Cholera

Vaccine investment strategy

Background document #1

November 2013

Executive Summary

GAVI support for planned recurring cholera vaccine campaigns could help prevent endemic cholera and mitigate the risk of epidemics in poor communities while significantly shaping supply

- Two-dose campaigns targeting high-risk areas every 3 or 5 years
- Would require country-tailored vaccination strategies (a change from GAVI's current programme support which is based on standard population/birth cohort projections)
- GAVI demand could incentivise expansion of supply from 3-4M to ~50M doses per year by 2020
- Endemic countries view cholera as a high priority

Key challenges: uncertainty around health impact of GAVI support for preventive approach in endemic settings and possible high cost per death averted relative to other GAVI vaccines due to recurring campaign costs

- Limited experience with preventive approach
- Campaigns are resource intensive in order to ensure high 2-dose coverage at regular 3 or 5 year intervals
- Questions about sustainability of repeated GAVI-funded campaigns
- Also, limited supply a risk to implementation in short and medium term, especially if outbreak response requires large proportion of supply capacity

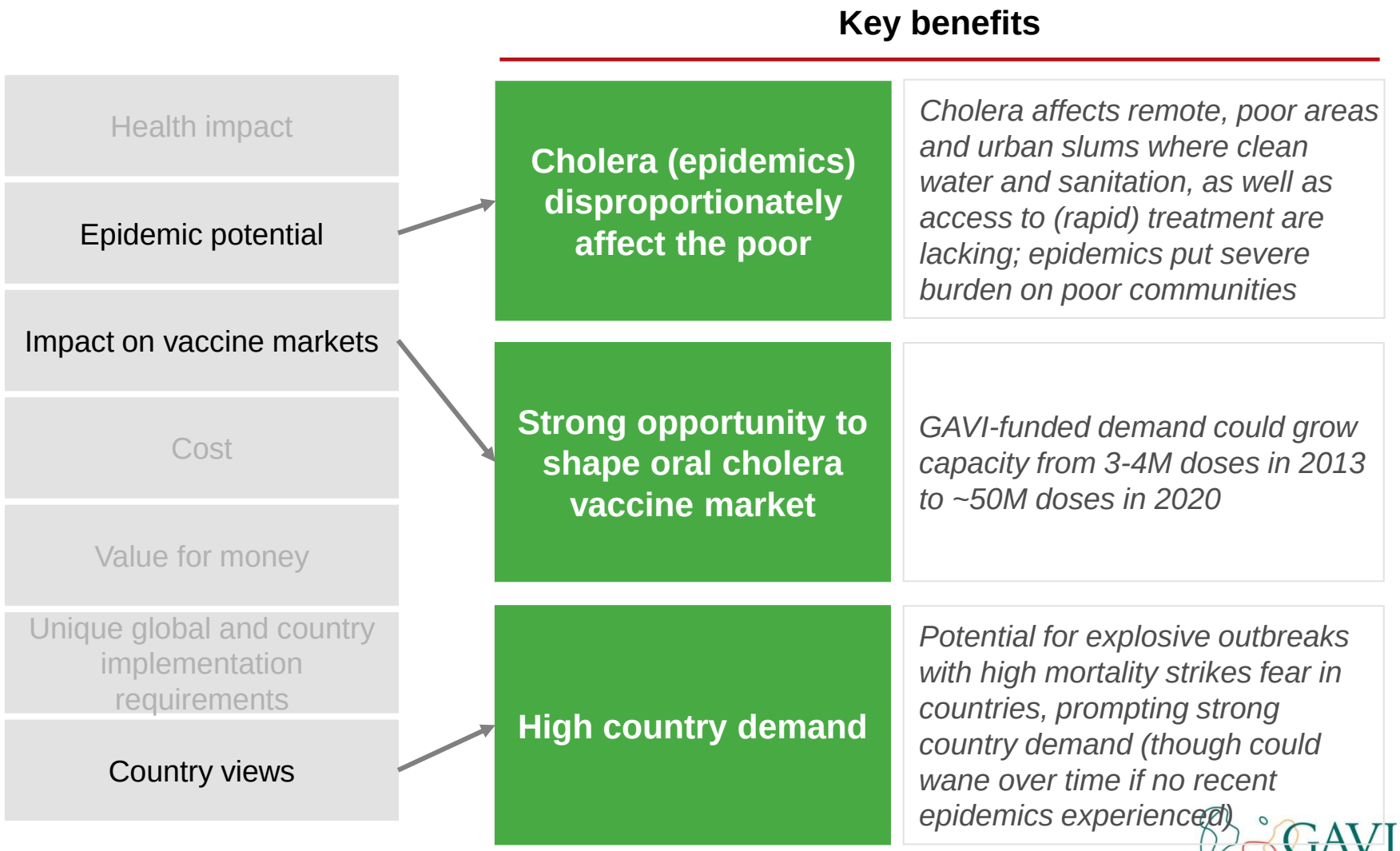
Recommendation: contribute to the global cholera stockpile for use in epidemic and endemic settings

- Do not open a 'routine' funding window
- Alternative investment in cholera stockpile to 1) shape the cholera market, 2) reduce deaths from epidemics, and 3) serve as a bridge to potential future support for planned recurring campaigns
- Projected cost: $115M over 2014-2018

GAVI ALLIANCE

Key cholera vaccine benefits

Planned, preventive campaign approach: prevent epidemics in poor communities, opportunity to shape cholera vaccine market, high country demand



Key cholera vaccine challenges:

Planned, preventive campaign approach : recurring campaigns could be a programmatic burden / costly and supply constraints may hinder implementation

Health impact

Epidemic potential

Impact on vaccine markets

Cost

Value for money

Unique global and country implementation requirements

Country views

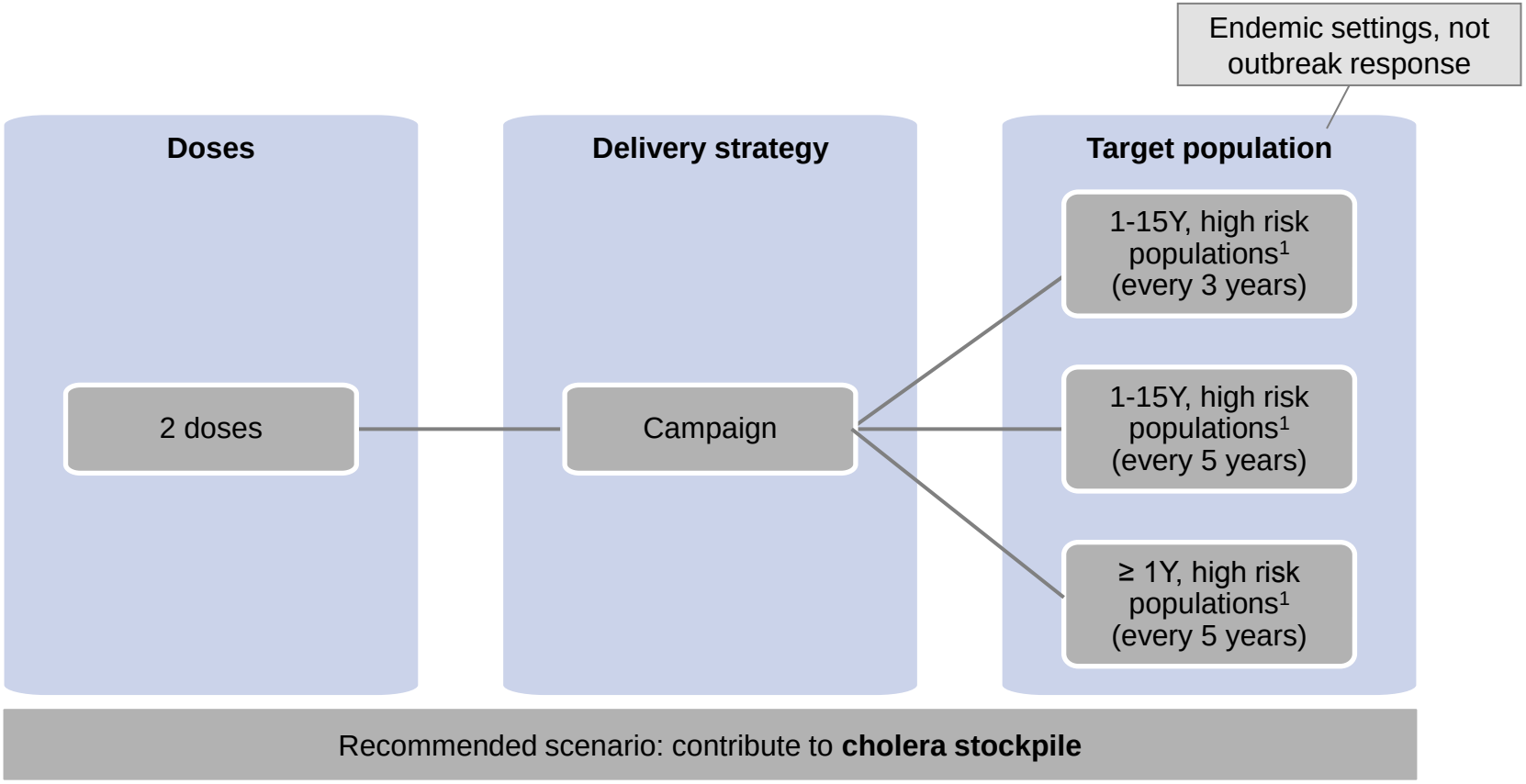
Key challenges

High recurring campaign costs	*Questions about sustainability of repeated GAVI-funded campaigns* *Estimate $388-606M in GAVI + country operational costs from 2015-2030*
Relatively low value for money (in terms of direct deaths averted)	*High operational costs of recurring campaigns increases cost per death averted; though benefits of epidemic mitigation extend beyond direct deaths averted*
Limited supply and irregular demand	*If increase in capacity not realised as quickly as forecasted, country introduction timing or vaccination strategy would need to be altered, affecting impact*

GAVI ALLIANCE

Cholera vaccine investment scenarios: planned, recurring campaigns and/or support stockpile

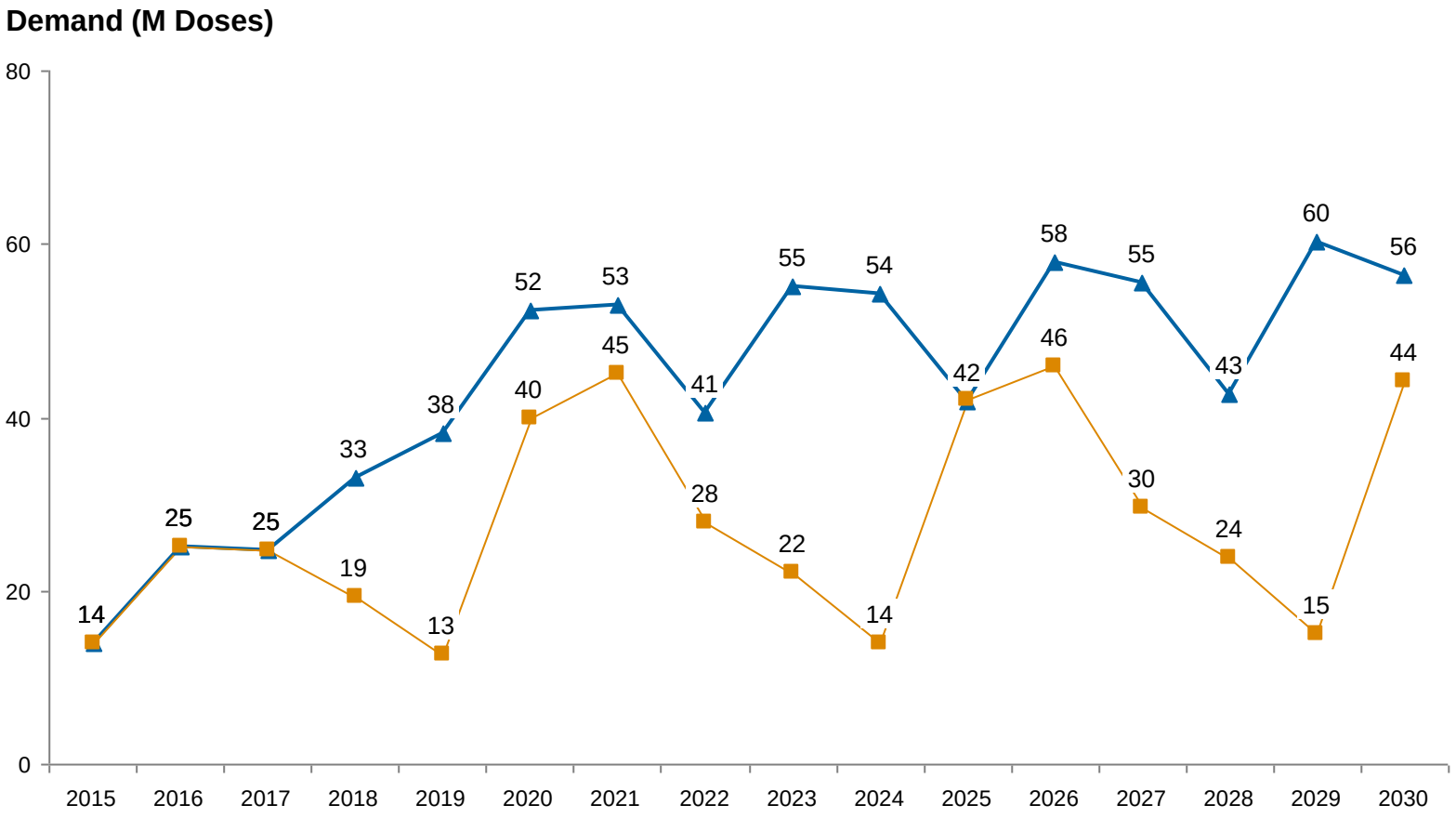
Strategies and assumptions are for modeling purposes. Actual implementation strategies will be based upon guidance received from WHO's Strategic Advisory Group of Experts and other WHO expert bodies. All strategies are modelled without financial constraints



Note: subsequent slides 5-15 present VIS assessment for planned, recurring campaign scenario (e.g. analyses of demand, impact, cost and implementation feasibility)

1. Country specific, eg urban slums and rural areas w/o access to clean water

Est. 444-704M doses needed through 2030 for periodic, preventive campaigns (supply constrained)



# countries introducing	*1*	*2*	*2*	*3*	*4*	*6*	*3*	*2*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*

1-15Y, every 3 years 1-15Y, every 5 years and >1Y, every 5 years (modelled demand equivalent)

Notes: (1) Includes demand from countries that graduate from GAVI support during 2015-2030 (following GAVI supported intro.)
(2) Forecasts for all scenarios developed with guidance from manufacturers on potential supply capacity
(3) Target population for >1Y scenario reduced to equal doses need for 1-15Y scenario in light of supply constraints

GAVI ALLIANCE

Uncertain estimate of 37,000 – 130,000 deaths averted over 2015-2030 at $934M-$1.4B

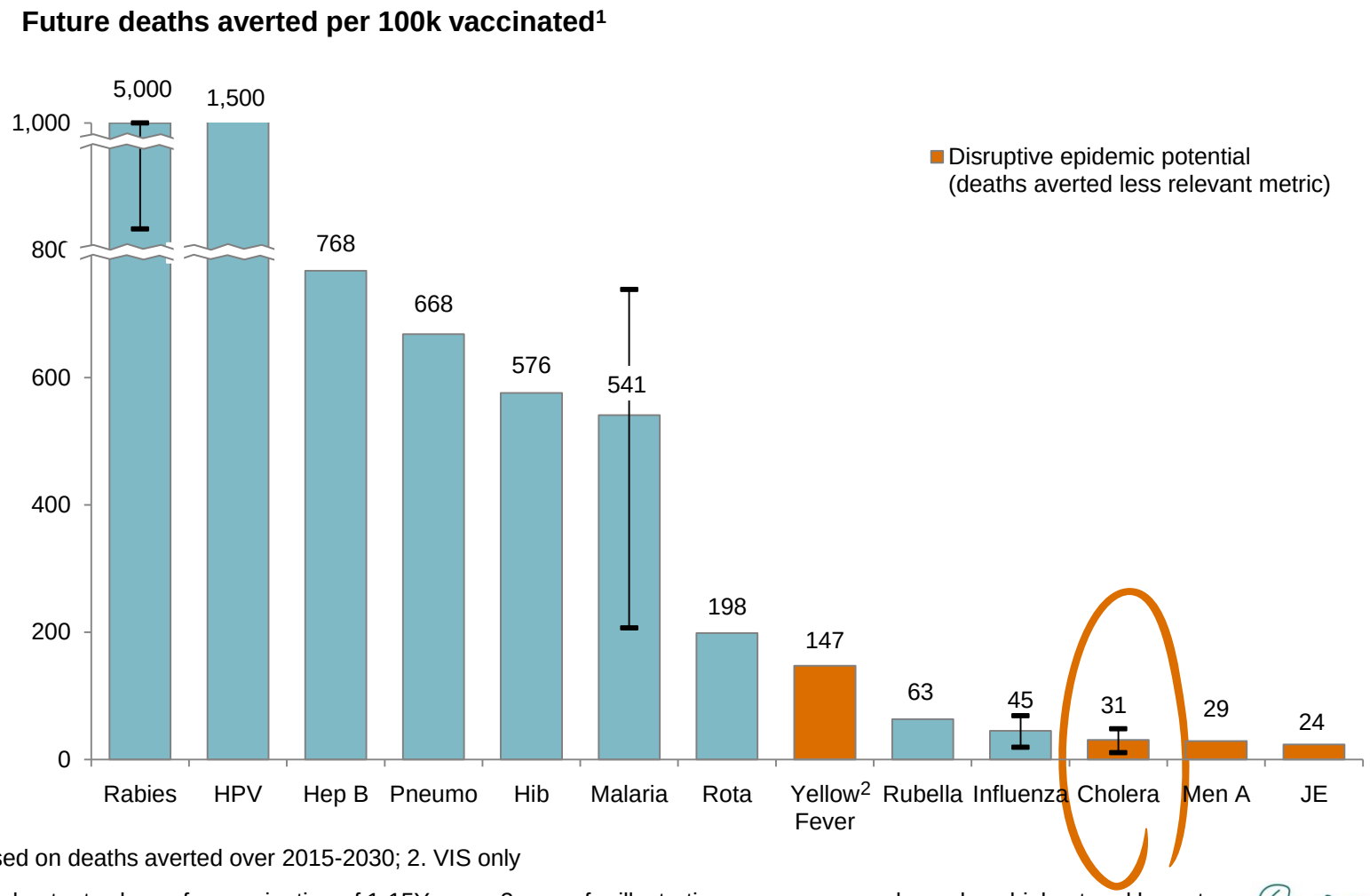
Separate consideration should be given to the mitigating effect of vaccination on preventing the serious social and economic consequences of epidemics.

		1-15Y, 3 years	1-15Y, 5 years	>1Y, 5 years
Impact	**Fully vaccinated persons**	272M	173M	173M
	Total future deaths averted	IVI: 130,000 CSQUID: 37,000[1]	Not available	Not available
	Deaths averted per 100k vaccinated	IVI: 48 CSQUID: 13	Not available	Not available
Cost	**GAVI procurement cost**	$840M	$546M	$546M
	GAVI operational costs	$387M	$246M	$246M
	Total GAVI cost	$1.2B	$792M	$792M
	Country operational costs	$220M	$142M	$142M
	Total cost	$1.4B	$934M	$934M
Value for money	**Total cost per death averted**	IVI: $11,000 CSQUID: 39,000	Not available	Not available

1. CSQUID estimates available for four countries only; impact calculated by extrapolating cases averted per 100k persons vaccinated; CFR of 1.5-2.5% was applied to convert cases averted to deaths averted.

GAVI ALLIANCE

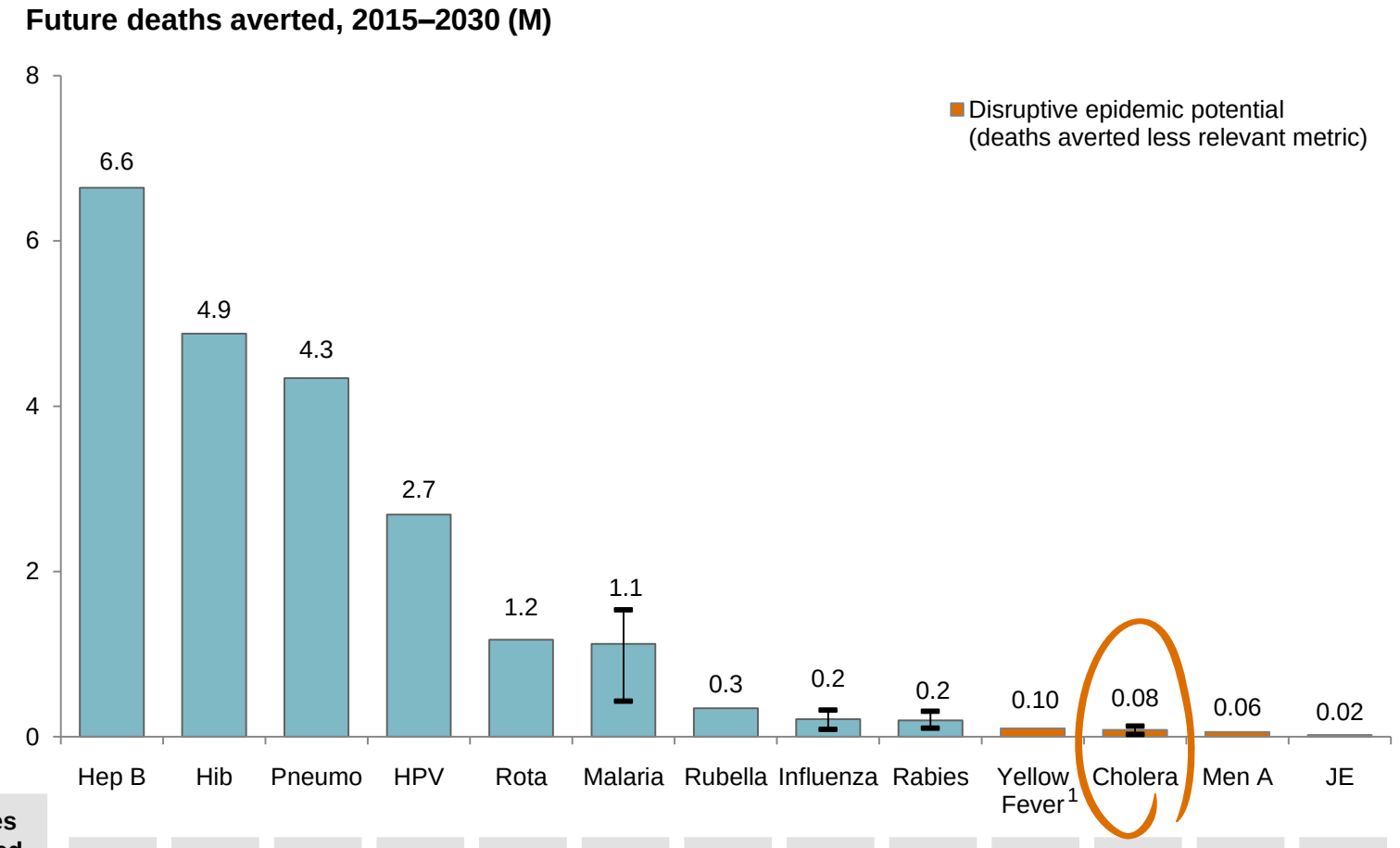
Direct health impact of recurring, preventive campaigns relatively low but estimates uncertain



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

Note: Model outputs shown for vaccination of 1-15Y every 3 years for illustrative purposes; error bars show highest and lowest value generated by sensitivity analyses and are driven by sensitivities in CSQUID estimate; point estimate represents midpoint of IVI and CSQUID estimates Source: VIS analysis

Relatively few total deaths averted in 2015-2030 (uncertain estimates and small country scope)



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

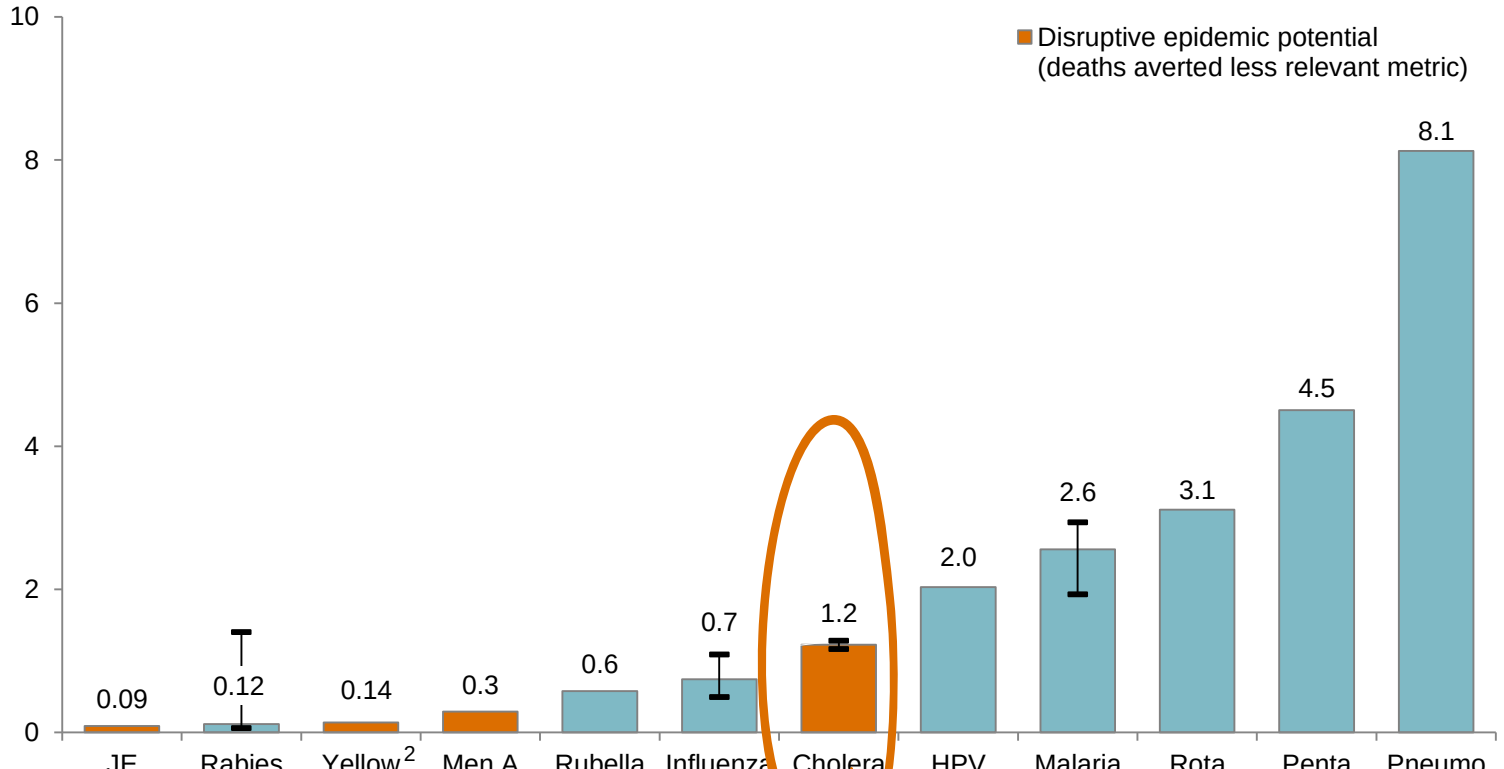
1. VIS only

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

Note: model outputs shown for vaccination of 1-15Y every 3 years for illustrative purposes; error bars show highest and lowest value generated by sensitivity analyses and are driven by sensitivities in CSQUID and IVI models; point estimate represents midpoint of IVI and CSQUID estimates Source: VIS analysis

Country support window for preventive campaigns at relatively low cost

Total cost to GAVI, 2015–2030 ($B)[1]

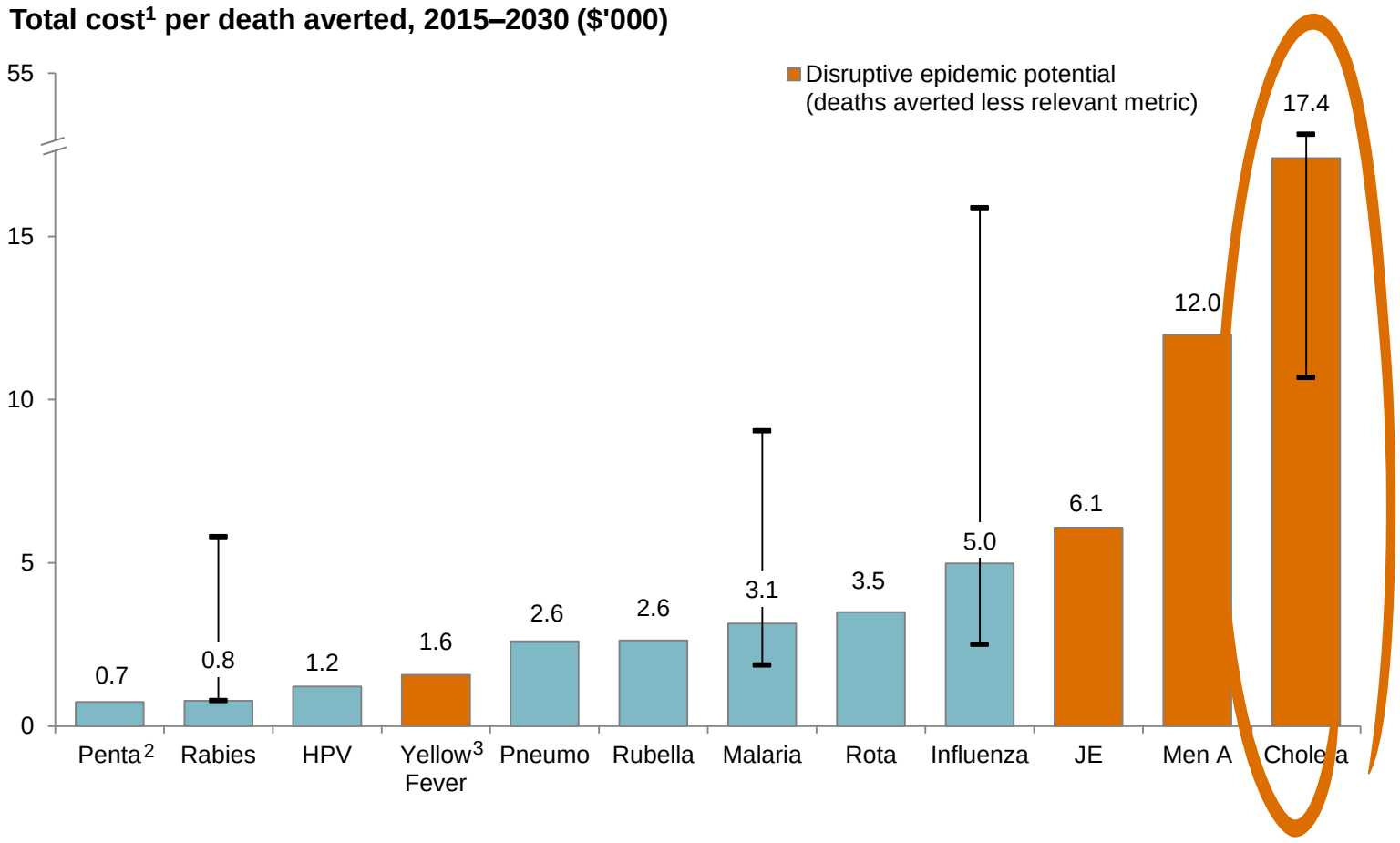


Countries introduced with GAVI support	JE	Rabies	Yellow Fever[2]	Men A	Rubella	Influenza	Cholera	HPV	Malaria	Rota	Penta	Pneumo
	6	45	10	26	34	45	21	48	34	50	66	63

1. Includes operational + procurement cost to GAVI and vaccine introduction grats 2. VIS only

Note: model outputs shown for vaccination of 1-15Y every 3 years for illustrative purposes; error bars driven by sensitivity analysis on vaccine price Source: GAVI Financial Forecast v7.0Fb as of July 2013, VIS analysis

High cost per death averted driven by campaign cost and relatively few deaths averted

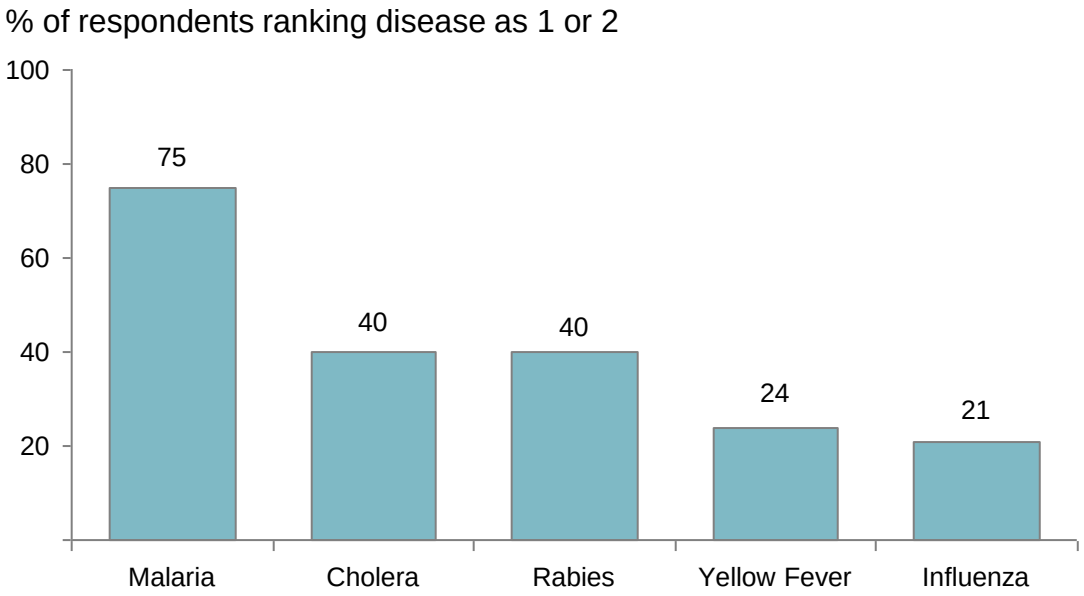


1. Includes operational + procurement cost to GAVI *and* country; 3. Includes deaths averted for Hep B and Hib; VIS only

Note: model outputs shown for vaccination of 1-15Y every 3 years for illustrative purposes; error bars based on highest cost / lowest impact and lowest cost / highest impact as generated iby sensitivity analyses; point estimate represents midpoint of IVI and CSQUID estimates Source: GAVI Financial Forecast v7.0Fb as of July 2013, VIS analysis

Cholera is a fairly high priority for respondents from endemic countries

Survey respondents: cholera vaccine ranked as second highest priority for country introductions



Average priority	1.9	2.8	3.1	3.8	3.4

Quotes from in-depth country interviews

"[Cholera] with political interest in [my country] and public demand, would likely introduce as early as possible"

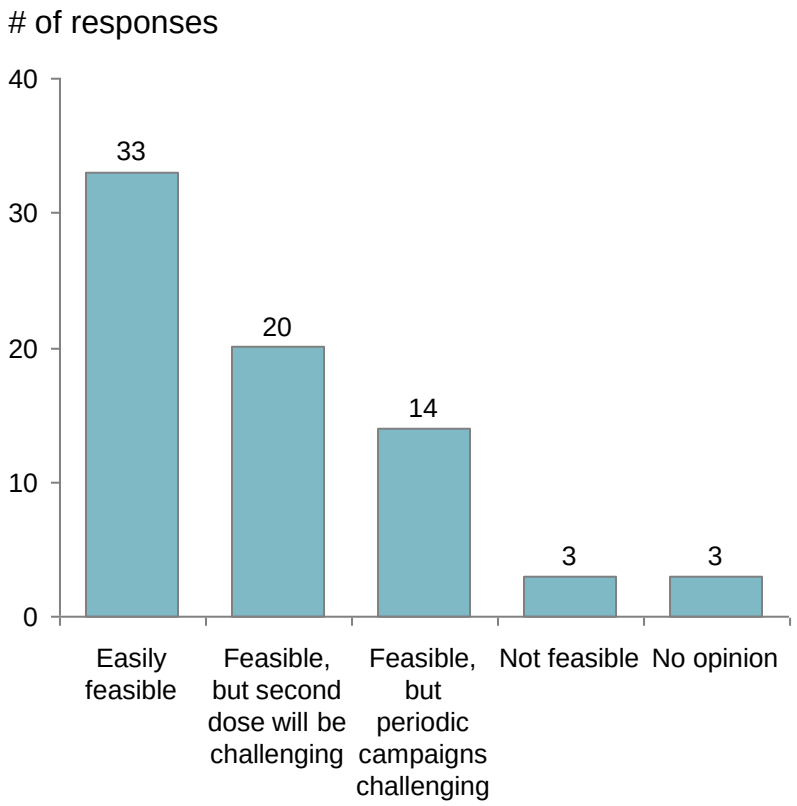
"We have experience doing campaigns in the <15Y group (measles, rubella, and JE). There should be no issue"

"It would be wise to start strengthening surveillance in [my country] before introducing the vaccine, to be able to identify high risk areas and changing target populations"

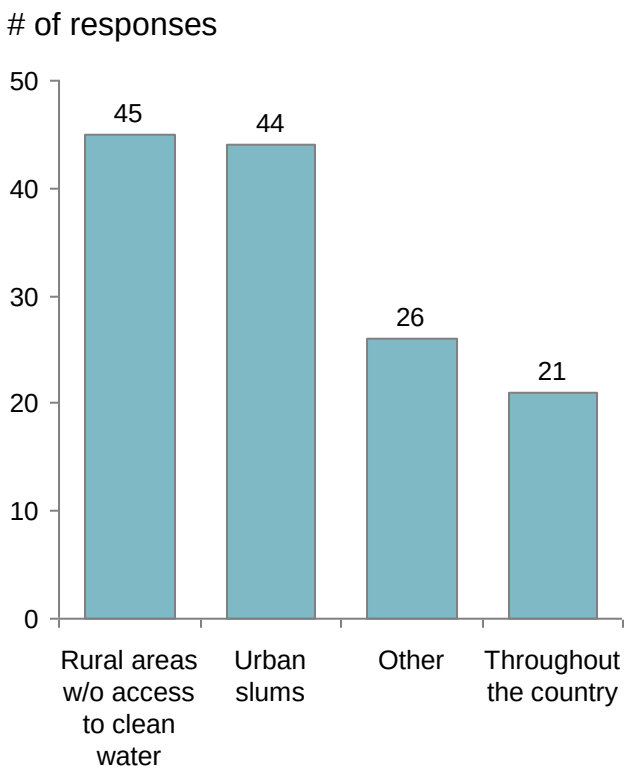
Survey question: please rank all of the following vaccines in terms of prioritisation for future introduction in your country
Note: survey focused on planned, preventive campaign scenario (not stockpile)
Source: 2013 GAVI country consultation survey, total responses = 182, 81 from countries in scope for GAVI support of cholera

Most respondents felt targeted, preventive cholera campaigns would be feasible

How feasible do you think the proposed periodic campaigns would be in your country?



Where would you implement cholera vaccine campaigns?

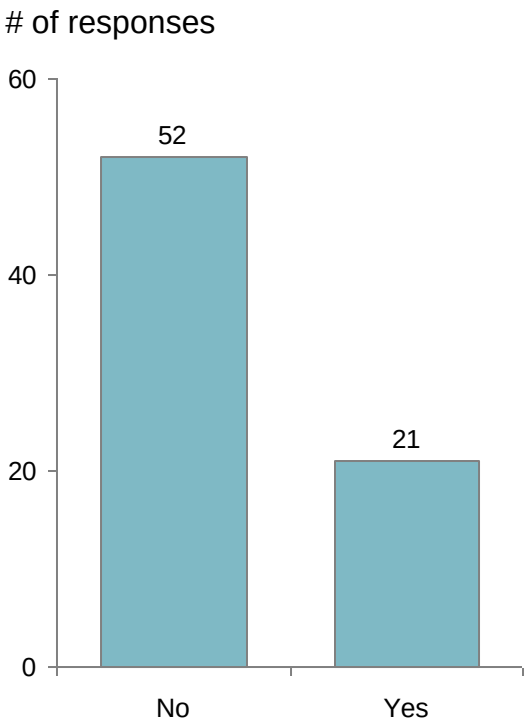


Source: 2013 GAVI Phase II country consultation survey, total n = 182

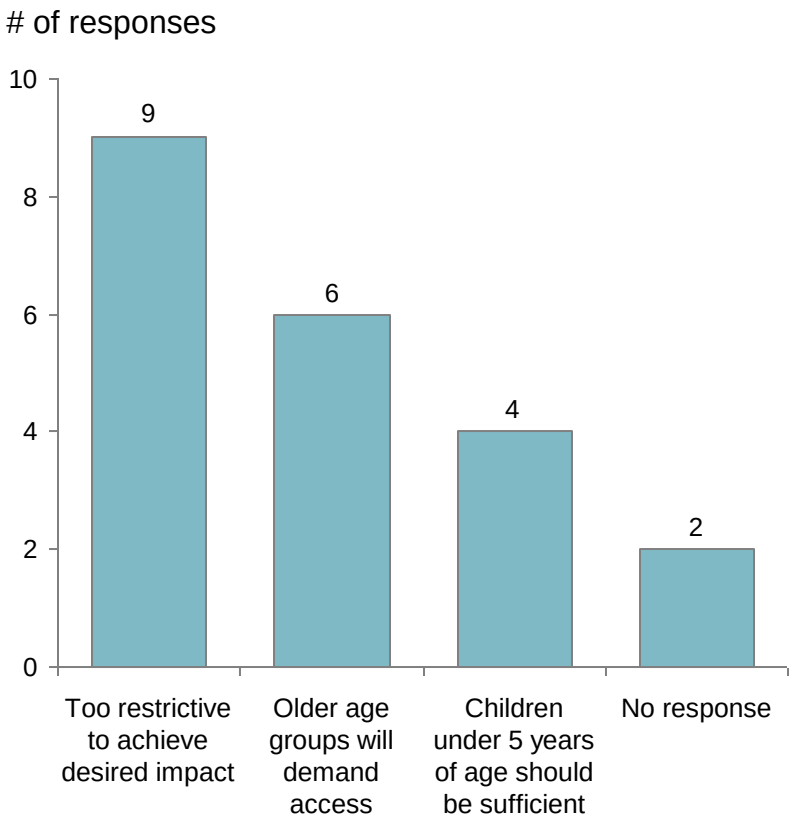
Note: cholera-specific questions asked only to respondents ranking cholera as a first or second priority for introduction

Most respondents not concerned about targeting 1-15Y though some prefer a broader age group

Would you have any concerns about targeting 1-15 years old?



If yes, specify why:

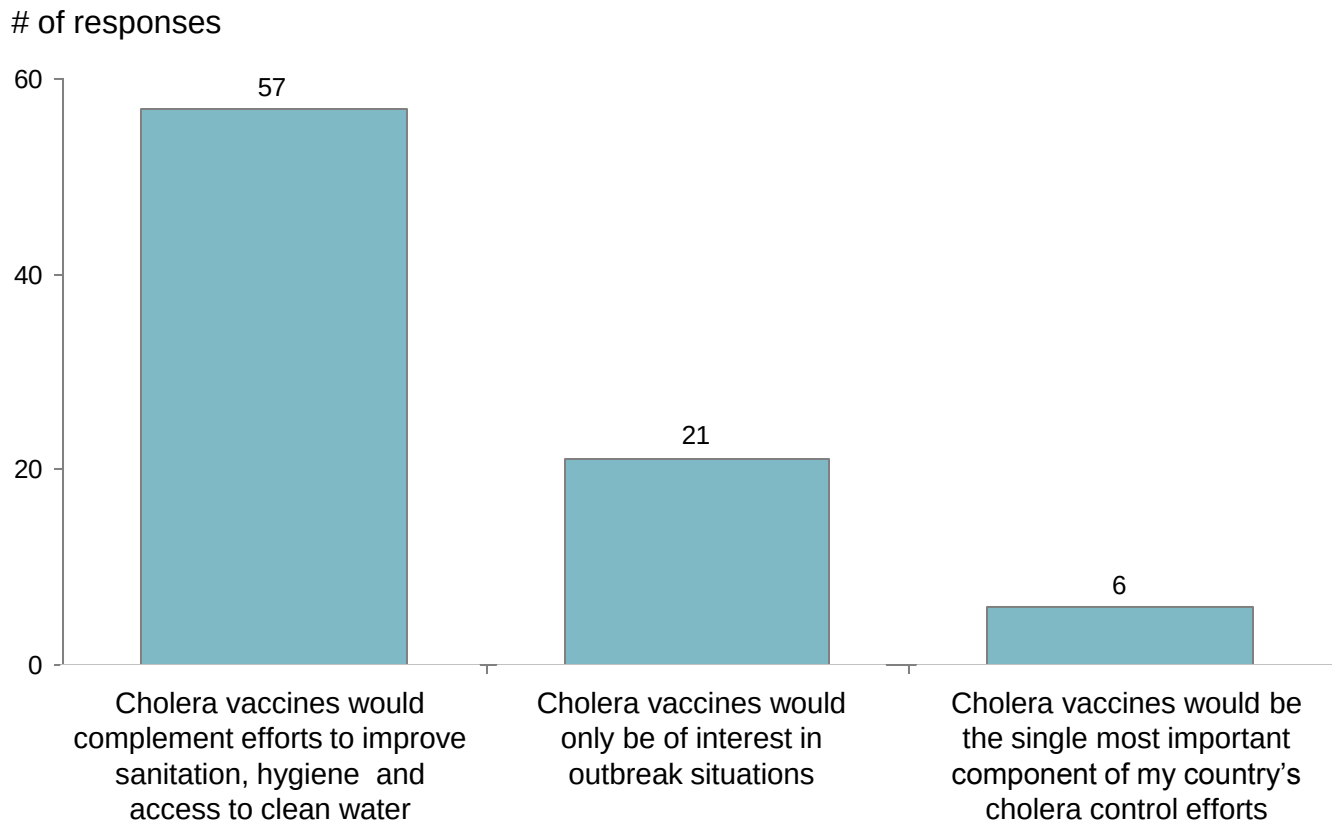


Source: 2013 GAVI Phase II country consultation survey, total n = 182

Note: cholera-specific questions asked only to respondents ranking cholera as a first of second priority for introduction

Most respondents view cholera vaccine as supplementary to WaSH improvements

Please indicate the statement(s) that most closely apply for your country:



Source: 2013 GAVI Phase II country consultation survey, n=182

GAVI support for cholera vaccine would come with several unique implementation requirements

	Area of focus	Unique implementation requirements	Unique costs
Global level	Policies and processes	▪ May require adaptation of GAVI co-financing policy given questions about sustainability of repeated GAVI-funded campaigns	▪ No direct costs
	Supply	▪ Severely limited production capacity forecasted through ~2020; need to ensure current efforts to overcome these difficulties are successful ▪ Manage periodic campaign supply with irregularity of demand between years	▪ No direct costs
Country level	Health workforce	▪ Periodic campaigns will require significant staff	▪ Cost accounted for in operational costs[1]
	Social mobilisation, education, communication	▪ Challenge of drop-out with two dose campaigns, especially among older individuals who are more mobile (note: studies underway to test whether 1 dose is sufficient for outbreak response settings (not testing for endemic settings) ▪ Acknowledgement of cholera burden (vs. 'watery diarrhea')	▪ Cost accounted for in operational costs[1]
	Supply chain infrastructure and logistics	▪ Periodic campaigns in rural areas increases transport requirements ▪ May require significant cold-chain capacity; thermostability studies on-going	▪ Cost accounted for in operational costs[1]
	Surveillance	▪ Build surveillance for on-going risk assessment and identification of hotspots (stool culture, rapid diagnosis, Polymerase Chain Reaction)	▪ Surveillance investments
	Planning, coordination, integration	▪ Coordination with WaSH (water, sanitation and hygiene) and case management efforts to ensure these are not negatively affected	▪ Focused organizational effort for coordination

Unique but manageable

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

1. Expected to be covered by GAVI co-financing, MoH, partners

Alternative investment: support for global stockpile at cost up to $115M over 2014-2018

Illustrative cost of stockpile: $115M over 2014-2018

	2014	2015	2016	2017	2018	5-year total
Doses	Gradually increasing up to 20M doses per year					
Cost	$8.5M	$17M	$25.5M	$34M	$29.3M	**$115M**

Note: Some of these costs may be reimbursed by countries under a revolving fund mechanism

Stockpile support would achieve three objectives

Bridge to future planned, preventive campaigns

- Raise awareness and increase country demand
- Demonstrate optimal implementation strategies (some doses to be reserved for preventive use)
- Improve surveillance systems and understanding of burden

Market shaping

- Increase overall OCV supply and annual regularity
- Attract additional manufacturers to the market, potentially lowering price
- Shorten lead time
- Incentivise new vaccine development

Aid global outbreak response

Options for a cholera investment

Open country support window for periodic, preventive campaigns

Also, contribute to global cholera stockpile

Open country support window for periodic, preventive campaigns

Contribute to global cholera stockpile

5-year investment over 2014-2018

- *~$115M total cost*
- *Up to 70M doses*

Recommended option

No GAVI support for cholera vaccine

Implications of no GAVI support

Continuing cholera in endemic and epidemic countries until longer term WaSH improvements materialize

Missed opportunity for market shaping with consequences for global OCV supply capacity

Other funders may step in to fund OCV stockpile

Cholera: experts and sources consulted

Sources

- WHO Cholera Fact Sheet N°107, July 2012
- WHO position paper, WER, No. 13, 2010, 85: 117-128
- SAGE Working Group: Vaccination in Acute Humanitarian Emergencies: a Framework for Decision-Making (Revised draft Oct 2012)
- WHA64.15 Resolution Cholera: mechanism for control and prevention (May 2011)
- Ali M, et al. The Global Burden of Cholera, Bulletin of the World Health Organization, 2012;90:209-218A.
- IHME Global Burden of Disease Study 2010
- IVI. An Investment Case for the Accelerated Introduction of Oral Cholera Vaccines. Seoul, Korea 2012.
- Sur D, et al. Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: An interim analysis of a cluster-randomised, double-blind, placebo-controlled trial. Lancet 2009;374:1694-1702.
- Sur D, et al. Efficacy of a low-cost, inactivated whole-cell oral cholera vaccine: Results from 3 years of follow-up of a randomized, controlled trial. PLoS Neglected Tropical Diseases 2011;5:e1289.

Experts consulted

- Raymond Hutubessy, WHO
- Helen Matzger, BMGF
- Tom Wierzba, IVI
- Vittal Mogasale, IVI
- Firdausi Qadri, icddr,b
- David Sack, JHPSH
- John Clemens, UCLA
- Dipika Sur, National Institute of Cholera & Enteric Diseases
- Suman Kanungo, National Institute of Cholera & Enteric Diseases
- Martin Mengel, AAMP
- Brad Gessner, AAMP
- Louise Ivers, Partners in Health
- Kate Alberti, UNICEF
- Francisco Luquero, MSF
- William Perea, WHO
- Alejandro Costa, WHO
- Carsten Mantel, WHO
- Stephen Martin, WHO
- Jon Abramson, Wake Forest
- Alan Hinman Task Force for Global Health
- Jan Holmgren, U of Gothenburg
- Zulfiqar Bhutta (The Aga Khan University)
- Ira Longini, University of Florida
- Dennis Chao, Fred Hutchinson Cancer Research Center
- Robert Tauxe, CDC
- Cholera Coalition
- Partners in Health

Appendix

Demand forecasting assumptions for cholera vaccination strategies

Element	Assumptions	Rationale
Country scope	• 23 high risk GAVI-eligible countries (per 2013 eligibility status); • 21 countries forecasted to introduce with GAVI support in modelled time period	Anticipated only early adopters to be included in the forecast (also in light of supply constraints)
Target population	• 1 to <15Y, 50% of high risk pop • 1 and older, 19%[1] of high risk pop	Urban slums or in rural areas without clean access to clean water (source: UN urban slum data and WHO / UNICEF Joint Monitoring Program (JMP) for Water Supply and Sanitation)
Introduction dates	First introduction: 2015	PQ product currently available
Uptake	Instant uptake (campaign analogue)	Standard GAVI uptake assumptions for campaign administration
Analogue coverage	Demand: MSIA Fully vaccinated persons: MSIA – 18%	18% dropout was the midpoint from past OCV campaigns
Products	1 dose liquid vial	Shanta's OCV
Logistics	• Wastage Factor: 1.05 • Buffer stocks = 0% of change between forecast years.	Standard WHO and GAVI SDF assumptions

1. Weighted average of reduced target population across countries to implement >1Y scenario in same countries within supply constraints

Cholera impact model assumptions: CSQUID

Model definition

Dynamic model for cholera transmission

- Basic SIR model run in one year increments with population-level immunity in one year being based on the number of infections in recent years
- Model has one-year age cohorts
- No seasonal forcing or sporadic major outbreaks

Modelling completed for four countries

- Bangladesh, DRC, Mozambique, and Uganda

Primary model output is cases averted per 100k vaccinated

Key assumptions

Vaccine effectiveness based on data from large trials of Dukoral and Shanchol

- 65% for adults (>4Y), 3 year duration of protection
- 38% for children (1-4Y), 2 year duration of protection

Incidence rates for each modelled country

- Bangladesh: 3.0 / 1,000
- DRC: 3.2 / 1,000
- Mozambique: 3.2 / 1,000
- Uganda: 1.4 / 1,000

Modelled with and without herd effects

Apply CFR of 1.5-2.5% to convert to deaths averted (not completed by modelling group)

Extrapolation method

Estimates from the four modelled countries scaled to full country scope using IVI's Phase I estimates (detailed on next page)

- Compare the ratio of deaths averted per 100k across the two models for the four countries
- Apply this ratio to the IVI estimates for the remaining countries
  - Maintains the general magnitude of CSQUID's four country estimate
  - Leveraging IVI's country-specific estimates to account for the possibility that CSQUID's four countries were not representative of broader country set

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

Cholera impact model assumptions: IVI

Model definition

Dynamic model for cholera transmission

- Dual transmission model with direct and indirect pathways as well as seasonality
- Four age groups: <1Y, 1 to 4Y, 5 to 14Y and ≥15yrs

Model assump-tions

Susceptibles	Exposed	Infected	Recovered/ dead
▪ Population not vaccinated ▪ Vaccine waning is 70% in first two years post-vaccination; 50% the third year ▪ 0.64% every week of those recovered become susceptible again ▪ Takes into account herd protection effects	▪ According to a dual transmission function (direct and indirect transmission), that takes into account, seasons, regions and the environmental reservoir ▪ 30-35% of those vaccinated are still susceptible to infection	▪ 10% symptomatic ▪ 90% asymptomatic ▪ 1 week incubation period	▪ Infectious period of 1.5 weeks ▪ Deaths obtained applying a CFR for symptomatic cases, country-specific

Vaccine efficacy:

- 1-15Y: 52% for 5 year campaign intervals, 61% for 3 year intervals
- >1Y: 60% for 5 year intervals

Underlying incidence rates:[1]

- Region specific; e.g. 2 / 1,000 in AFRO-D

Case fatality rates:[1]

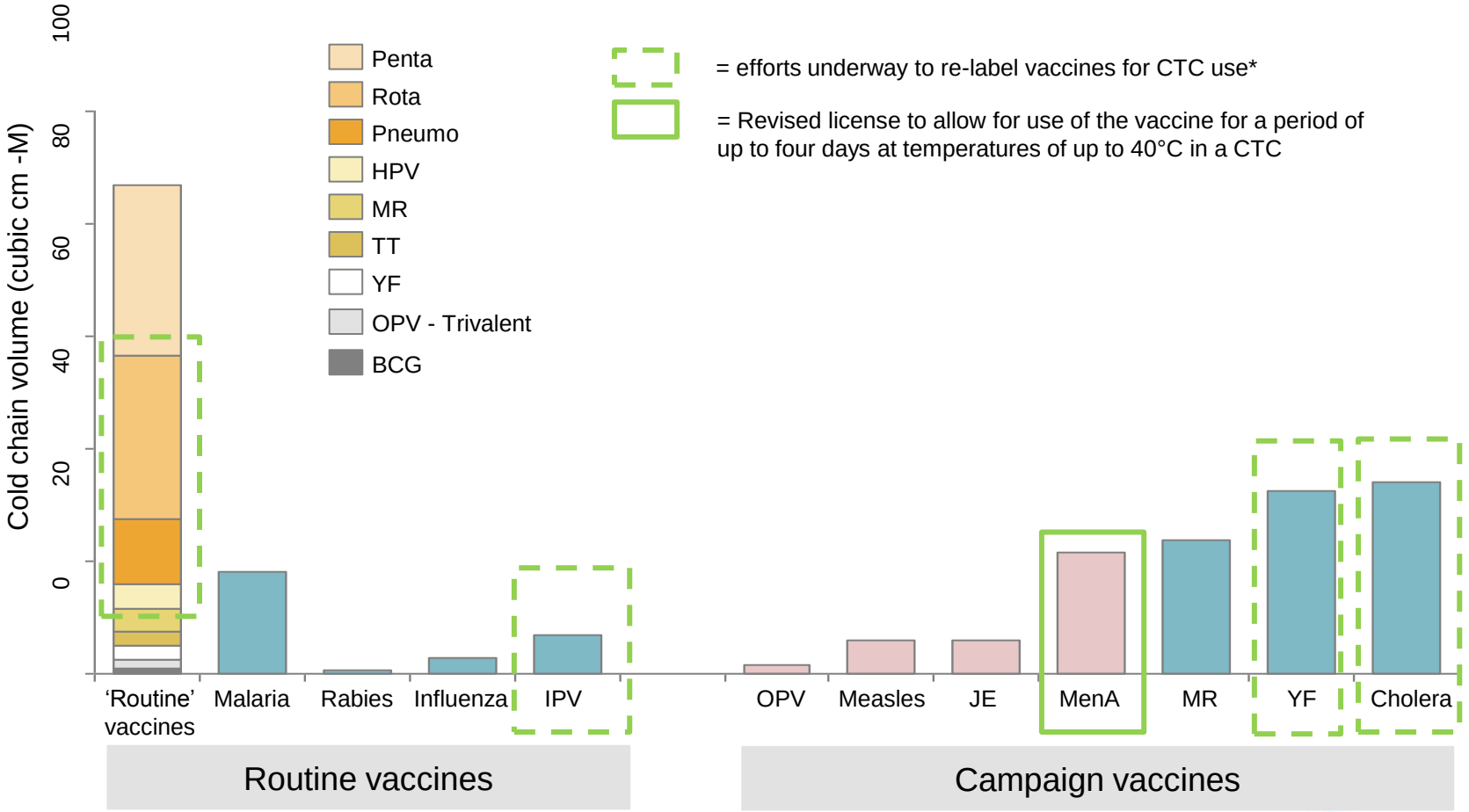
- Region specific; e.g. 3.8% in AFRO-D

1. From variety of trial sources based on WHO region

Source: International Vaccine Institute; detailed impact modeling methods available on request, please contact vis@gavialliance.org

Efforts underway to re-label vaccines for CTC use outside 2-8C

Cold chain volume requirements to fully immunise respective target populations through the routine programme over one year or through a campaign (in illustrative country)



*According WHO/IVB/13.04 Use of MenAfriVac™ (meningitis A vaccine) in a controlled temperature chain (CTC) during campaigns http://apps.who.int/iris/bitstream/10665/86018/1/WHO_IVB_13.04_eng.pdf

Source: VIS 2013 analysis; WHO Vaccine Volume Calculator 2012 database: http://www.who.int/immunization_delivery/systems_policy/logistics/en/index4.html

24