Influenza

Vaccine investment strategy

Background document #2

November 2013

Executive Summary

GAVI support for maternal influenza immunisation could strengthen maternal and child health by potentially protecting three groups: pregnant woman, fetus and infant under 6 months old (incl. neonate)

- Vaccination of pregnant women (WHO highest priority target group) at first antenatal care contact
- Maternal immunization a unique platform to reaching fetus and neonates
- Potential to avert ~210K mother / infant deaths from 2015-2030 if broad adoption across GAVI countries
- Estimate excludes potential benefits to fetus due to lack of data on long-term outcomes; if initial evidence is verified, these benefits may increase health impact
- Opportunity to shape influenza vaccine market to serve countries with year-round influenza more efficiently; also, increases country preparedness for pandemic response

But, significant uncertainty of vaccine health impact, potential complications with year-round supply, and low country demand

- Vaccine efficacy in infants under 6 months of age based on single small randomized controlled trial and observational studies from developed countries (results of three additional efficacy studies in developing countries may become available in 2014)
- Significant logistical changes required to enable effective year-round provision
- Low country demand and awareness in many GAVI countries due in part to lack of burden data

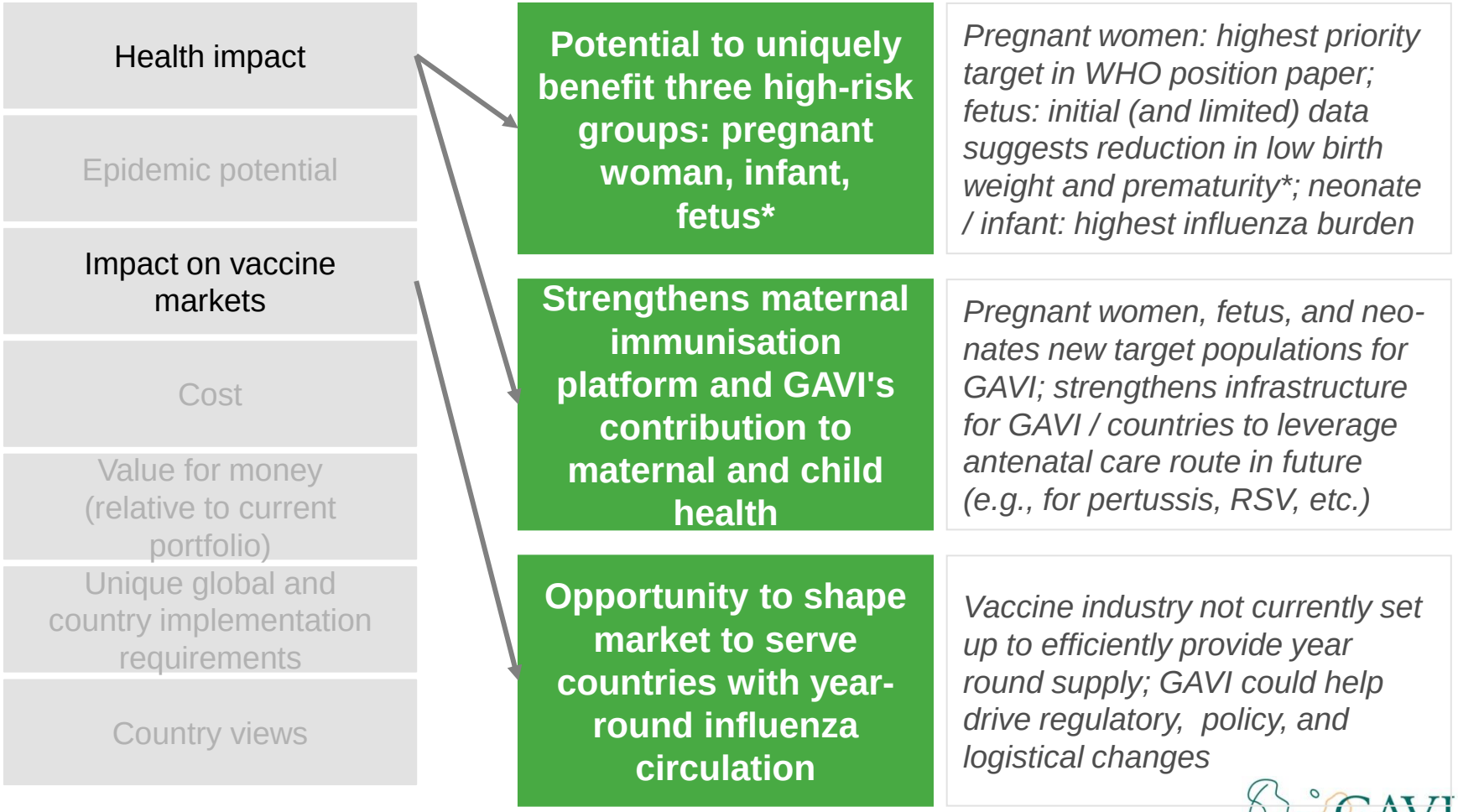
Recommendation: note the potential public health impact of vaccinating pregnant women against seasonal influenza and the need to assess the emerging evidence of impact of vaccination on neonates, but do not open a funding window for influenza vaccines at this time.

- Insufficient evidence base for health impact
- Monitor outcomes from three critical studies on influenza vaccine health impact to be released in 2014
- Re-evaluation of influenza vaccine support in the next VIS process
    - Will need to address questions relating to the logistics of seasonal vaccine supply, surveillance and strain matching, and optimal delivery strategies for pregnant women

GAVI ALLIANCE

Key influenza vaccine benefits:

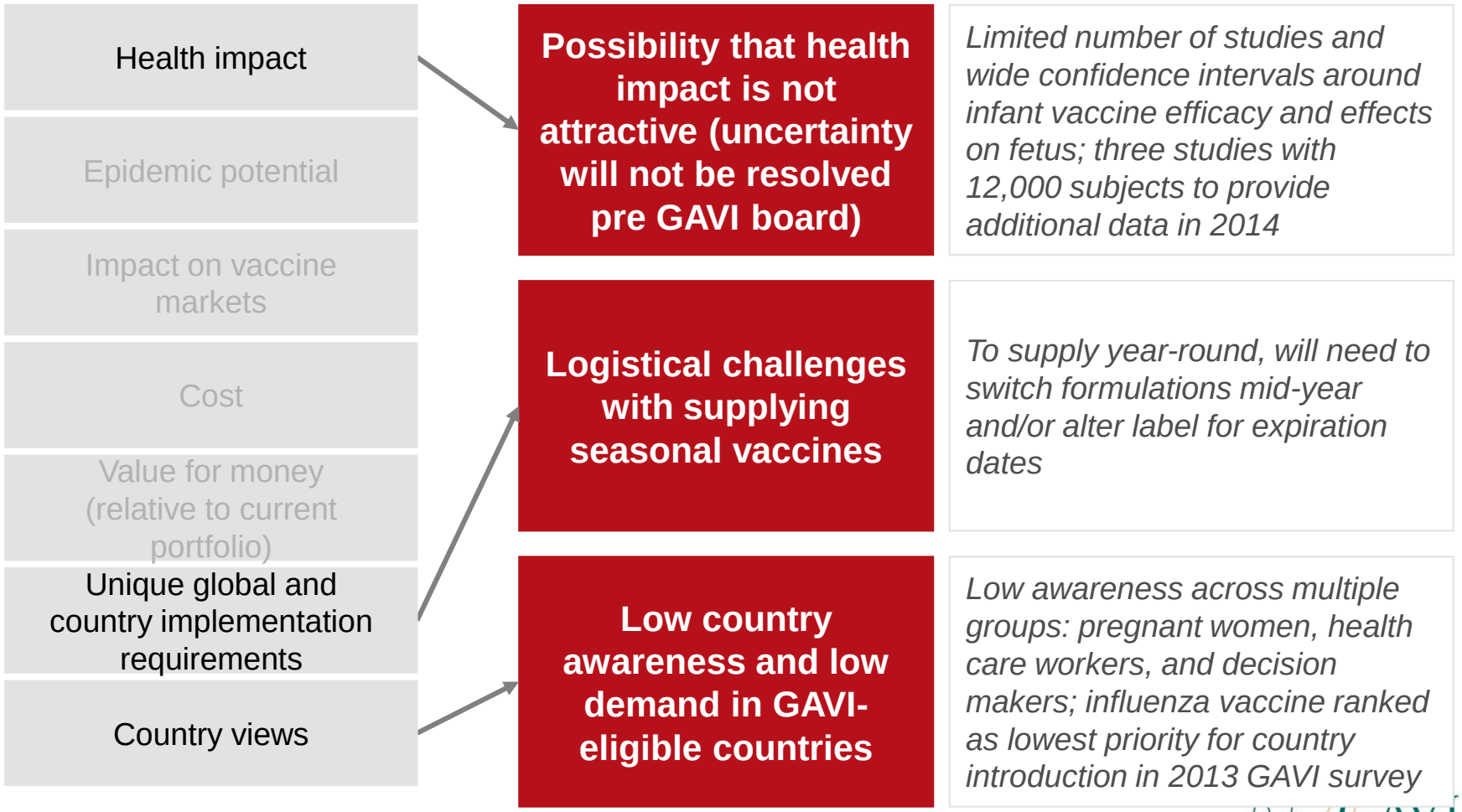
Uniquely benefits three groups, strengthens maternal immunisation, catalytic market-shaping opportunities



* Effects on fetus highly uncertain and not included in VIS impact estimates

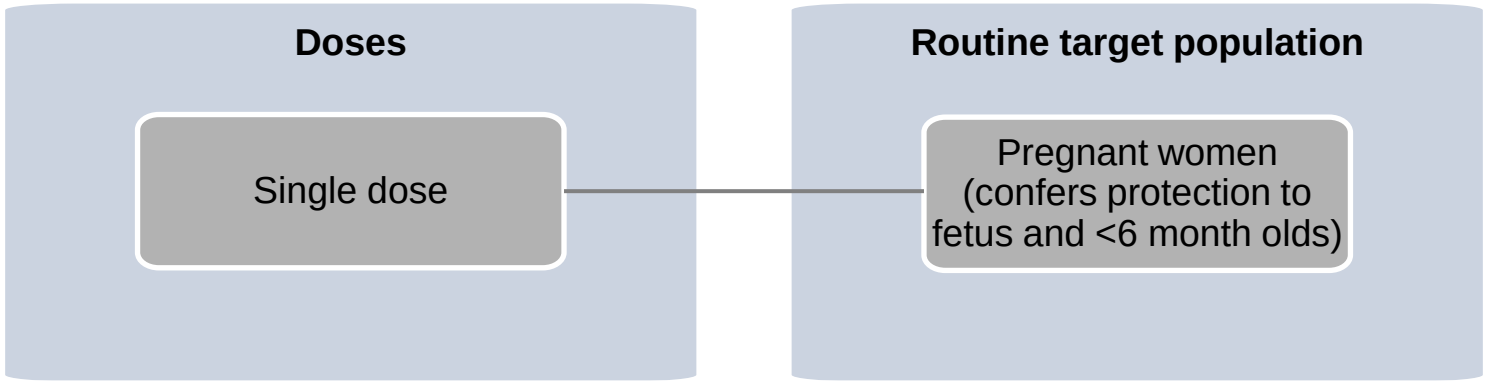
Key influenza vaccine challenges:

Uncertainty in impact, complex provision of year-round supply, low awareness / demand



Influenza vaccine investment scenario: immunisation of pregnant women at first antenatal contact

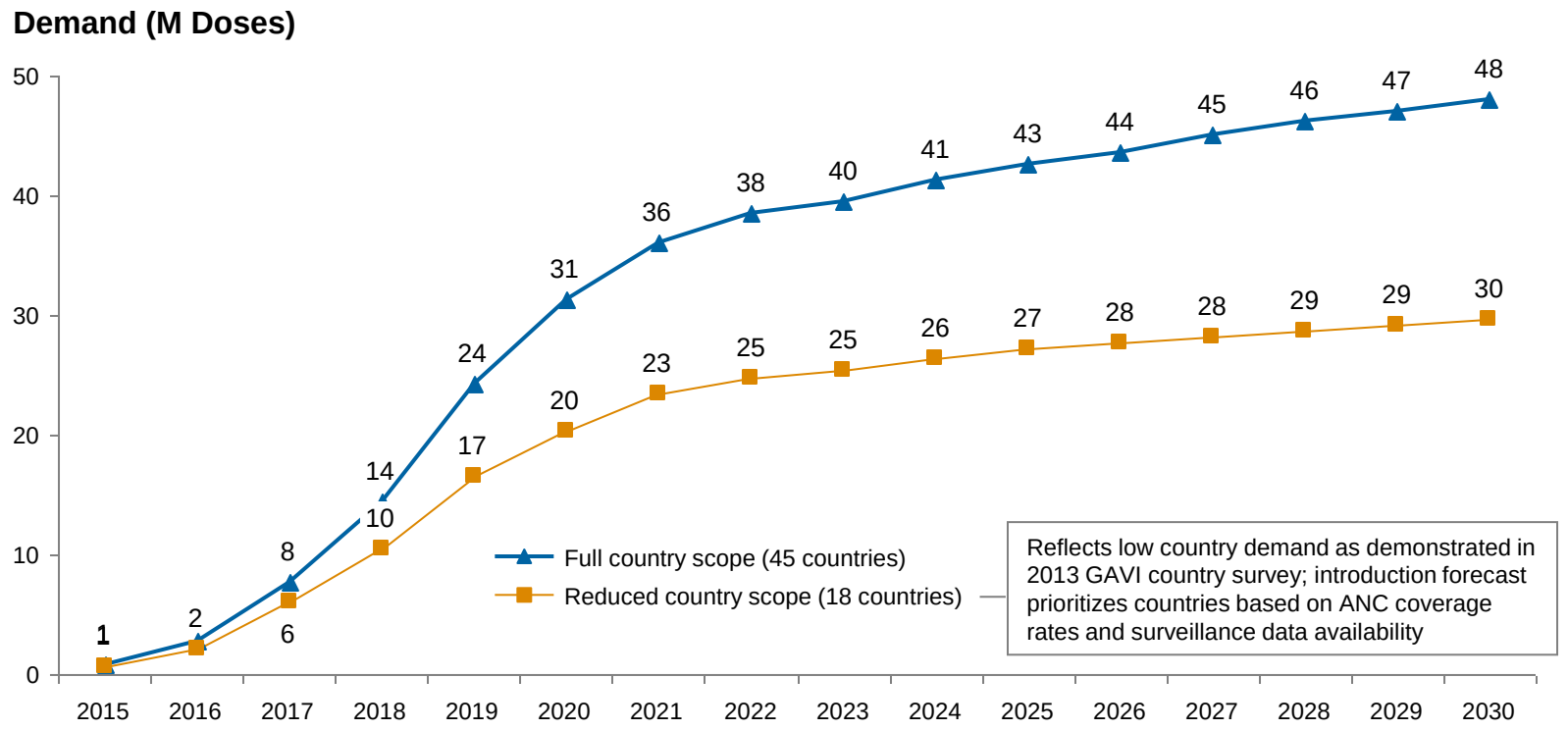
Strategies and assumptions are for modeling purposes. Actual implementation strategies will be based upon guidance received from WHO's Strategic Advisory Group of Experts and other WHO expert bodies. All strategies are modelled without financial constraints



Notes:

- *Any leftover doses may be used in other high-risk age / population groups*
- *Year-round, routine provision modelled based on principles of maximizing protection to infants (highest-burden group), higher value for money and stronger country ownership*
- *However, campaign-based approach may be appropriate for some countries*

Cumulative demand estimated to be 327M-509M doses through 2030



# countries introducing (full scope)	*3*	*6*	*10*	*10*	*7*	*2*	*1*	*0*	*2*	*2*	*0*	*1*	*1*	*0*	*0*	*0*
(Reduced scope)	*2*	*3*	*6*	*3*	*2*	*0*	*0*	*0*	*1*	*1*	*0*	*0*	*0*	*0*	*0*	*0*

Note: Includes demand from countries that graduate from GAVI support during 2015-2030 (following GAVI supported introduction)

Over 2015-2030, potential to avert 130,000-210,000 deaths at total cost of $665M-$1.1B

		Introduction in 45 GAVI countries	Introduction in 18 GAVI countries[1]
Impact	Fully vaccinated persons	471M	298M
	Total future deaths averted	210,000	130,000
	Deaths averted per 100k vaccinated	45	44
Cost	GAVI procurement cost	$704M	$398M
	GAVI introduction grant	$39M	$22M
	Total GAVI cost	$742M	$420M
	Country procurement costs	$261M	$214M
	Country operational costs	$50M	$31M
	Total cost	$1.1B	$665M
Value for money	Total cost per death averted	$5,000	$5,100

Excludes potential effect on fetus due to lack of data on long-term outcomes

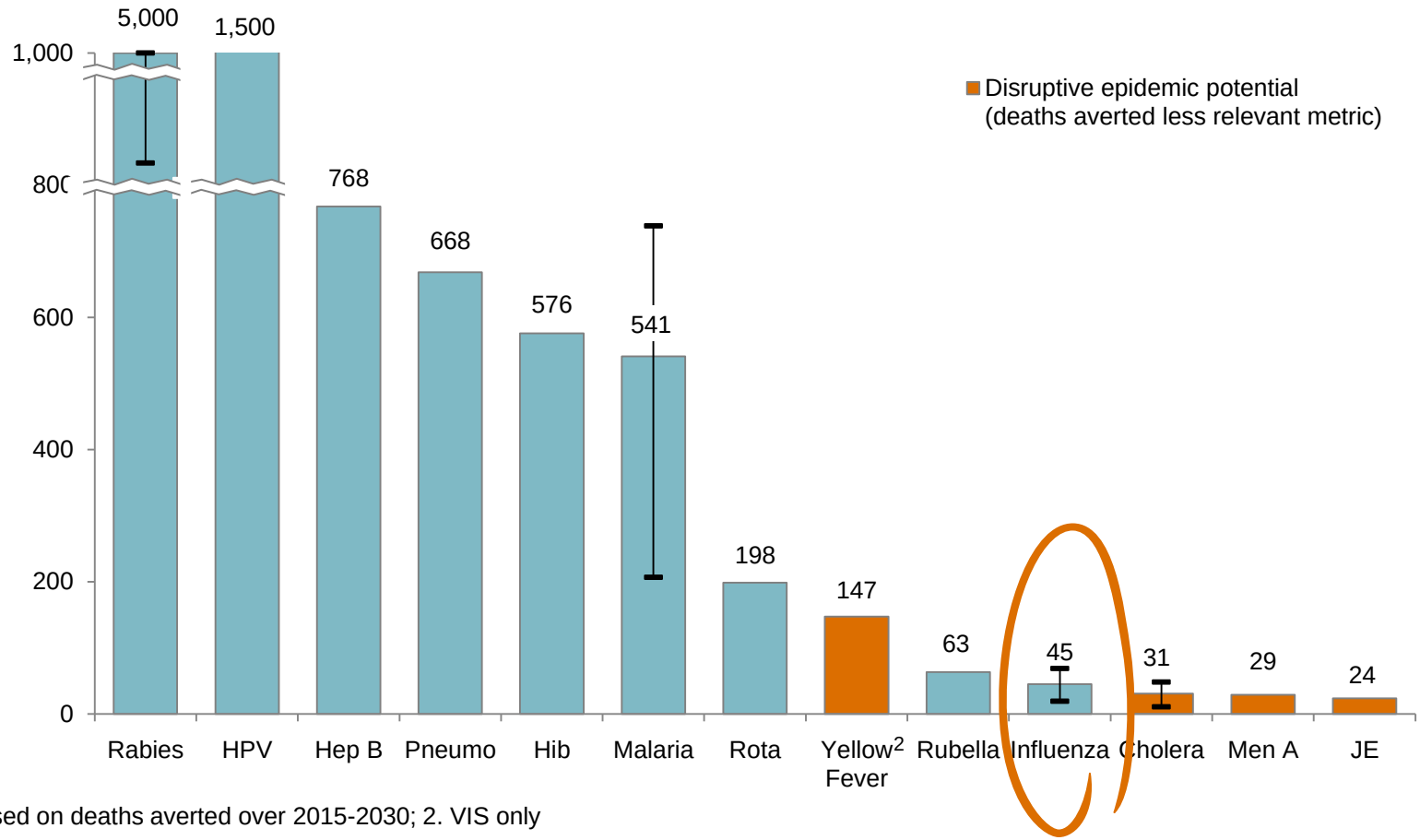
1. Reflects likely low country demand as demonstrated in 2013 GAVI country survey

Note: impact includes deaths averted in pregnant women and infants < 6 months; ~80% of deaths averted are from infants, ~20% from pregnant women. Estimate does not include impact on fetus (e.g., reduction in preterm birth), these possible effects are explored separately in slide 11

GAVI ALLIANCE

Influenza impact low relative to current GAVI portfolio (estimates uncertain)

Future deaths averted per 100k vaccinated[1]

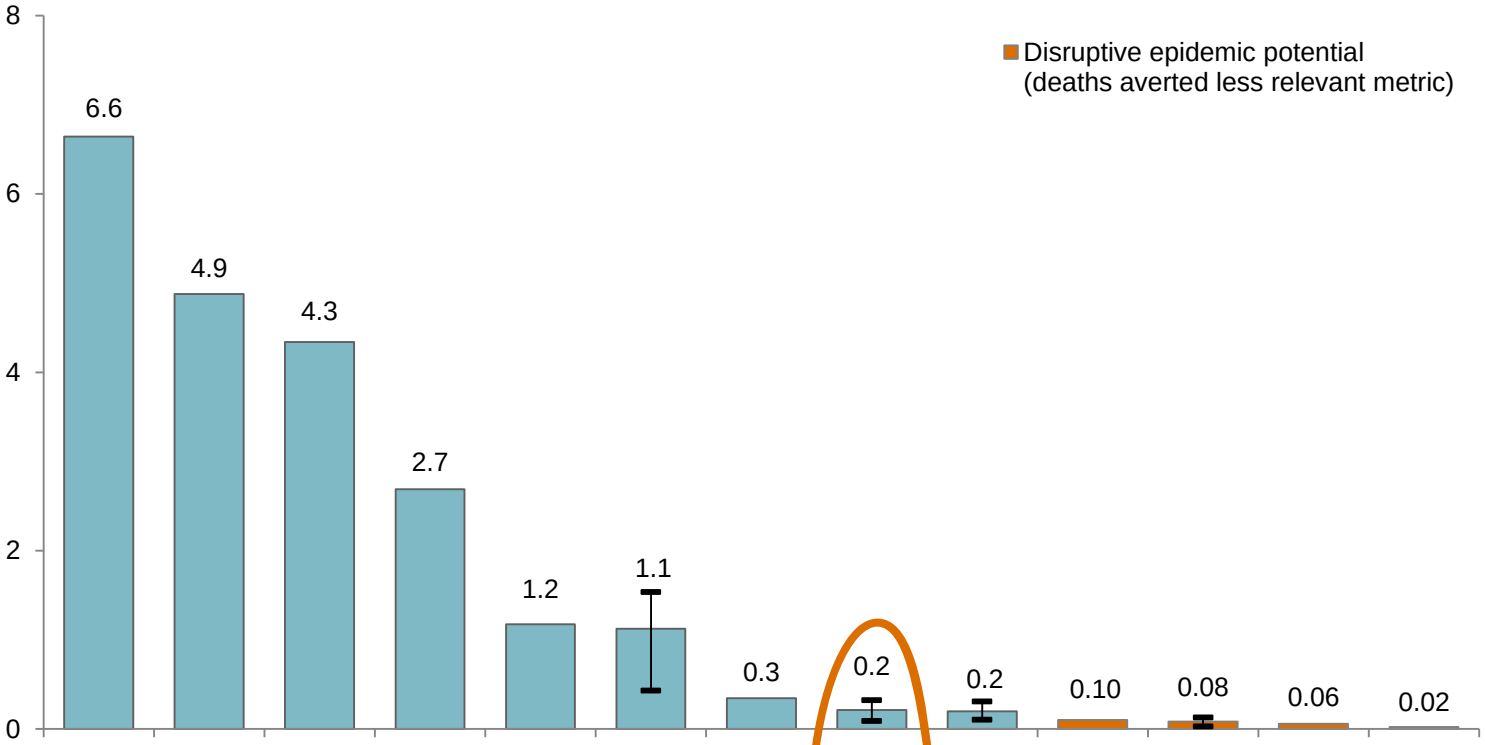


1. Based on deaths averted over 2015-2030; 2. VIS only

Note: model outputs shown for introductions in 45 GAVI-eligible countries for illustrative purposes; error bars show highest and lowest value generated by influenza sensitivity analyses and are driven by uncertainties in baseline infant mortality
Source: VIS analysis

Low impact relative to existing GAVI portfolio due to comparatively small disease burden

Future deaths averted, 2015–2030 (M)



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

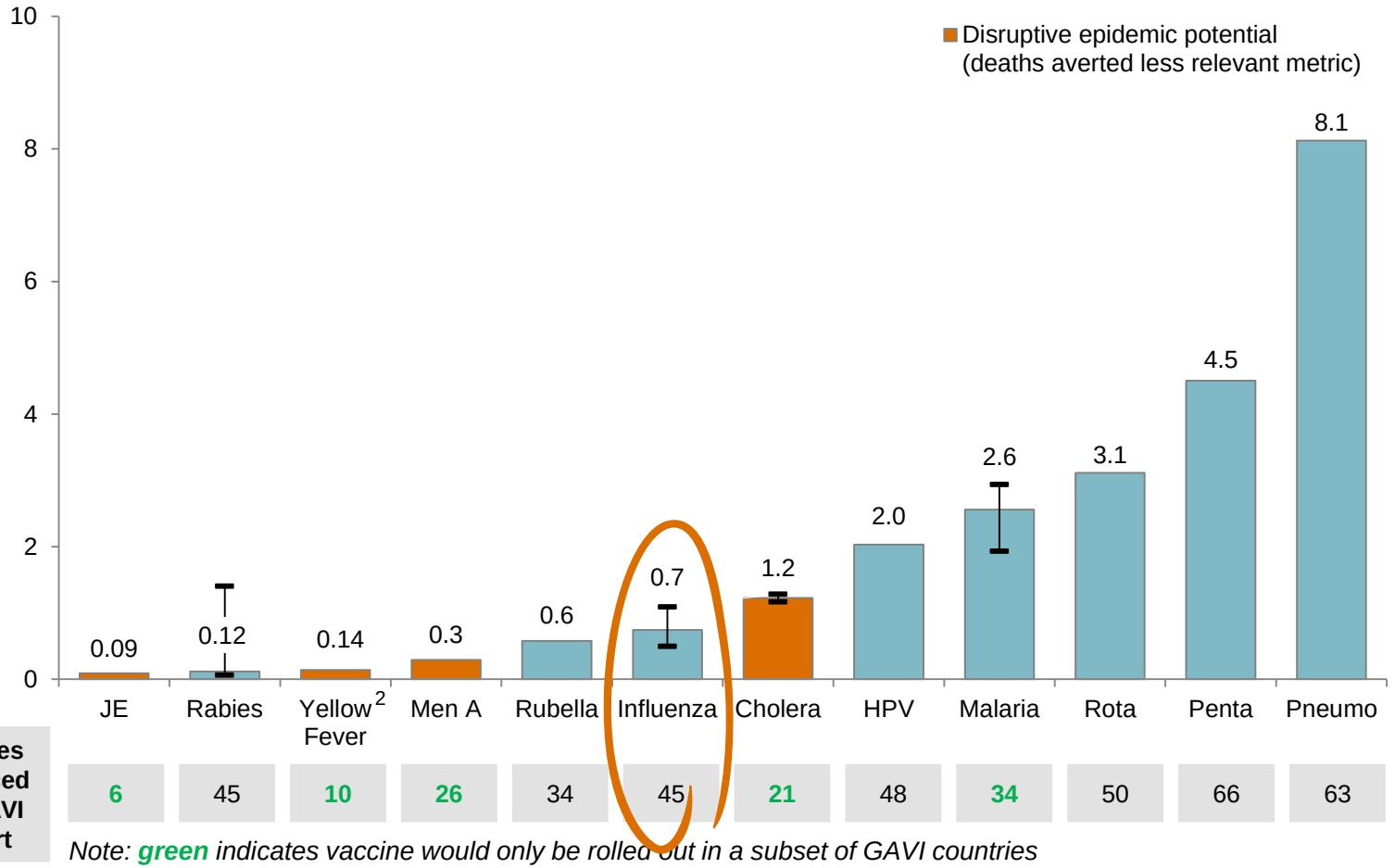
1. VIS only

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

Note: model outputs shown for introductions in 45 GAVI-eligible countries for illustrative purposes; error bars show highest and lowest value generated by influenza sensitivity analyses and are driven by uncertainty in baseline infant mortality
Source: VIS analysis

Moderate total cost of influenza vaccine support window

Total cost to GAVI, 2015–2030 ($B)[1]

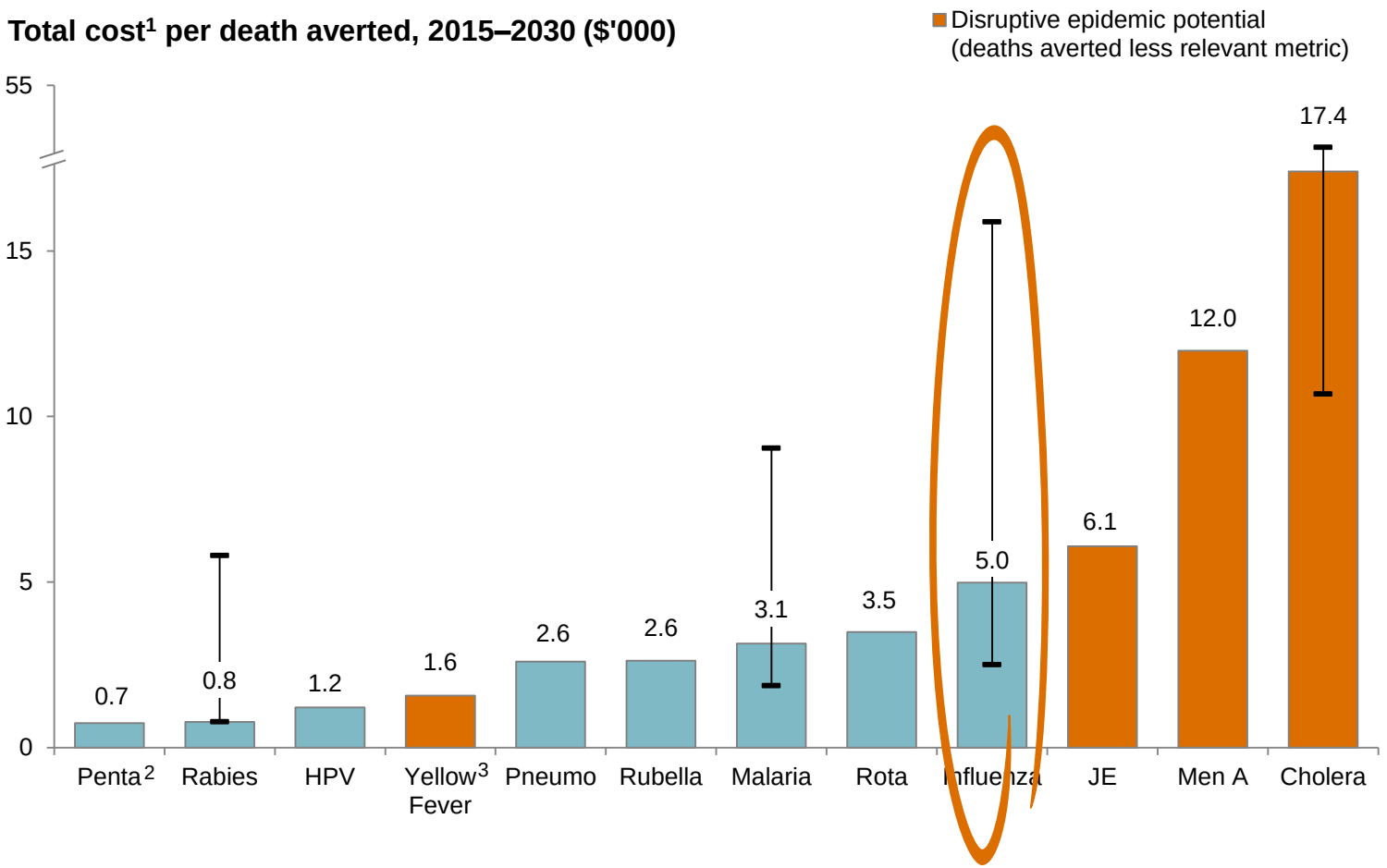


*Note: **green** indicates vaccine would only be rolled out in a subset of GAVI countries*

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

Note: Model outputs shown for introductions in 45 GAVI-eligible countries for illustrative purposes; error bars show highest and lowest value generated by influenza sensitivity analyses and are driven by vaccine price assumptions; Source: GAVI Financial Forecast v7.0Fb as of July 2013, VIS analysis

Significant uncertainty on influenza value for money



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 introductions in 45 GAVI-eligible countries for illustrative purposes; error bars based on highest cost / lowest impact and lowest cost / highest impact as generated in sensitivity analyses
Source: GAVI Financial Forecast v7.0Fb as of July 2013, VIS analysis

Initial evidence of additional benefits to fetus/ newborns with potentially significant impact

Note: not included in VIS impact estimates

Initial evidence of maternal influenza immunisation benefit to fetus / newborn[1]

Prevention of preterm birth

- 17% prevented fraction (odds ratio CI: .55-1.26) across all seasons[2]

Increase in birth weight

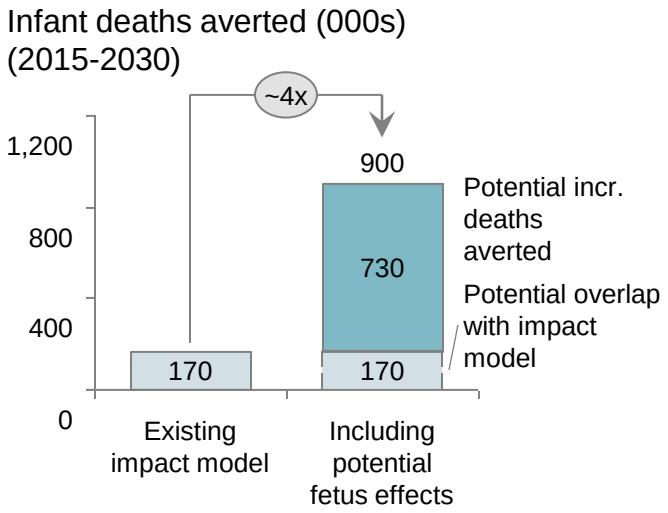
- Increase of 200g (CI: 191-209) in mean birth weight during putative flu season[3]

Reduction in small for gestational age (SGA) births

- Percent SGA decreases from 45% (CI: 31-57) to 26% (CI: 14-36) when flu circulating[3]

These three effects have potential for life-long benefits to mortality and morbidity, but significant variability in results across studies[4] and limited data on link to long-term health outcomes; to be further validated / refuted in future studies

Rough calc. suggests, if confirmed, impact to fetus potentially ~4x larger than impact to infants < 6 months



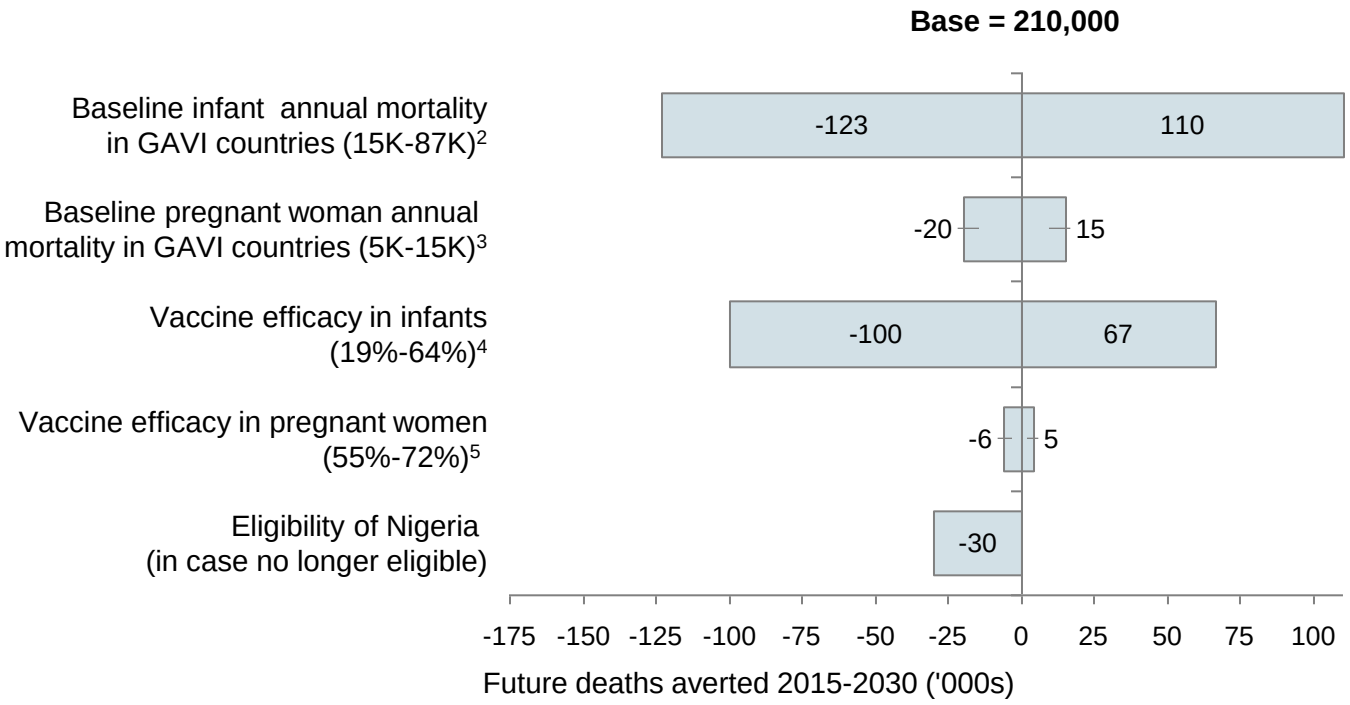
Calculation based on preventing 17% of U5 deaths from preterm birth complications[5]

Quantification is rough given limited studies and lack of data on long-term outcomes; thus, ***not included in VIS impact model***

1. List of studies not exhaustive; meant to show examples of effects on fetus / newborn 2. Omer et al. 2011 3. Steinhoff et al. 2012; base birth weight is ~3kg 4. Additional sources: McNeil et al. 2011, Mendez-Figueroa et al. 2011, Piece et. al 2011 5. Assumes 17% of U5 deaths from preterm birth complications (CHERG) could be avoided; scaled to reflect vaccination of 450M mothers per GAVI demand forecast; see appendix for details

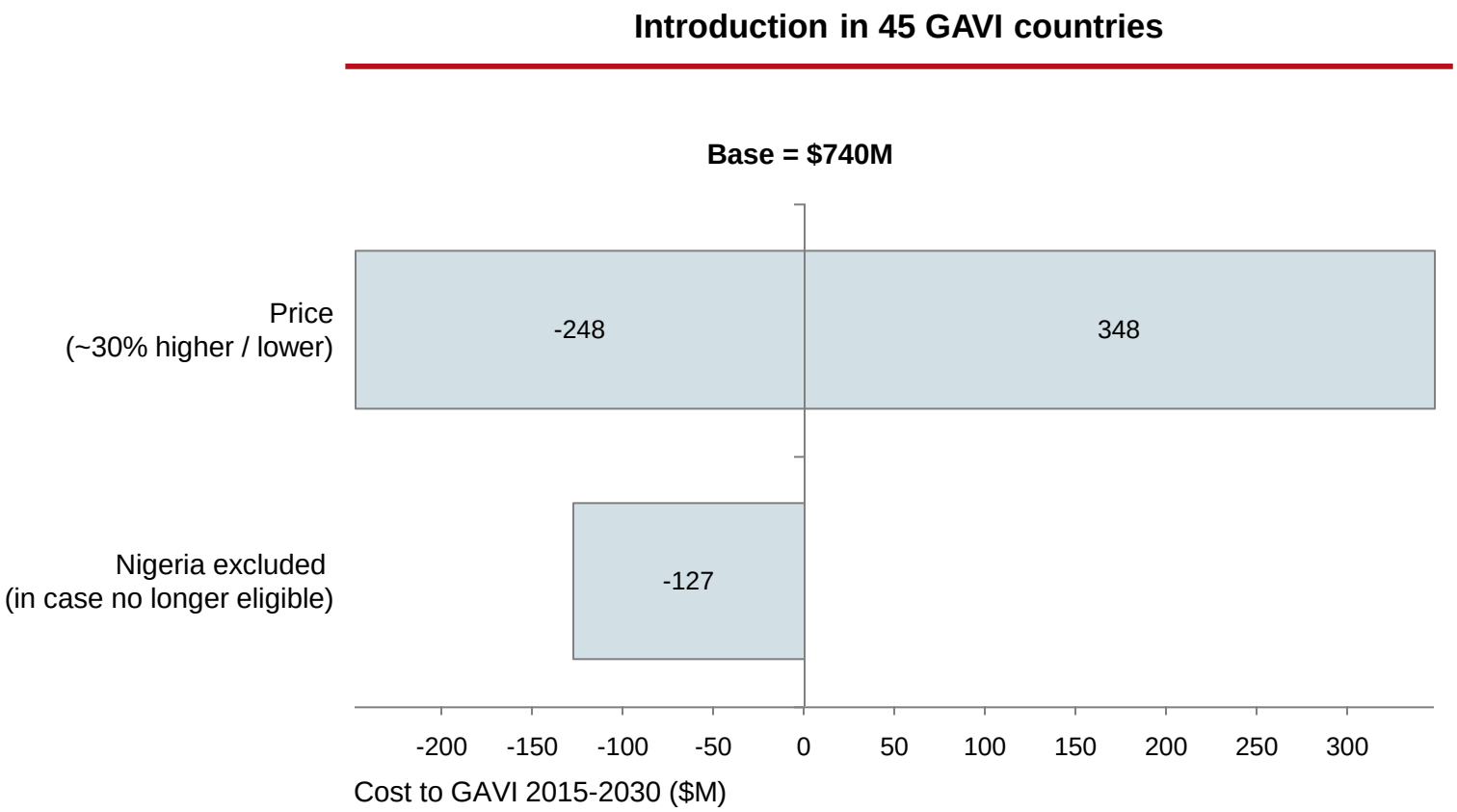
High uncertainty on health impact estimates due to sensitivity on burden & vaccine efficacy

Introduction in 45 GAVI countries[1]



1. Assumes high uptake in GAVI-eligible countries 2. Based on confidence intervals from IHME and CHERG influenza / pneumonia burden data and confidence interval of percent of pneumonia deaths due to influenza, from Walker et al. 2013
3. Upper bound based on confidence interval on risk ratios of death from influenza in pregnant women vs. general population, from Kerkhove et al. 2011; lower bound assumes pregnant woman risk is equal to general population 4. Based on meta-analysis of vaccine effectiveness in lab confirmed influenza from the following studies: Zaman, Poehling, Eick, and Benowitz
5. Based on confidence intervals from a draft study from Orenstein

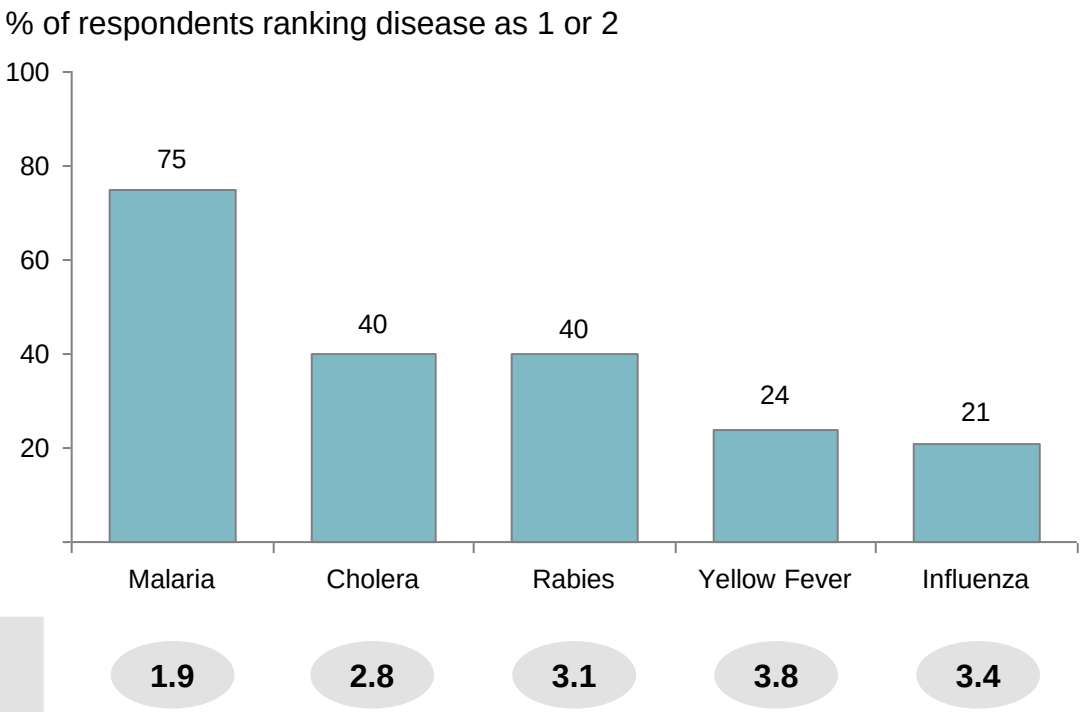
Key uncertainties underlying costs are price and inclusion of Nigeria



Note: Baseline assumes high uptake in GAVI-eligible countries

Influenza vaccine is lowest priority for survey respondents

Survey respondents: influenza vaccine ranked as lowest priority for country introductions



Quotes from in-depth country interviews

"Data is important to convince decision makers. We need to understand the burden... [influenza] not seen as high mortality and morbidity"

"Many cannot differentiate influenza from the common cold"

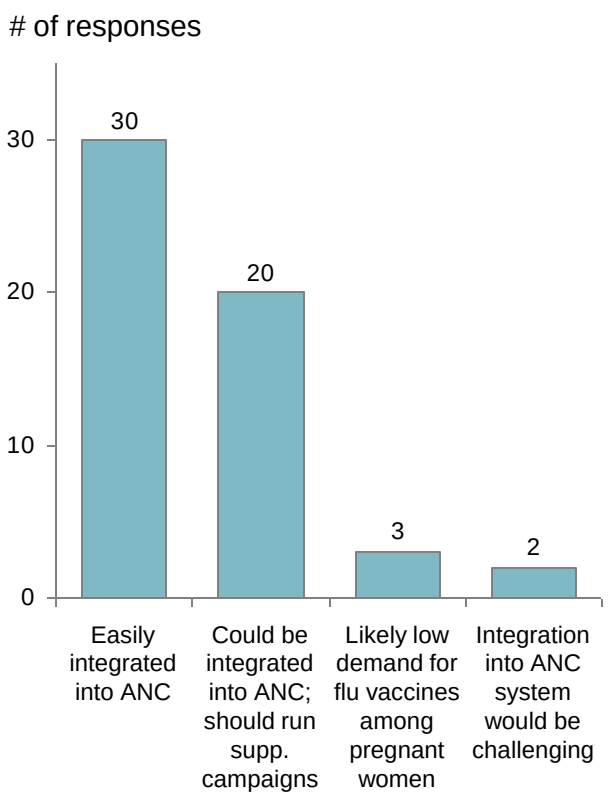
“We have no good flu surveillance in [my country]"

"Concerns about expiry. I recently saw 2011 H1N1 vaccines still sitting in the cold store"

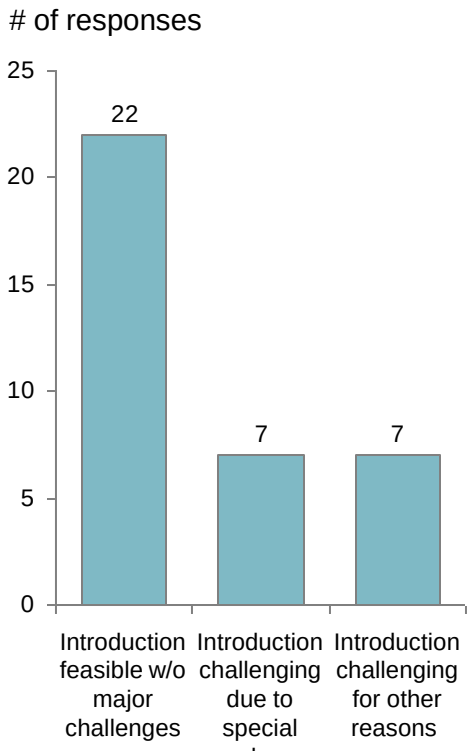
Source: 2013 GAVI country consultation survey, total responses = 182, 87 from countries in scope for GAVI support of influenza
Question: Please rank all of the following vaccines in terms of prioritisation for future introduction in your country

Respondents believe possible to integrate vaccine in ANC & overcome seasonal supply challenges

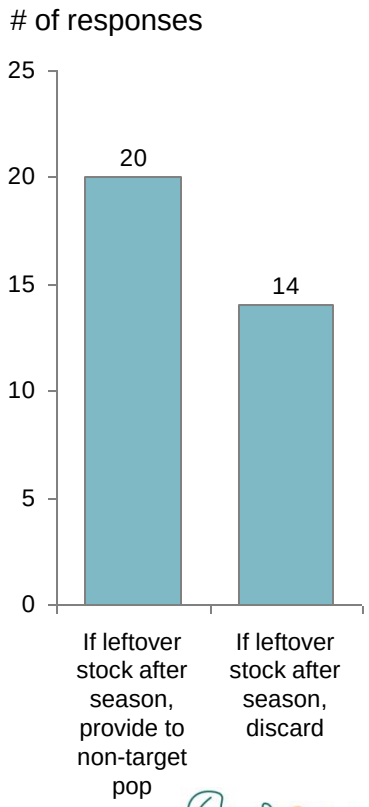
Ease of integration with antenatal care in your country?



Ease of logistical challenges associated with seasonal vaccine?



Use of leftover stock at the end of the season



Source: 2013 GAVI Phase II country consultation survey, total n = 182; influenza-specific questions asked only to respondents ranking influenza as a first of second priority for introduction in their countries

Potential challenges with seasonal supply logistics and awareness/demand generation

	Area of focus	Unique implementation requirements	Unique costs
Global level	Policies and processes	▪ Coordination with vaccine community to develop strain recommendations for tropical countries and/or adapt expiration dates	▪ Focused organizational effort
Global level	Supply	▪ Capacity exceeds demand today and the surplus is projected to continue	▪ N/A
Country level	Health workforce	▪ Staff already in place at antenatal care clinics; integration (e.g., with Tetanus Toxoid vaccine delivery) should be straightforward	▪ N/A
Country level	Social mobilisation, education, communication	▪ Build awareness and generate demand at multiple levels – national policy makers, pregnant women, health care workers	▪ May require ADIP-type investment
Country level	Supply chain infrastructure and logistics	▪ Manage logistics of supplying antenatal care clinics with both northern and southern hemisphere vaccines for countries with year-round influenza	▪ Cost accounted for in operational costs[1]
Country level	Supply chain infrastructure and logistics	▪ Potential cold-chain capacity issues if vaccine released in bolus and subsequently stored in country facilities ▪ Manage use of remaining doses in other age groups	▪ Cost accounted for in operational costs[1]
Country level	Surveillance	▪ Build surveillance data (incl. Adverse Events Following Immunisation) and disseminate to decision makers at all levels; surveillance levels have improved since 2009 pandemic	▪ May require ADIP-type investment
Country level	Planning, coordination, integration	▪ N/A	▪ N/A

Unique but manageable

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

1. Expected to be covered by introduction grant, MoH, partners

Options for an influenza investment

Open funding window for influenza vaccines

Do not open a funding window for influenza vaccines now

Monitor outcomes of three ongoing studies that are testing vaccine efficacy and safety in infants, mothers, and fetus and potentially reconsider in next VIS

Recommended option

Potential preparatory activities to support reconsideration of influenza in next VIS

Objectives

Acquire additional data on implementation feasibility

- Logistics of seasonal supply
- Delivery strategy
- Regulatory and policy issues
- Demand generation

Goal would be to inform future GAVI decision (e.g., next VIS) around whether to support influenza vaccination

Key questions / activities

Supply and logistics

- What is the optimal approach to allow year-round supply: for manufacturers to release vaccine throughout the year (as opposed to a bolus at start of temperate flu season) or for countries to store the vaccine throughout the year?
- What are the implications of a year-round strategy on country cold-chain capacity?
- To what degree can influenza leverage the distribution platform of maternal and child health services and/or EPI?

Delivery strategy

- Would a campaign based approach (as opposed to year-round routine delivery) be preferable in any countries, in terms of operational feasibility and/or impact?

Regulatory and policy

- Are regulatory and policy changes needed (e.g., expiry date) and if yes, how can they be expedited?

Demand generation

- Analyze/re-package and disseminate data on burden of disease and health impact

Implications of no GAVI support

Preserves the status quo: influenza is 'silent' health burden in GAVI-eligible countries

- Awareness and demand remain low
- No or slower progress made on policy recommendations and implementation steps needed for effective influenza supply in GAVI-eligible countries

Influenza: experts and sources consulted

Sources

- IHME Global Burden of Disease Study (2010)
- Evaluate Pharma product reports
- Manufacturer vaccine data
- WHO Influenza Position Paper (2012)
- WHO Influenza Fact Sheet (2012)
- WHO Influenza Programmes and Projects (2012)
- "Maternal Influenza Immunization Convening", Bill and Melinda Gates Foundation (2011)
- "Global burden of respiratory infections due to seasonal influenza in young children: a systematic review", Nair et al. (2011)
- "Global, regional, and national causes of child mortality: an updated systematic analysis for 2010", CHERG (2010)
- "Influenza is a major contributor to childhood pneumonia in a tropical developing country", Brooks et al. (2009)
- WHO unpublished study
- "Risk factors for severe outcomes following 2009 influenza A (H1N1) infection", Kerkhove (2011)
- "Effectiveness of maternal influenza immunization in mothers and infants", Zaman et al. (2008)
- "Neonatal outcomes after influenza immunization during pregnancy: a randomized controlled trial", Steinhoff et al. (2012)
- "Influenza vaccine strategies for broad global access", Oliver Wyman (2007)
- "Global production capacity for seasonal influenza vaccines in 2011", Partridge et al. (2013)
- "Incidence, seasonality, and mortality associated with influenza pneumonia in Thailand", Simmerman (2009)
- "Maternal Influenza Immunization and Reduced Likelihood of Prematurity and Small for Gestational Age Births: A Retrospective Cohort Study," Omer et al. (2011)
- "Maternal influenza vaccination and effect on influenza virus infection in young infants," Eick et al. (2011)
- "Impact of maternal immunization on influenza hospitalizations in infants" Poehling et al. (2011)
- "Global burden of childhood pneumonia and diarrhoea," Walker et al. (2013)
- "Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries," Rudan et al. (2013)
- "Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis," Nair et al. (2013)

Experts

- Niteen Wairagkar (BGMF)
- John Tam (WHO)
- Tony Mounts (WHO)
- Joachim Hombach (WHO)
- Sanofi
- GSK
- Kathy Neuzil (PATH)
- Justin Ortiz (PATH)
- Ahmadu Yakabu (WHO)
- Maurice Bucagu (WHO)
- Mark Steinhoff (Cincinnati Children's Hospital Medical Center)
- Mike Levine (U of Maryland)
- Saad Omer (Emory)
- Andrew Corwin (CDC)
- Joseph Bresee (CDC)
- Mark Jit (UK HPA)
- Alba Maria Ropero Alvarez (PAHO)
- Daniel Rodriguez (PAHO)
- Zulfiqar Bhutta (The Aga Khan University)
- Jon Abramson (Wake Forest)
- Evan Orenstein (Emory)
- Bruce Gellin (National Vaccine Program Office, US Department of Health & Human Services)
- Anthony Scott (London School of Hygiene and Tropical Medicine)

Appendix

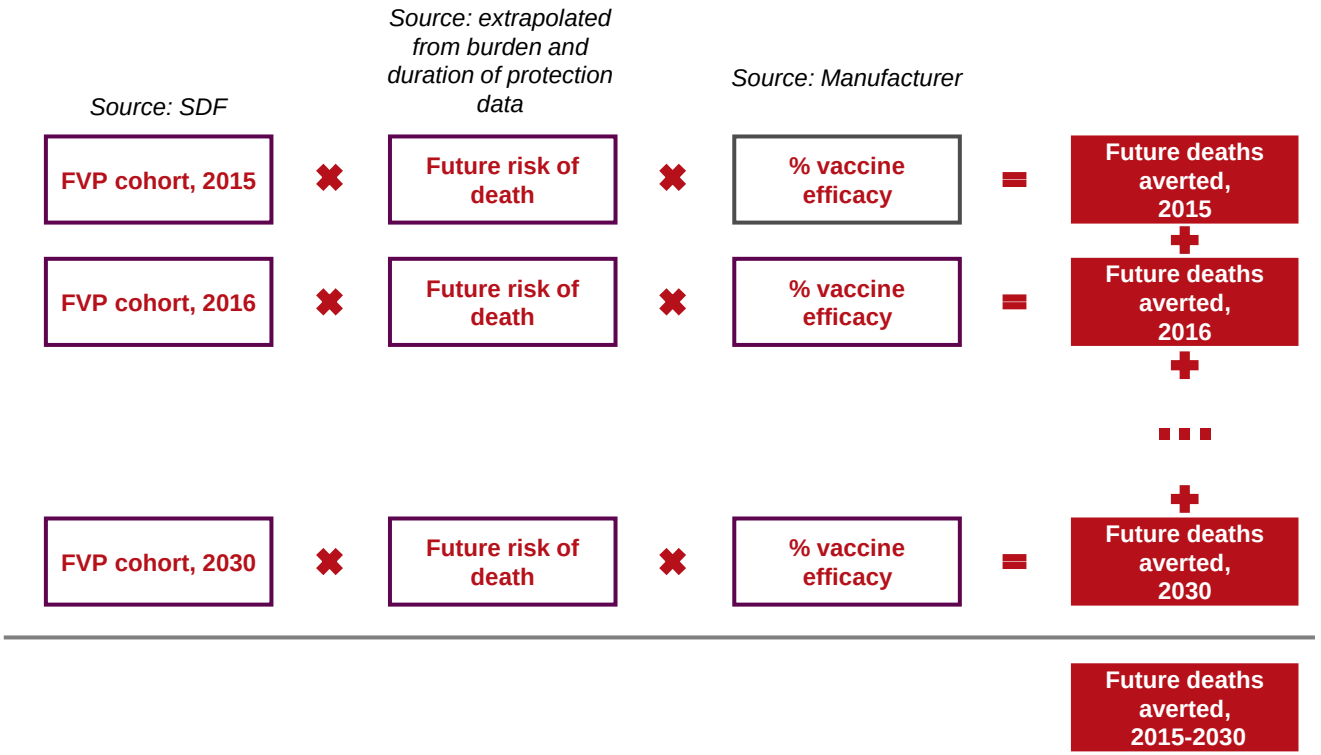
Demand forecasting assumptions

Modelled scenario: vaccinate pregnant women routinely at first antenatal care contact

Element	Assumptions	Rationale / source
Country scope	• 45 countries forecasted to introduce with GAVI support in 2015-2030 in full country scope scenario • 18 countries forecasted to introduce with GAVI support in alternative, conservative demand scenario	▪ 45 countries: Burden is global ▪ 18 countries: Demand is relatively low in GAVI-eligible countries as demonstrated by 2013 GAVI country survey
Target population	Pregnant women	▪ WHO recommended strategy ▪ Cost-effective
Introduction dates	First introduction: 2016	▪ Several vaccines available now
Uptake	2 to 4 years to max uptake, depending on country size	▪ New vaccine with analogue schedule
Coverage	ANC1 analogue	▪ Nearest analogue given administration at antenatal clinics
Products	Schedule: 1 dose Presentation: single-dose vial	▪ Standard intramuscular guidelines
Logistics	Wastage factor: 1.05	▪ WHO assumption for single-dose vial ▪ Excess, expiring supply could be used for other target groups or campaigns

Influenza impact modelling assumptions

Modelling approach



Key assumptions

- Deaths: ~15,000-100,000 global deaths annually in <6 month olds and ~10,000-25,000 in pregnant women (source: IHME, WHO, Kerkhove, CHERG, Brooks, Walker)
- Duration of protection: 1 year in pregnant women, 6 months in infants (source: WHO, Zaman)
- Vaccine efficacy: 55-72% in pregnant women, 19-64% in <6 month olds (source: pregnant woman value from draft paper by Orenstein; infant value from meta-analysis of Zaman, Benowitz, Eick, Poehling)
- Incidence assumed to remain constant at 2013 levels in absence of vaccine

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

Limitations of impact modelling

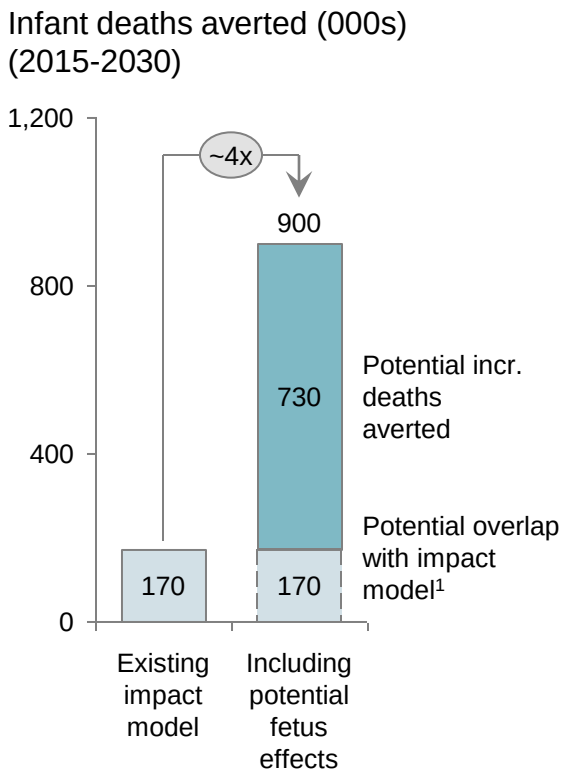
	Pregnant women	Infant
Influenza death / incidence rate	▪ Pregnant women risk ratios for death and incidence of H1N1 applied to all strains of influenza (Kerkhove study only done on H1N1) ▪ Independent relationship between probability of dying from flu and getting vaccinated ▪ Case definitions do not capture all influenza-positive illnesses (could be 10 times higher based on WHO attack rate)	▪ Proportion of pneumonia deaths and cases in children caused by influenza in GAVI-eligible countries is the same as the proportion of pneumonia cases associated with influenza in Bangladesh (10%, from Brooks) ▪ Independent relationship between probability of dying from flu and getting vaccinated ▪ Case definitions do not capture all influenza-positive illnesses (could be 10 times higher based on WHO attack rate)
Vaccine efficacy (VE)	▪ General adult population VE applied to pregnant women ▪ VE efficacy against lab-confirmed influenza directly translated to reduction in mortality	▪ VE in Bangladesh applied to other GAVI-eligible countries; possible differences across geographies, e.g., ▪ Health infrastructure, seasonality affecting positive predictive value of influenza rapid test ▪ VE efficacy against lab-confirmed influenza directly translated to reduction in mortality ▪ Follow-up in Bangladesh study was only through 6 months of age; duration of protection may be longer

Additionally, model does not account for potential effects to fetus/newborns or reductions in pandemic impact

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

Rough quantification of fetus effects: impact and calculation methodology

Rough estimation of deaths averted accounting for fetus effects



Methodology

	Step	Calc.	Source	Comment
1	Neonate deaths from preterm complications in flu country scope	500K	CHERG	2010 data
2	Infant population in flu country scope	42.3M	UN	2013 data
3	Average death rate from preterm complications	1.2%	Calc.	[1]/[2]
4	FVPs in flu country scope (2015-2030)	450M	Demand forecast	
5	Neonate deaths from FVPs if no vaccine	5.3M	Calc.	[3]*[4]
6	Prevented fraction of preterm births	17%	Omer	
7	**Deaths averted**	**900K**	**Calc.**	**[5]*[6]**
8	Infant deaths averted in impact model	170K	Model	
9	**Incremental deaths averted if estimates overlap**	**730K**	**Calc.**	**[7]-[8]**

1. Impact model already estimates potential reduction in infant influenza deaths, so only to avoid any overlap those deaths removed from potential impact of fetus effects

Source: "Global, regional, and national causes of child mortality: an updated systematic analysis for 2010", CHERG (2010); Omer et al. "Maternal Influenza Immunization and Reduced Likelihood of Prematurity and Small for Gestational Age Births: A Retrospective Cohort Study" PLOS (2011)