency could contribute to improved value for money

- Ongoing research and proposed learning agenda to identify opportunities to reduce number of doses and increase campaign intervals
- Improved cholera vaccines in the pipeline could provide greater protection through enhanced efficacy and longer duration of protection

RECOMMENDATION

Transition the oral cholera vaccine programme to include a preventive immunisation programme with vaccine co-financing, beginning in 2021

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Key benefits / challenges and strategic rationale

Strategic rationale for consideration of investment case

VIS 2013 decision and changes to vaccine context since

In 2013 Gavi Board approved $115M from 2014-18 for global OCV stockpile to improve demand-supply dynamics, reduce outbreaks and strengthen evidence base for pre-emptive campaigns

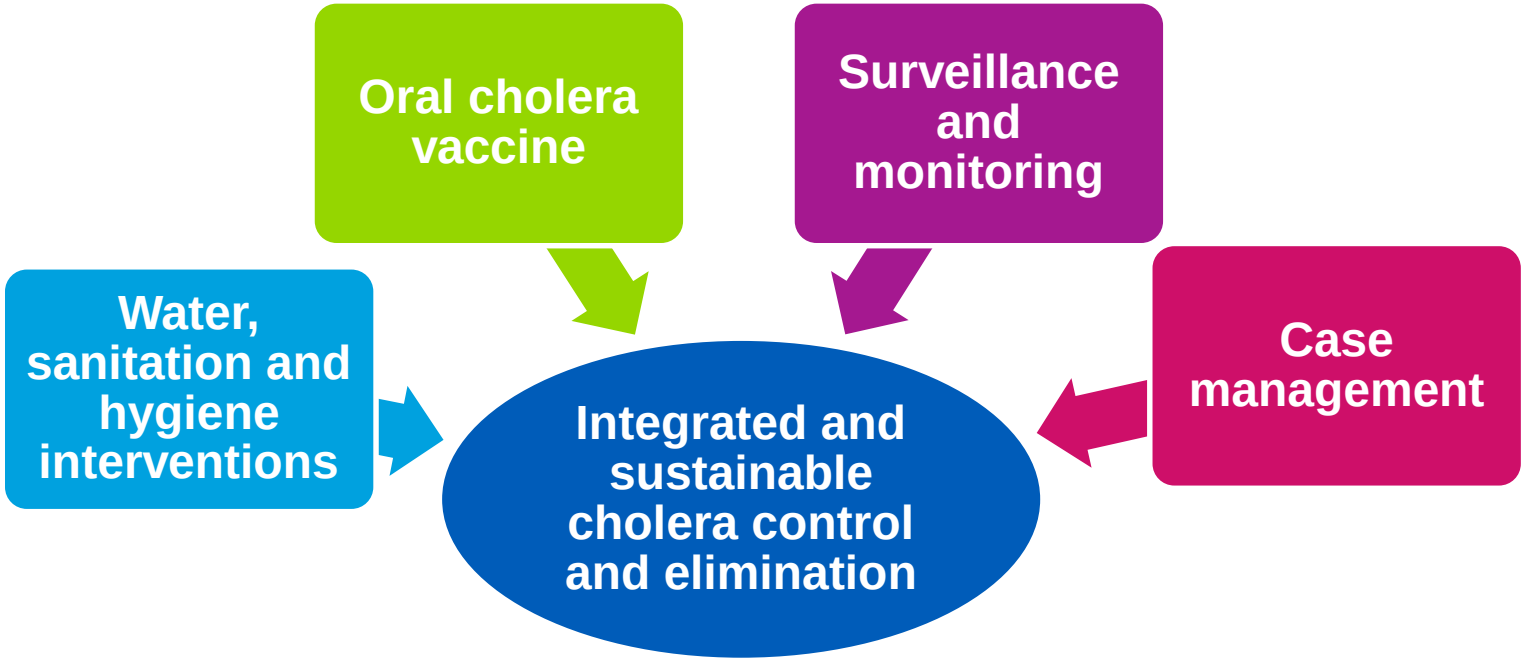
Many changes since 2013

- Increase in demand (from 4-5M doses to more than 20M doses) regardless of severe supply constraints
- New vaccine prequalified (PQ'd)
- Improved presentation from new manufacturer PQ'd
- Decrease in weighted average vaccine price of ~28%
- Improved understanding of burden, impact and effectiveness, and implementation feasibility in conflict and humanitarian settings and alternative delivery strategies to decrease operational costs were explored
- In 2017, updated SAGE recommendations to clarify vaccination strategy (slide 14)
- In 2016 Gavi Board approved use of existing funding for operational costs and extended support for all Gavi-funded emergency vaccine stockpiles including OCV (no longer time-limited Gavi support)
- In 2017 the Global Task Force on Cholera Control launched "Ending Cholera: A Roadmap to 2030" – with OCV playing a key role in cholera control
- In 2018 Gavi Board extended funding of use of OCV in endemic settings through the global stockpile through 2019 to ensure no programme discontinuation while awaiting VIS 2018 decision on long-term support for planned, periodic immunisation

OCV complements other health interventions for comprehensive and sustainable disease control

Cholera control is multisectoral:

- Long-term sustainability built on a foundation of WASH
- OCV use is complementary to other interventions including case management and surveillance and monitoring



A planning-oriented approach can improve demand predictability and maximise OCV impact

Current situation

Poor WASH results in periodic outbreaks, and lack of long-term planning leads to ad hoc requests for OCV from stockpile and fragmented demand

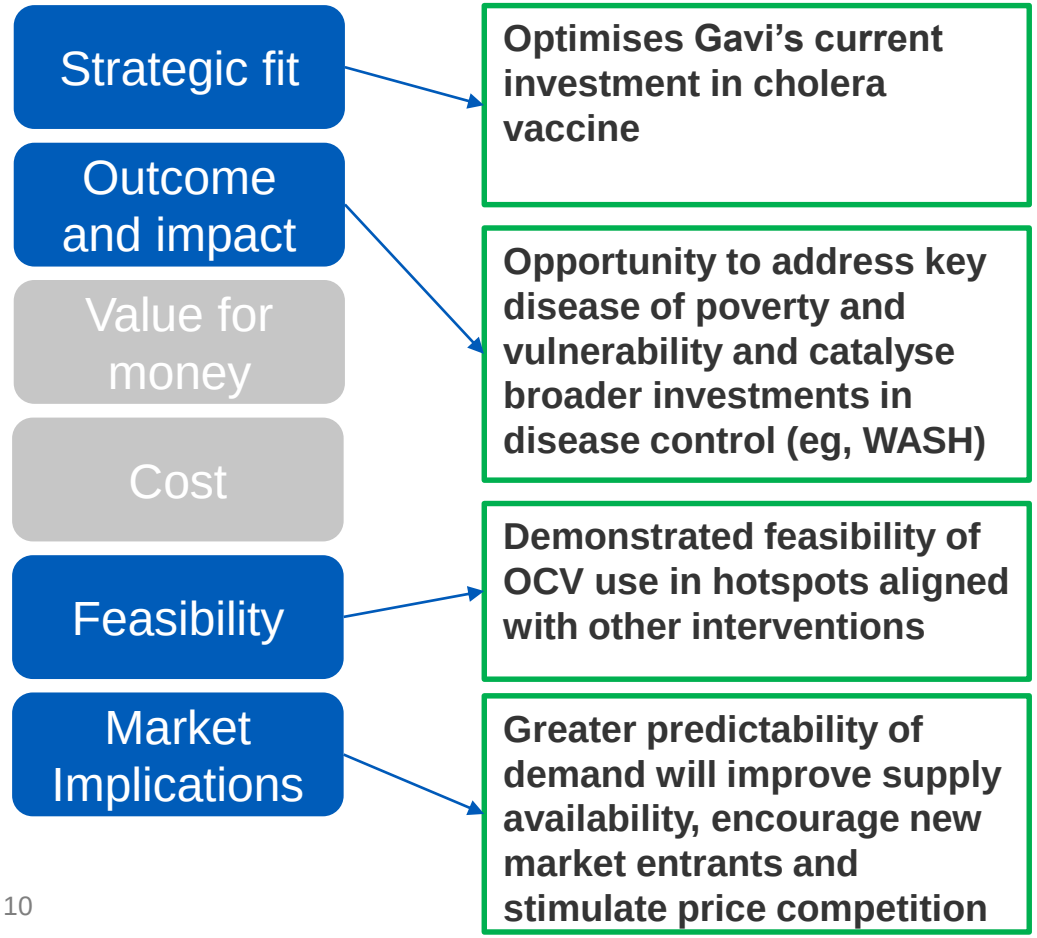
Gavi investment

Planned OCV use demonstrates reduction of cholera incidence and provides momentum for countries to consider multisectoral approaches for more sustainable cholera control (eg, development of comprehensive cholera control plan)

Aspiration

Periodic immunisation is planned and timed appropriately, providing visibility to future OCV demand to unlock supply, and are coordinated with scale-up of broader efforts to control cholera; long-term reliance on OCV campaigns reduced as WASH scales up

Key vaccine benefits



Comments

- Moves towards more predictable planning for future OCV campaigns vs outbreak response
- Supports enhanced learning agenda to improve feasibility and efficiency in cholera campaigns, and measure impact of OCV on global transmission
- Mitigates risk of large-scale socio-political and economic consequences from outbreaks
- Supports the global strategy for cholera control (*Ending Cholera – Global Roadmap to 2030*)

- Targeted campaigns in difficult-to-reach areas have been shown to be feasible
- Opportunity for collaboration to catalyse investments in non-vaccine interventions (eg, WASH) and support multisectoral disease control

- Short-term outbreak response gives manufacturers limited visibility to future demand
- Improved demand forecasting could also incentivise improved vaccines

Key vaccine challenges

Investment framework element	Key challenges	Comments
Strategic fit	**Integrated disease control approach means vaccine is necessary but not sufficient**	• OCV is complementary measure implemented in the short-medium term[1], long-term programmatic success is dependent on activities outside of Gavi's mandate (i.e., WASH)
Outcome and impact		
Value for money	**Potential high cost to Gavi of repeated vaccine campaigns and associated operational support compared to other candidates**	• Hotspot vaccination targets wide age groups for maximum protection, resulting in higher costs due to larger use of doses and high cost of implementing campaigns
Cost		
Feasibility	**Integrated disease control approach requires intersectoral interdependencies**	• Long-term cholera control requires scale-up of WASH, which is more difficult to implement than OCV campaigns • Political will and policy and regulatory enabling environment unclear for WASH and broader integrated cholera control
Market implication		

1. WHO Position Paper, 2017

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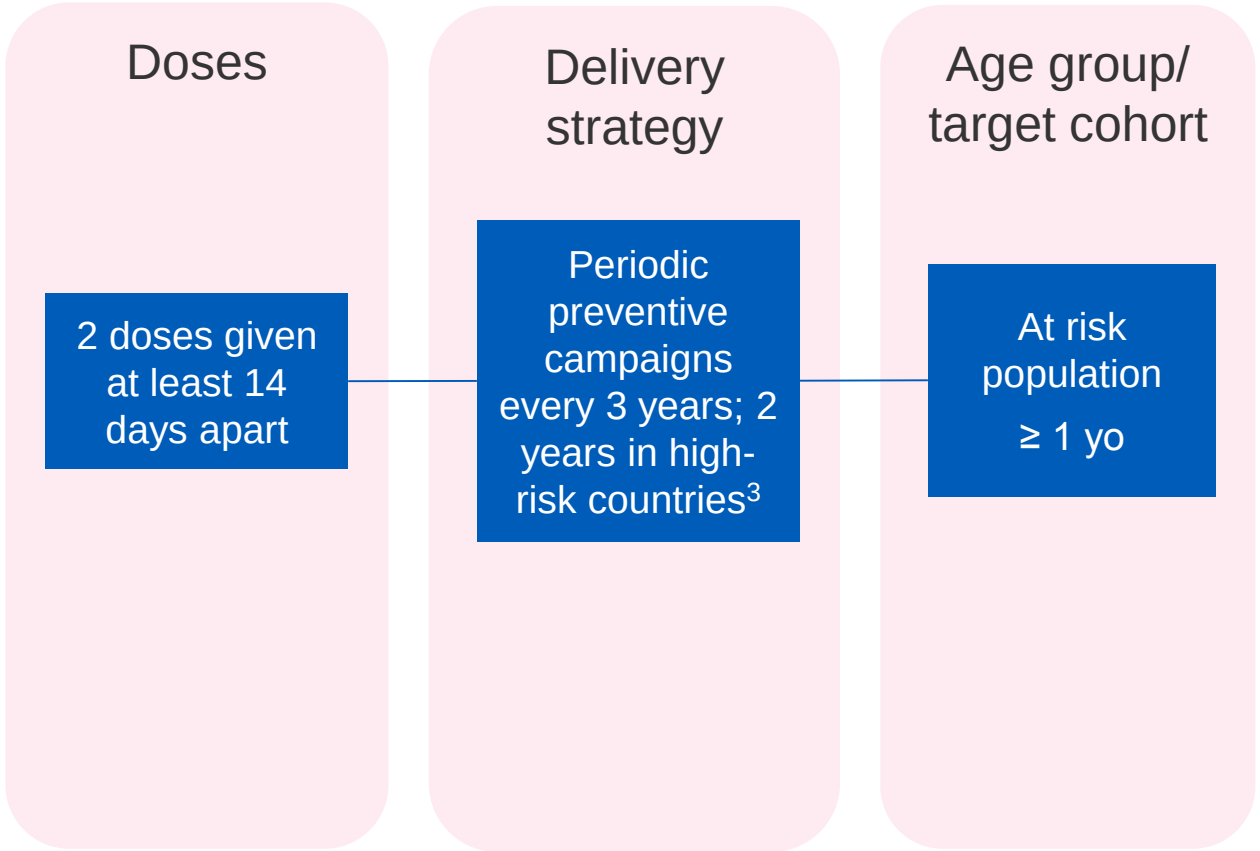
Policy approach

Cholera vaccination strategy for preventive campaigns[1, 2]



1. Vaccination strategy presented for preventive campaigns only; Gavi's investment in outbreak response via stockpile would remain unchanged.
2. WHO's position paper on OCV use (2017) recommends dose intervals of 14 days, and campaign intervals of 3 years, assuming adequate coverage, in populations at risk in cholera-endemic areas ('hotspots'). Some emerging evidence suggests campaigns could be spaced further, such as every 5 years. Expectation would be WASH scale-up in parallel with campaigns.
3. Such as, countries in protracted crisis

Multisectoral approach and country ownership to support efficient OCV use and reduced cholera incidence

Immediate impact of OCV use can shift perception that cholera can be controlled, but ultimately, sustainable approach requires reduced reliance on OCV in favour of sustainable interventions and domestically mobilised financing

Demonstrated commitment to multisectoral cholera control plan

- Includes approach to non-immunisation interventions, such as WASH, to reduce cholera incidence in the long term
- Developed with guidance of global entity (e.g., Global Task Force for Cholera Control [GTFCC])

Cost-sharing of planned campaigns

- Campaigns to be co-financed by Gavi and countries
- Reduced reliance on OCV campaigns to shift attention to more sustainable approaches of cholera control (e.g., WASH)

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Demand, health impact, cost and value for money

Cholera key assumptions

xx: included in model uncertainty range
xx: not included

Models	IPM direct	Johns Hopkins University
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[3]
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; 3. Not modelled but currently being investigated by researchers
2. 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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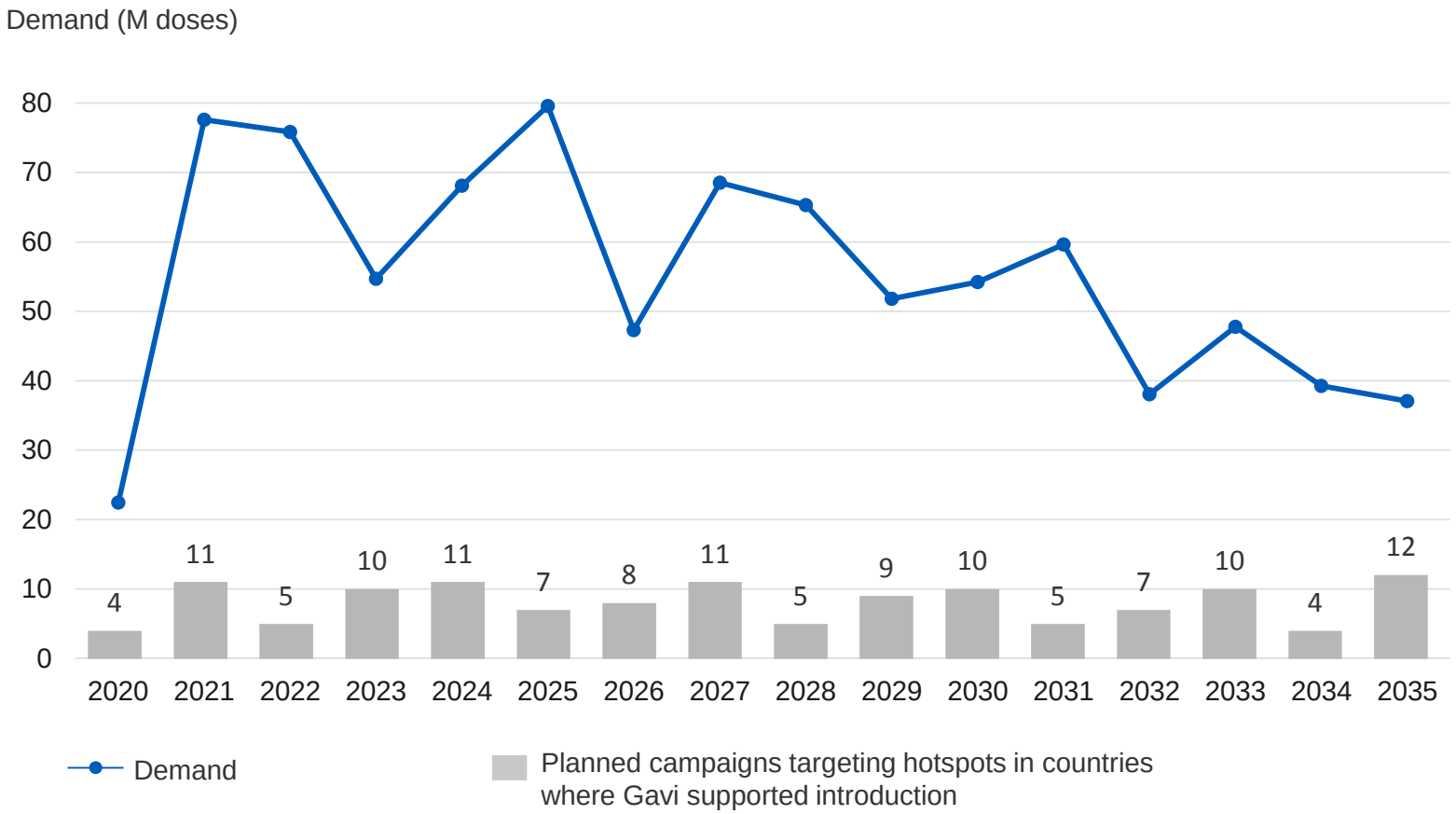
Demand in countries that introduce with Gavi support ~887M through 2035[1]



Nigeria excluded

Scenario: 2 doses for >1 yo. every 3 years with WASH scale-up[2]

Total cumulative demand from countries that introduce with Gavi support (2020-2035)

~887M

Demand represents campaigns in 40 Gavi-eligible countries

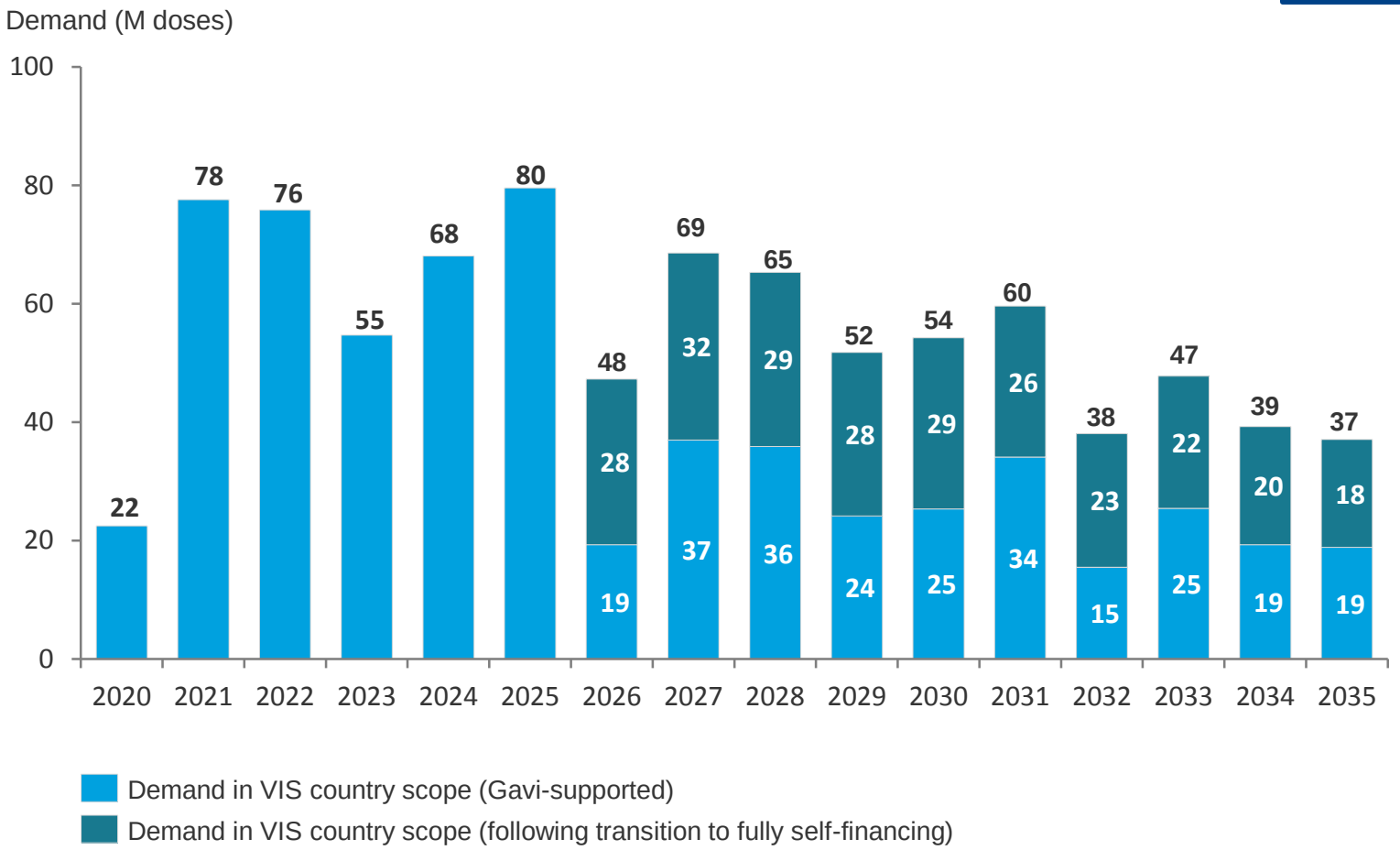
1. Based on Gavi's current eligibility and transition policy
2. Gavi VIS forecast; Demand estimated assuming primary demand forecast of 2 doses to at risk population >1 yo, with base hypotheses of burden, effectiveness (76%) and duration of protection (3 years). Assumes a scale-up of WaSH interventions complementing OCV as described in the Ending Cholera Roadmap. 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 ~633M doses between 2020-2035[1]

Nigeria excluded

Countries supported by Gavi for introduction

Scenario: 2 doses for >1 yo. every 3 years with WASH scale-up[2]



Total cumulative demand from countries that introduce with Gavi support (2020-2035)

Gavi-supported demand[2] ~633M

Post-transition demand ~254M

1. Based on Gavi's current eligibility and transition policy
2. Demand estimated assuming primary demand forecast of 2 doses to at risk population >1 yo, with base hypotheses of burden, effectiveness (76%) and duration of protection (3 years). Assumes a scale-up of WaSH interventions complementing OCV as described in the Ending Cholera Roadmap.
3. This demand is used to calculate 'procurement cost to Gavi and countries', which itself is used in the calculation of 'value for money'
4. Source: Gavi SDS
5. 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

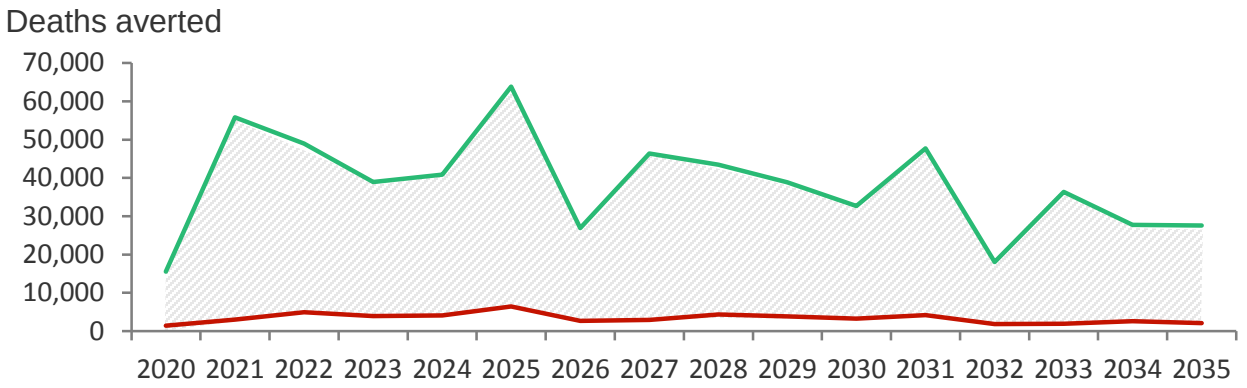
Vaccination could avert between ~61K-608K future deaths and ~2M-25M future cases through 2035

Nigeria excluded

Range of projected impact: Maximum / Minimum

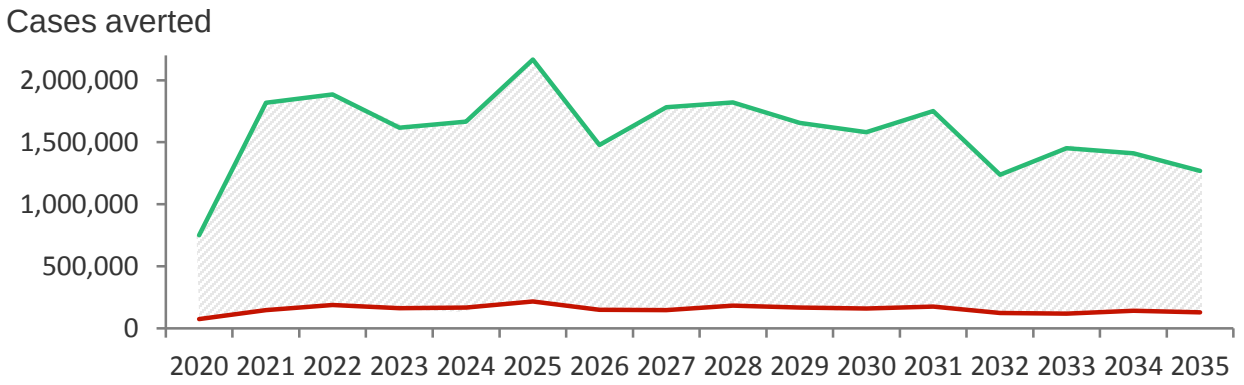
Scenario: 2 doses for >1 yo. every 3 years with WASH scale-up; variable effectiveness and disease burden[1]

Deaths



	Total deaths averted (2020-2035)	Deaths averted per 100K vaccinated
Max	~608K	~182
Min	~61K	~16

Cases



	Total cases averted (2020-2035)	Cases averted per 100K vaccinated
Max	~25M	~7 593
Min	~3M	~709

1. IPM (direct impact only) and JHU models; data includes projected impact for 2 doses to at risk population >1 yo, with variable vaccine effectiveness (62%, 76%, 85%), duration of protection of 3 years and variable burden of disease (low/base/high). Assumes a scale-up of WaSH interventions complementing OCV as described in the Ending Cholera Roadmap.
Range in impact outcomes driven mainly by uncertainty in burden data.
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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Summary of health impact, cost, and value for money (2020-2035)

Nigeria excluded

Cost projections are unconstrained. Values do not account for anticipated introduction of current portfolio and other VIS candidate vaccines that may reduce the number of planned OCV campaigns.

Scenario: 2 doses for >1 yo. every 3 years with WASH scale-up; variable effectiveness and disease burden[1]

		Primary modelled scenario
Impact	Fully vaccinated persons	~334M
	Total future deaths averted	~61 – 608K
Cost	Gavi procurement costs	$657M
	Gavi operational costs	$192M
	Total Gavi cost	$849M
	Country procurement costs	$596M
	Country operational costs	$145M
	Country recurrent delivery costs	$0
	Total Country cost	$741M
	Total cost	*$1,590M*
Value for money	Cost per death averted[2]	~$2,059 – 20,594

1.IPM (direct impact only) and JHU models; data includes projected impact for 2 doses to at risk population >1 yo, with variable vaccine effectiveness (62%, 76%, 85%), duration of protection of 3 years and variable burden of disease (low/base/high). Assumes a scale-up of WaSH interventions complementing OCV as described in the Ending Cholera Roadmap.

2. Calculated using procurement cost only

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

Assessment of uncertainty in demand and impact analyses

	Comments
Demand	• High uncertainty around baseline disease burden • Timing of country introductions uncertain due to political stigma, lack of clarity around whether and when to use vaccine • Under reporting may drive an underestimation in demand
Price	• In addition to existing suppliers, forecast considers projected new entrants with uncertain pricing
Health impact	• Models used different method generation/datasets for estimating future burden, giving rise to variation in impact estimates • Lack of incidence data for India and Bangladesh • Mortality highly uncertain and variable between settings and years • JHU model considers herd immunity and waning efficacy of the vaccine: IPM model does not • Secular and infrastructure changes (eg, WASH) reduces size of campaigns

High uncertainty | Medium uncertainty | Low uncertainty

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Implications for demand, health impact and cost when including Nigeria

	% increase if Nigeria included
Demand	~6%
Deaths averted	~8%
Cases averted	~5%
Cost	6%

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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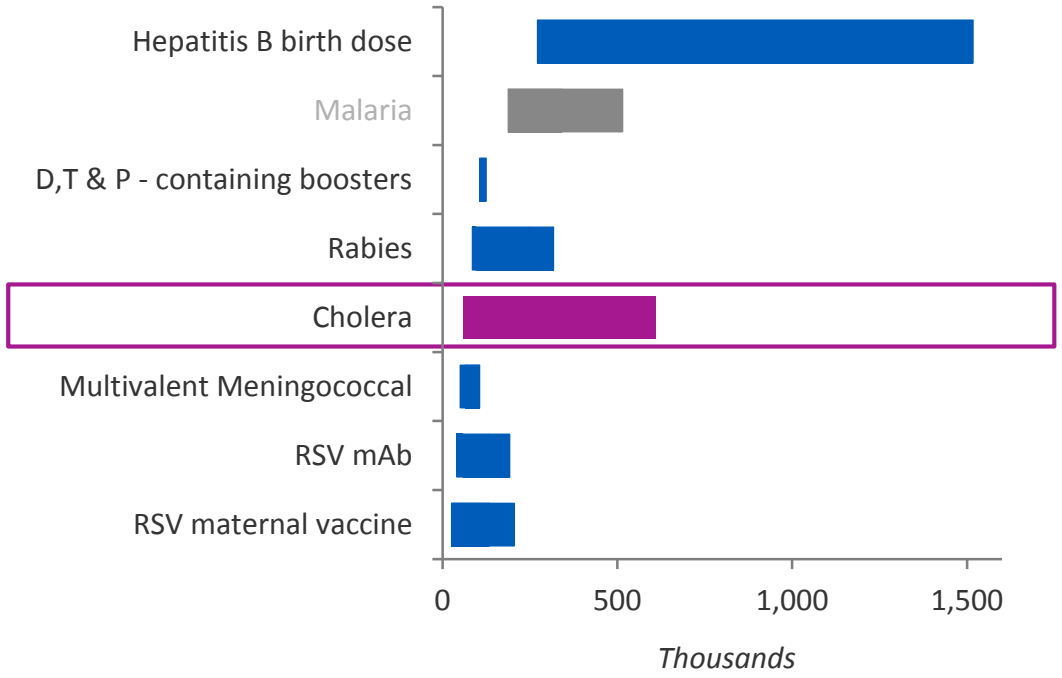
Impact and value for money compared to VIS candidates

Health impact compared across VIS candidates

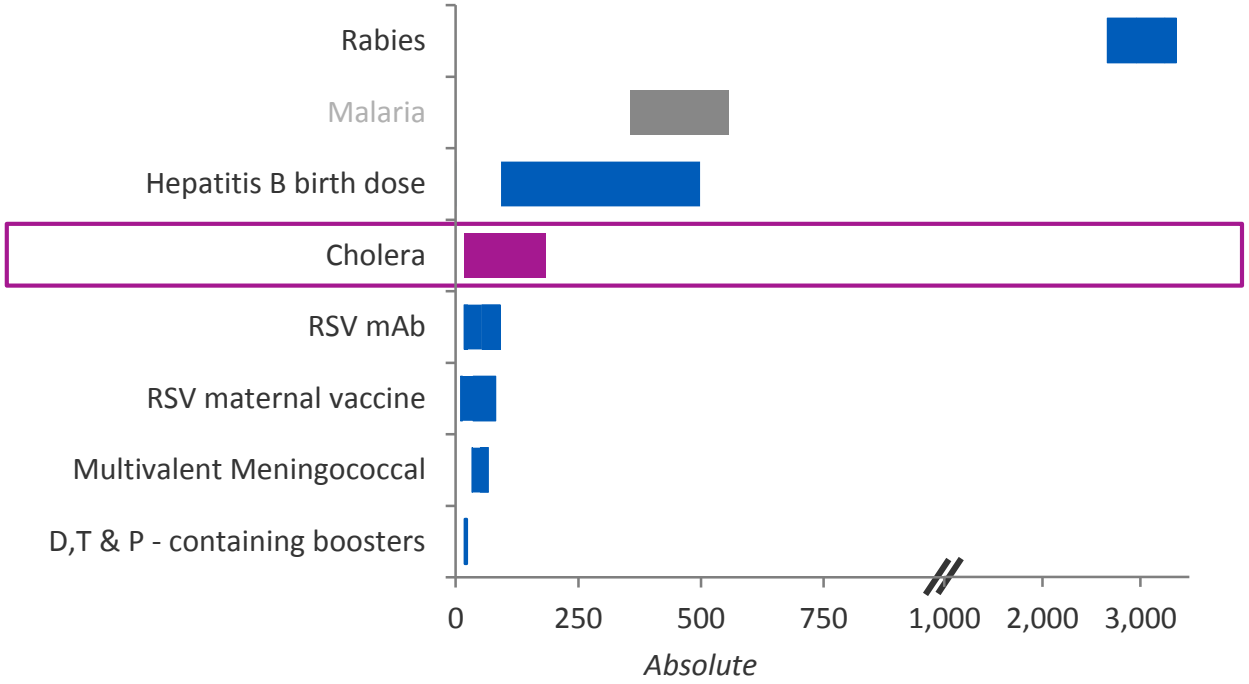
Nigeria excluded

Scenario: 2 doses for >1 yo. every 3 years with WASH scale-up; variable effectiveness and disease burden

Total future deaths averted (K), 2021-2035



Total future deaths averted per 100K vaccinated, 2021-2035



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Range in impact outcomes driven mainly by uncertainty in burden data.
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

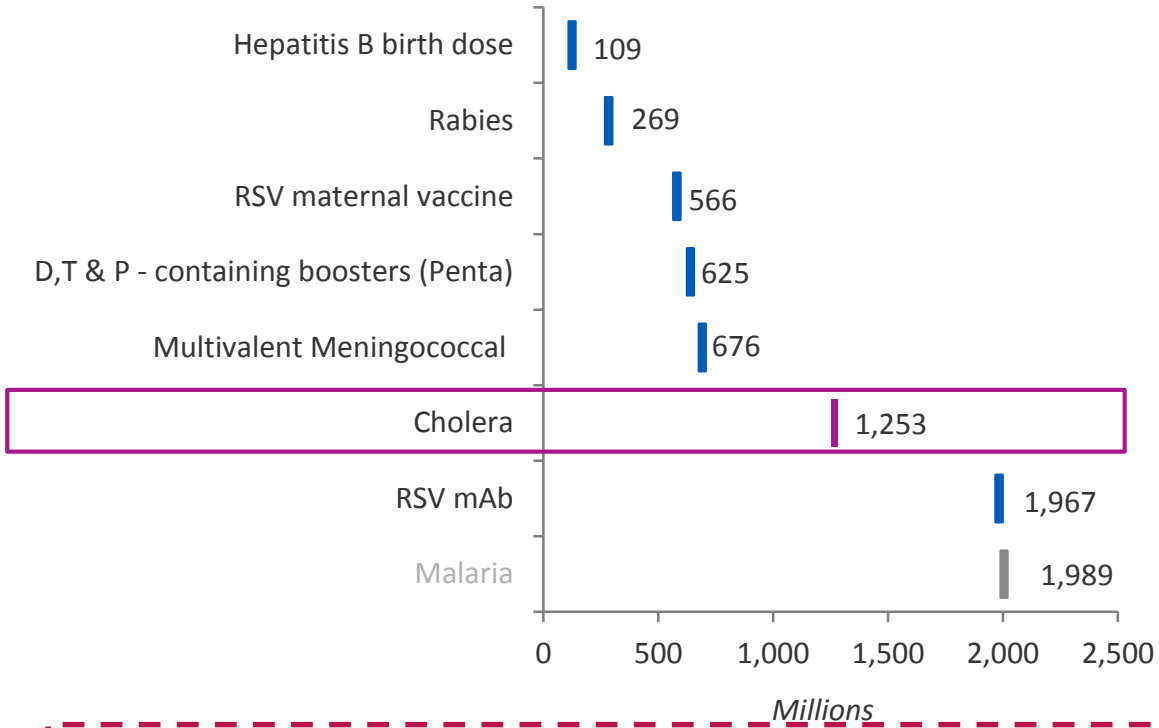

Range of projected impact

Procurement cost and cost per death averted compared across VIS candidates

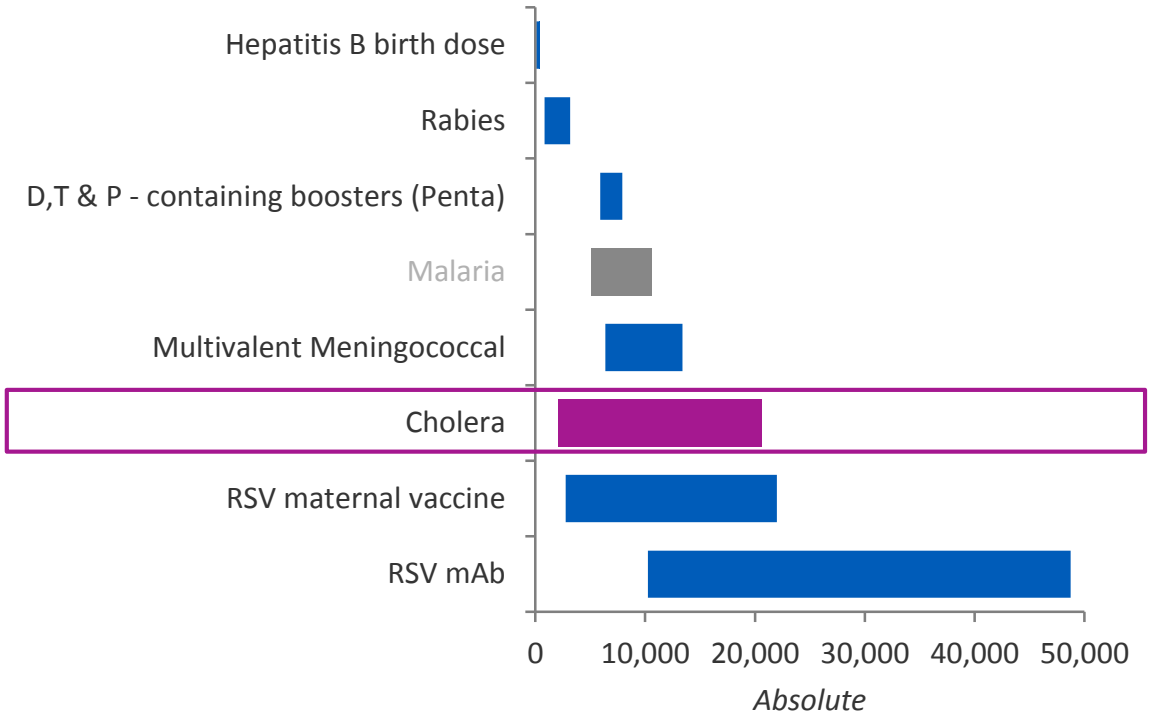
Nigeria excluded

Scenario: 2 doses for >1 yo. every 3 years with WASH scale-up; variable effectiveness and disease burden[1]

Total procurement cost to Gavi & countries (M$), 2021-2035



Procurement cost to Gavi & countries per death averted ($), 2021-2035



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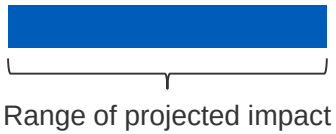

1. IPM (direct impact only) and JHU models; data includes projected impact for 2 doses to at risk population >1 yo, with variable vaccine effectiveness (62%, 76%, 85%), duration of protection of 3 years and variable burden of disease (low/base/high). Assumes a scale-up of WaSH interventions complementing OCV as described in the Ending Cholera Roadmap. Range in impact outcomes driven mainly by uncertainty in burden data.

Note: D,T&P –containing boosters represent Penta as first booster

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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Country perspective

Interviews with country stakeholders revealed that campaigns are of high importance in endemic areas

Priorities and approach

- High priority for most countries where it is a disease of importance, though a few countries with high burden have not yet begun discussions on control
- Some respondents felt they could leverage epidemic/pandemic preparedness mechanisms as cholera is mainly viewed as outbreak disease, though interested in preventive approach

Burden of disease and hotspot identification

- Most respondents felt that they have some way of identifying hotspots, but the approach is not standardised
- Surveillance for cholera is mixed; some countries have diarrheal disease surveillance

Integrated disease control and coordination

- Respondents identified varying levels of coordination within government, but everyone recognised its importance
  - E.g., EPI not involved in cholera control in some countries; some felt OCV could be delivered through EPI, while others noted EPI cold chain being used at national level
  - In one country, EPI sits on a working group; in another country, there is a weekly meeting and data shared
  - Strong sense that EPI should be included as has the expertise of training vaccinators and conducting campaigns
- One respondent cited coordination as the reason why a recent outbreak was controlled successfully
- Respondents felt that cholera control would be most sustainable if led by strong government leadership
- WASH is viewed as important but often a fragmented intervention that sits in a different sector and reliant on donor funding

Campaign challenges

- Respondents noted some difficulty in accessing cholera vaccine due to current supply mechanism (global stockpile) and limited supply
- WASH activities are not always implemented during campaigns; some respondents felt it would not be difficult to do so but key would be to identify appropriate interventions
- Cost, access and security also highlighted as key challenges; hotspots are often inaccessible or located in conflict areas

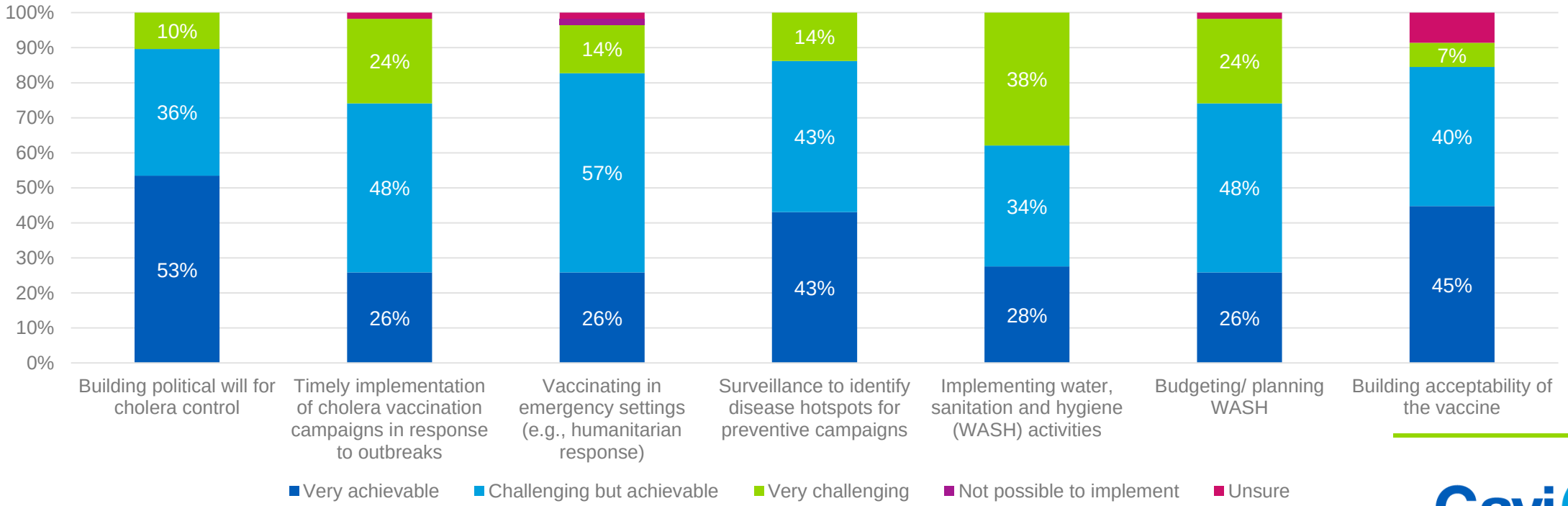
Source: VIS Phase III in-depth country interviews

Respondents view identifying hotspots and timely vaccination of at risk populations achievable though still with challenges

59/85 respondents indicated that their country experiences cholera outbreaks, representing 27 countries

How challenging do you find each of the following activities related to cholera control?

% of respondents indicating level of challenge for each cholera-related activity



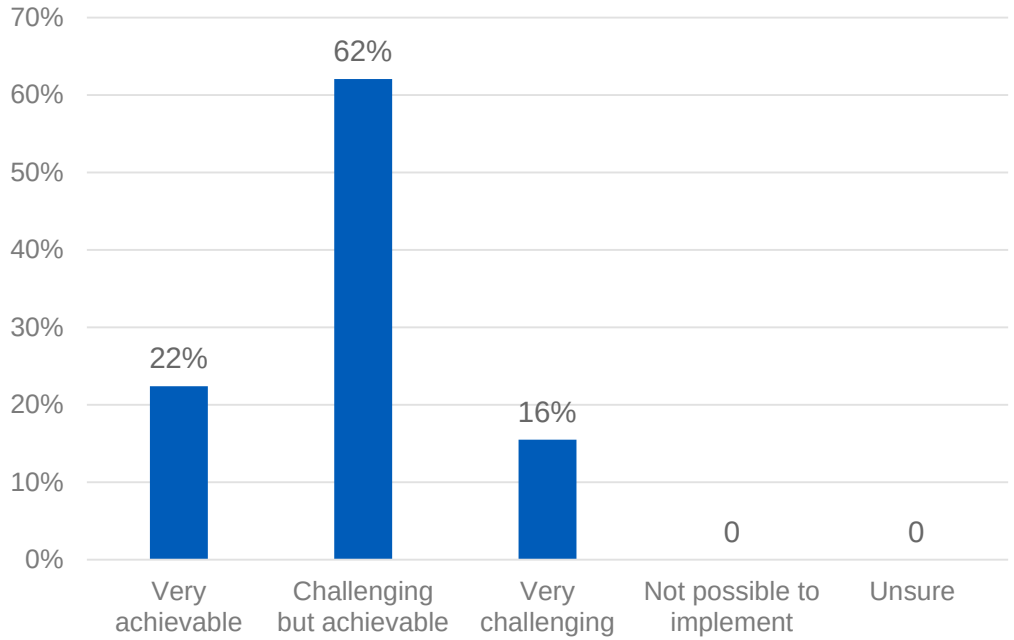
Source: VIS Phase III country survey

The majority of respondents would find WASH scale up challenging but achievable

59/85 respondents indicated that their country experiences cholera outbreaks, representing 27 countries

If Gavi support for oral cholera vaccine for preventive campaigns were contingent on having up to date, comprehensive national cholera control plans that include WASH activities, how challenging would you find this to be?

% of respondents indicating level of challenge for scaling up WASH



Challenges highlighted by respondents

- WASH is often solely donor-funded, and there is a lack of donor alignment regarding support, with need for greater investment
- Coordination with other government ministries is challenging
- Lack of political will
- Shortage of human resources
- Frequent displacement of population due to security issues
- Rapid urbanisation with high populations
- Illiteracy & difficulty in communicating to communities

Source: VIS Phase III country survey

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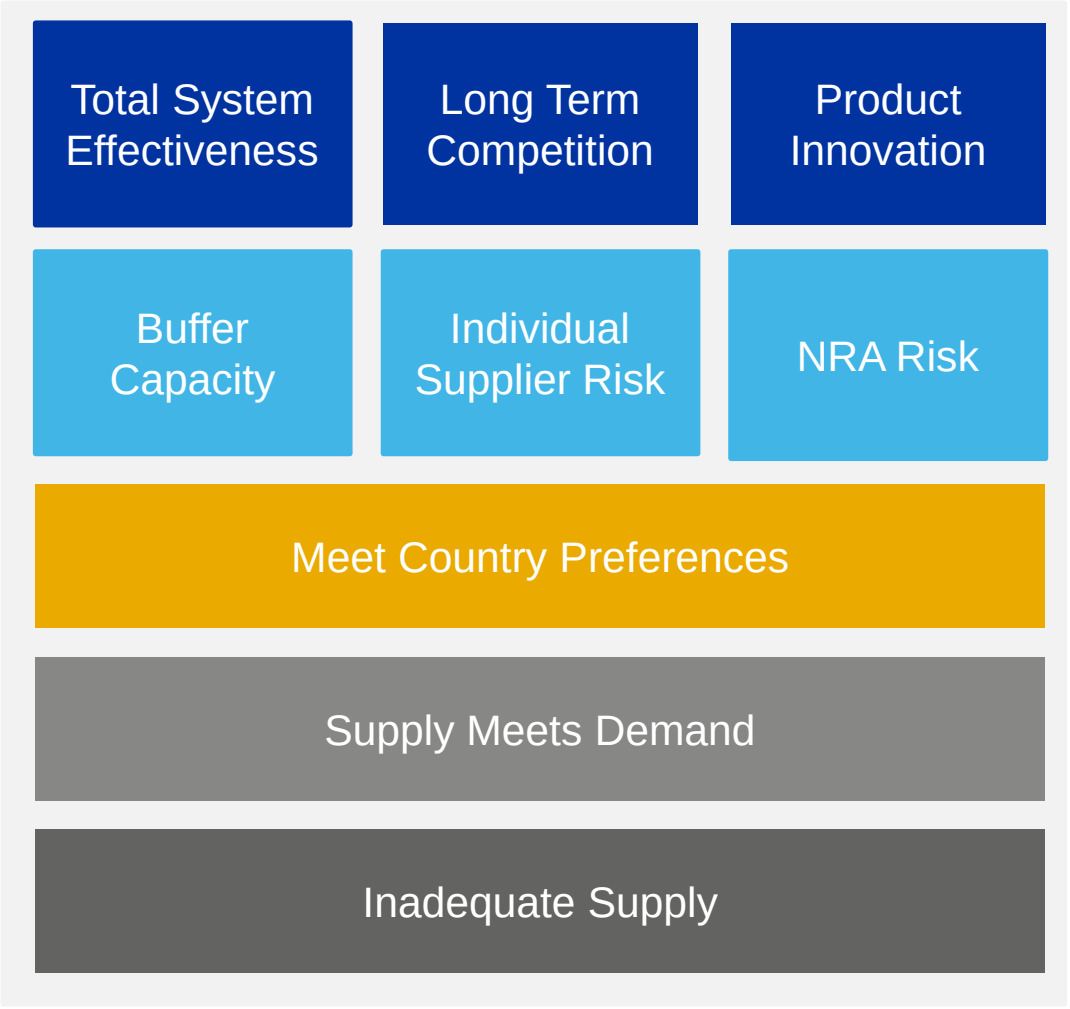
Implementation requirements

Unique implementation requirements

	Area of focus	Unique implementation requirements	Associated costs
Global level	Policies and processes	• Development of multisectoral national cholera control plans	• Additional foundational support or technical assistance
	Supply	• Market shaping interventions required to expand supply, improve supplier base, and obtain an appropriate price.	
Country level	Planning, coordination, integration	• Strong intersectoral coordination is required to plan and implement campaigns as part of broader disease control;	• National level coordination costs
	Supply chain infrastructure and logistics	• Can use EPI supply chain; CTC guidelines in place; migrating and remote populations more difficult to reach; could leverage multi-antigen campaigns	
	Health workforce	• Oral vaccine, easier to administer, oral polio vaccine vaccinators can be leveraged	
	Social mobilization, education, communication	• Broader opportunities to engage additional stakeholders given multi-sectoral nature of comprehensive disease control	• Additional costs to include non-vaccine components (eg, WASH) for awareness building
	Surveillance	• Greater requirement for identification and characterisation of hotspots and other prioritised areas for vaccination at sub-national level	• Additional surveillance measures

Most challenging Unique but manageable Few unique implementation requirements

Improved demand predictability should help increase supply; in long-term, improved vaccines are desirable



Current OCVs are convenient orally administered vaccines available at reasonably affordable prices. However, the two-dose schedule and the need to re-vaccinate after 3 years reduce systems effectiveness. Development of vaccines with long-term protection (>10 years) is a desired long-term improvement.

Current manufacturers have recently shown good reliability on supply forecasts and capacity increase but performance at significantly higher capacity is untested. Buffer capacity is expected to be available only from 2023.

It is expected that countries will start expressing a preference for the improved vaccine presentation (plastic tube) and that supply will not be able to meet demand

Supply has increased rapidly and is expected to meet the 2018 demand levels. However, this 2018 demand forecast is supply-constrained and supply will not meet the ideal unconstrained demand from 2019. India demand may not be satisfied within the next ten years.

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Risks and mitigation

Risks of inaction (Gavi investment not approved)

Strategic concern	Risk
Financial	• Continued reliance on stockpile for OCV in lieu of preventive use; Gavi will need to consider increased stockpile investment • Stockpile is under strain due to increased but unpredictable demand
Market	• Supply continues to be constrained and manufacturers unable to plan production to meet demand due to continued reactive approach
Programmatic	• Implementation barriers to OCV use persist, including identification of hotspots, leading to continued outbreaks and high risk of economic and social disruption • Missed opportunity to control cholera pre-emptively and leverage OCV use to catalyse engagement on longer-term cholera control interventions, such as WASH, which has broader impact beyond cholera
Reputational	• Gavi's endorsement of Ending Cholera: Global Roadmap weakened; adherence to principles of sustainability and country ownership diminished

Risk and mitigation plan if Gavi investment approved

Strategic concern	Risk	Mitigation plan
Financial	• Long-term plans do not result in progress on cholera control, requiring continued repetition of campaigns • Repeat campaigns and operational costs carry high cost to Gavi • Funding for other health interventions does not materialise • Co-financing requirement could delay planned campaigns in favour of outbreak response	• Global entity (eg, GTFCC) to engage with countries on broader control plans to ensure plans are well designed and resourced • Co-financing alleviates some costs and brings greater country ownership • Global cholera control community seeking to mobilise funding for non-immunisation investments at global level • Countries informed with adequate time for budgeting; clear communication that planned immunisation brings long-term reduction of cholera incidence reducing need for future campaigns
Market	• Supply constraints do not ease	• Targeted use of OCV in highest priority settings continues; ongoing engagement with manufacturers
Programmatic	• Hotspots are misidentified • Remote populations not reached	• Global engagement with countries to identify hotspots; ongoing improvements in surveillance

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Investment recommendation

Recommended investment scenario

No support for preventive programme (continue support for global cholera vaccine emergency stockpile only), and wait for improved vaccines

Transition the oral cholera vaccine programme to include a preventive immunisation programme with vaccine co-financing, beginning in 2021

Recommendation

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Illustrative oral cholera vaccine components of a VIS learning agenda

Objective	Key questions	Indicative cost
Disease burden	• Assessment of predictive value of hotspot identification	$500,000 for retrospective study
Optimal schedule and campaign frequency	• Assessment of duration of protection • Effect of population characteristics (migrating, urban, fragile) on optimal scheduling	$3-4 million for multi-site study

Note: Impact is measured through the Vaccine Impact Modelling Consortium and Secretariat accountability measures; surveillance funded separately as part of programme roll-out

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Experts and sources

Cholera: key experts

Experts consulted	
Abdinasir Abubakar - WHO EMRO	Justin Lesser – JHU
Andrew Azman - JHU	Myron M. “Mike” Levine – U of MD
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Linda Omar Haj – WHO AFRO	Helen Matzger – WHO HQ
Alan Hinman – independent	Lorenzo Pezzoli – WHO HQ
Shannon Larsen - BMGF	David Sack – JHU
Dominique Legros – WHO HQ	

Note: Materials represent the view of the Gavi Secretariat based on expert input. Individual experts might not agree with all presented information

Cholera: sources

Key Sources

- WHO Position Paper, 2017 (and SAGE background paper)
- Weekly Epidemiological Reports
- Vaccine packet inserts
- Ending Cholera by 2030 -- Global Roadmap
- Johns Hopkins University- Cholera Mapping
- Country Post-Campaign Reports
- Global Task Force for Cholera Control and its Working Groups

Key Articles

- Kanungo S. et al. Flexibility of oral cholera vaccine dosing
- Bi, Q et al, Protection against cholera from killed whole cell oral cholera vaccines: a systematic review and meta-analysis
- Ali M et al. Updated Global Burden of Cholera in Endemic Countries. PLoS Neglected Tropical Diseases 2015, 9(6)
- Ferreras, E. et al. Single-Dose Cholera Vaccine in Response to an Outbreak in Zambia. N Engl J Med. 2018 Feb 8
- Poncin, M. et al. Implementation research: reactive mass vaccination with single-dose oral cholera vaccine, Zambia. Bull World Health Organ. 2018
- Deployments from the oral cholera vaccine stockpile, 2013–2017. Wkly Epidemiol Rec. 2017 Aug 11;92(32):437-42
- Lessler, et al. Mapping the burden of cholera in sub-Saharan Africa and implications for control: an analytic synthesis of data across geographic scales, The Lancet, 2018
- Innovative vaccine delivery strategies in response to a cholera outbreak in the challenging context of Lake Chilwa. (unpublished)
- Sevilimedu V et al. Gender-based differences in water, sanitation and hygiene-related diarrheal disease and helminthic infections: a systematic review and meta-analysis.

Appendix

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

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Relevant cholera-related definitions

- **Cholera-endemic area:** an area where confirmed cholera cases resulting from local transmission have been detected in the last 3 years. An area may be any subnational administrative unit including state, district, or small localities. Any country that has one or more subnational administrative units that are defined as endemic is considered a cholera-endemic country.
- **Cholera hotspot:** a geographically limited area (e.g., city, administrative level 2, or health district catchment area) where environmental, cultural, and / or socioeconomic conditions facilitate the transmission of disease and where cholera persists or re-appears regularly. Hotspots play a central role in the spread of cholera to other areas
- **Cholera outbreak:** the occurrence of at least one confirmed case of cholera and evidence of local transmission. Outbreaks can also occur in areas with sustained (year-round) transmission, and are defined as an unexpected increase (in magnitude or timing) of suspected cases over 2 consecutive weeks of which some are laboratory confirmed.

Phase II scorecard: Oral cholera *(June 2018)*

Modelled strategy: campaigns with 2 doses to at risk population ≥ 1 year old

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	~$ 1,490-47,600 procurement cost per death, ~$ 40-480 procurement cost per case averted	
Equity & social protection impact	Impact on vulnerable groups	Burden concentrated among lower socioeconomic groups and displaced populations	
	Benefits for women and girls	Some evidence for increased burden in women >5 yo and differences in access to treatment	
Economic impact	Direct medical cost averted	~1% of average consumption per capita averted in out-of-pocket medical costs	
	Indirect cost averted	~$2-47 productivity loss averted, 2020-2035, per vaccinated person	
Global health security impact	Epidemic potential	IHR notifiable; antigenic changes previously caused epidemics; outbreaks in areas of low sanitation and poor access to clean water	
	Impact on AMR	High impact of vaccination on AMR (4.1/10 points in expert consultation)	
Vaccine cost	Total procurement cost	~$ 1.0-1.8 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	

Additional considerations

- Significant under-reporting of disease burden due to socio-political and economic disincentives, which may drive large incidence ranges and lower impact estimates
- Strong stakeholder momentum and improved understanding of implementation feasibility since 2013
- In 2016, the Gavi Board confirmed future Gavi support for vaccine procurement and operational costs for emergencies
- Reduced impact of future propensity for illness following exposure to diarrheal diseases

1. Evaluation based on comparison with other VIS 2018 candidates. For Health impact and Value for money, evaluation based on deaths averted. Details on evaluation methodology can be found in Methodology appendix

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Phase II secondary criteria and financial implications: Oral cholera *(June 2018)*

Modelled strategy: campaigns with 2 doses to at risk population ≥ 1 year old

VIS criteria	Indicator	Results	Evaluation[1]
Other impact	U5 deaths averted, total	~1-80K U5 deaths averted, 2020 – 2035	
	U5 deaths averted, per 100K	~0-22 U5 deaths averted, 2020 – 2035, per 100K vaccinated population	
	DALYs averted (cost per DALY)	~0.7-20 million DALYs averted, 2020 – 2035, ~$ 50-1370 cost per DALY	
	DALYs averted, per 100K	~190-5,420 DALYs averted, 2020 – 2035, per 100K vaccinated population	
Gavi comp. advantage	Vaccine market challenges	High potential to influence the market (e.g., stabilize supply by increasing supplier base, further decreases in price)	
	Catalytic investment	High potential to catalyse investments in complementary investments (e.g.,WASH, data/surveillance, GTFCC)	
Implementation feasibility	Ease of supply chain integration	Packed volume of 3-17cc; 24-30 months shelf life at 2-8°C; VVM = 14-30	
	Need for HCW behaviour change	Some need for HCW behaviour change: Campaign with outreach requiring some training	
	Feasibility of vaccination time point	Campaigns outside routine vaccination schedule	
	Acceptability in target population	Ranked 5/9 in country stakeholder survey, but likely need for high-level advocacy	
	Long-term financial implications	Falls within the category of price per course $ 2-10	
Alt. interventions	Alternative interventions	No alternative interventions but complementary prevention measures include improvements in water and sanitation (e.g.,WaSH), effective ORS treatment, antibiotics and case management	
Broader health system impact[2]	Broader health system impact	Opportunity to promote WaSH interventions	
Operational cost[3]	Incremental costs per vac. person	High incremental cost of ~$ 1.80: Already used in ~20 Gavi countries; costs mostly due to technical assistance, micro-planning, and data-related costs	
Implementation costs	Additional costs for introduction	Medium: already used in ~20 Gavi countries; costs mostly due to technical assistance, micro-planning, and data-related costs	

1. Evaluation based on comparison with other VIS 2018 candidates 2. Contextual information, not evaluated 3. Generic methodology based on routine campaigns. Details on evaluation methodology can be found in Methodology appendix

Rationale for vaccination strategy

Element	Modelled strategy	Rationale/Source
Vaccination schedule	• Campaigns every 3 years for all countries except those in protracted crisis; crisis countries campaigns every 2 years (Primary strategy)	• 2017 WHO position paper • Variation on interval between doses: Expert inputs; Kanungo S. et al. Flexibility of oral cholera vaccine dosing; and submitted article from campaign conducted in Zambia indicates feasibility of approach
Age group	• ≥ 1 year olds	• 2017 WHO position paper • Vaccine insert
Target population	• At risk population • Estimated at risk population decreases over time based on assumptions in the WHO Ending Cholera: A Global Roadmap to 2030 which includes increases in WaSH interventions	• Defined via estimates from Johns Hopkins University based on cholera reporting and hotspot mapping • Likely underestimated given underreporting • Uncertainty exists in the future estimates of the at risk population, various scenarios to be modelled assuming different • 95% confidence intervals modelled as part of strategic demand scenarios

Demand forecasting assumptions

Element	Assumptions	Rationale/Source
Country scope	• 48 endemic countries; • Includes 7 non Gavi 73 countries (not modelled in VIS)	• Expert inputs • WHO Ending Cholera: A Global Roadmap to 2030
Target population	• ≥ 1 year olds	• 2017 WHO Position Paper & vaccine insert
Delivery Strategy	• Preventive campaigns	• 2017 WHO Position Paper
Introduction dates	• First introduction: 2019, modelled as a continuation of Gavi support	• Expert inputs
Vaccine uptake	• 100%	• ‘Instant’ uptake
Coverage	• Medium higher scenario: • Demand: 100% 1st dose / 95% 2nd dose • FVP: 90% 1st dose / 85% 2nd dose	• Similar assumptions used across different vaccines • M&E OCV campaigns completed since 2013 • Additional low and high scenarios to be modelled
Products	• Both products are PQed • Presentation: 1-dose glass vial or plastic tube	• Shanchol packet insert • Euvichol packet insert
Logistics	• Wastage Factor: No wastage factor • Buffer stocks = 0%	• Based on M&E results from OCV campaigns and WHO guidance on planning OCV campaigns

Demand scenario assumptions: S2, S3 and S5 were used for impact modelling[1]

Higher volumes

Lower volumes

	1	2	3	4	5	6	7
Scenario	**Target population***	**Target population dynamics over time**	**Country adoption**	**Pace of adoption**	**Campaign frequency**	**Coverage**	**Product, wastage**
S1 Very high	JHU estimate upper bound of 95% CI	Follows UN Medium Variant population growth rate	All High and Medium, 2/3 of Low confidence countries introduce	High confidence countries: 2019-20 Medium: 2019-22 Low: 2020-23	Every 3 years; every 2 years in crisis countries	Volume calculation: 100%/100% Coverage calculation: 95%/90%	1-dose vial, with negligible wastage
S2 Higher		Flat until 2023, then decreases 90% by 2040; crisis countries flat					
S3 Medium-Higher	JHU estimate of population in districts with incidence > 10 per 10,000	Flat until 2020, then decreases 90% by 2035; crisis countries flat	All High, 2/3 of Medium, 1/3 of Low confidence countries introduce	High confidence countries: 2019-21 Medium: 2019-23 Low: 2021-25		Volume calculation: 100%/95% Coverage calculation: 90%/85%	
S4 Medium-Lower		Flat until 2020, then decreases 90% by 2030, then flat; crisis countries flat					
S5 Lower	JHU estimate lower bound of 95% CI	Flat until 2020, then decreases 90% by 2028, then decrease by 2% per year; crisis countries also decrease	All High; 1/3 of Medium; none of Low confidence countries introduce	High confidence countries: 2019-22 Medium: 2021-25 Low: n/a	Every 3 years	Volume calculation : 90%/85% Coverage calculation: 80%/75%	
S6 Very low					Every 5 years		

1. S5 excluded for JHU. See annex for additional details on assumptions, including country-specific exceptions.
   - 1 year and older target population to be approximated by 96.5% of JHU estimate of “total population in districts where >10% of population (or more than 100,000) at mean annual incidence level (based on 2010-2016 reported incidence estimates) of > 10 per 10000”.
   - Three crisis countries modelled

Impact modelling assumptions

Element	Assumptions	Rationale/Source
Efficacy	• 2 doses: 76% (95%CI: 62%-85%)	• 2017 WHO position paper; • Bi, Q et al, Protection against cholera from killed whole cell oral cholera vaccines: a systematic review and meta-analysis
Duration of protection	• 2 doses: 3 years (base scenario) • 1 study indicates potentially 5 years but data is limited and needs to be generated after VIS (high scenario)	• 2017 WHO position paper • Expert input
Source of disease incidence data	• IPM: Ali M et al. Updated Global Burden of Cholera in Endemic Countries, 2017 • JHU: Combined information on cholera incidence in sub-Saharan Africa from 2010 to 2016 from datasets from WHO, Médecins Sans Frontières, ProMED, ReliefWeb, ministries of health, and the scientific literature. They divided the study region into 20 km × 20 km grid cells and modelled annual cholera incidence in each grid cell assuming a Poisson process adjusted for covariates and spatially correlated random effects. Incidence was assumed to be constant throughout the modelled period in the absence of OCV.	• Expert input • Ali M et al. Updated Global Burden of Cholera in Endemic Countries, 2017 • Lessler, et al. Mapping the burden of cholera in sub-Saharan Africa and implications for control: an analytic synthesis of data across geographic scales, The Lancet, 2018