# Rabies

## Vaccine Investment Strategy

*Background document #4*

*November 2013*

# Executive Summary

**Rabies vaccines (post-exposure) could avert ~198,000 future deaths over 2015-2030 at a low total cost per death averted relative to other GAVI vaccines**

- GAVI investment would supplement existing public and private supply of post-exposure prophylaxis vaccines, aiming to meet unmet demand
- GAVI involvement could be an opportunity to shift countries to intradermal administration (may require off-label use); 60%-80% lower cost relative to status quo (intramuscular)

**But, due to several challenges and special requirements for effective implementation this impact could be difficult to achieve**

- Demand forecasting challenges: large uncertainty around treatment-seeking assumptions
- Risk of displacing public / private vaccine and government funding (though in many GAVI-eligible countries PEP supply and distribution are inadequate or nonexistent)
- Risk of de facto user fees and possible misuse of vaccine for profit-seeking purposes (private market); would require strict protocols to enable free provision of GAVI vaccine while avoiding excessive (unnecessary) use
- Demand-driven use requires more regular, reactive stock management (different from EPI vaccines) to avoid stock-outs
- Improved provision may not be sufficient to improve access/use; additional investments in health systems may be required
- For category 3 exposures, administration of Immunoglobulin is also required to achieve 100% PEP efficacy

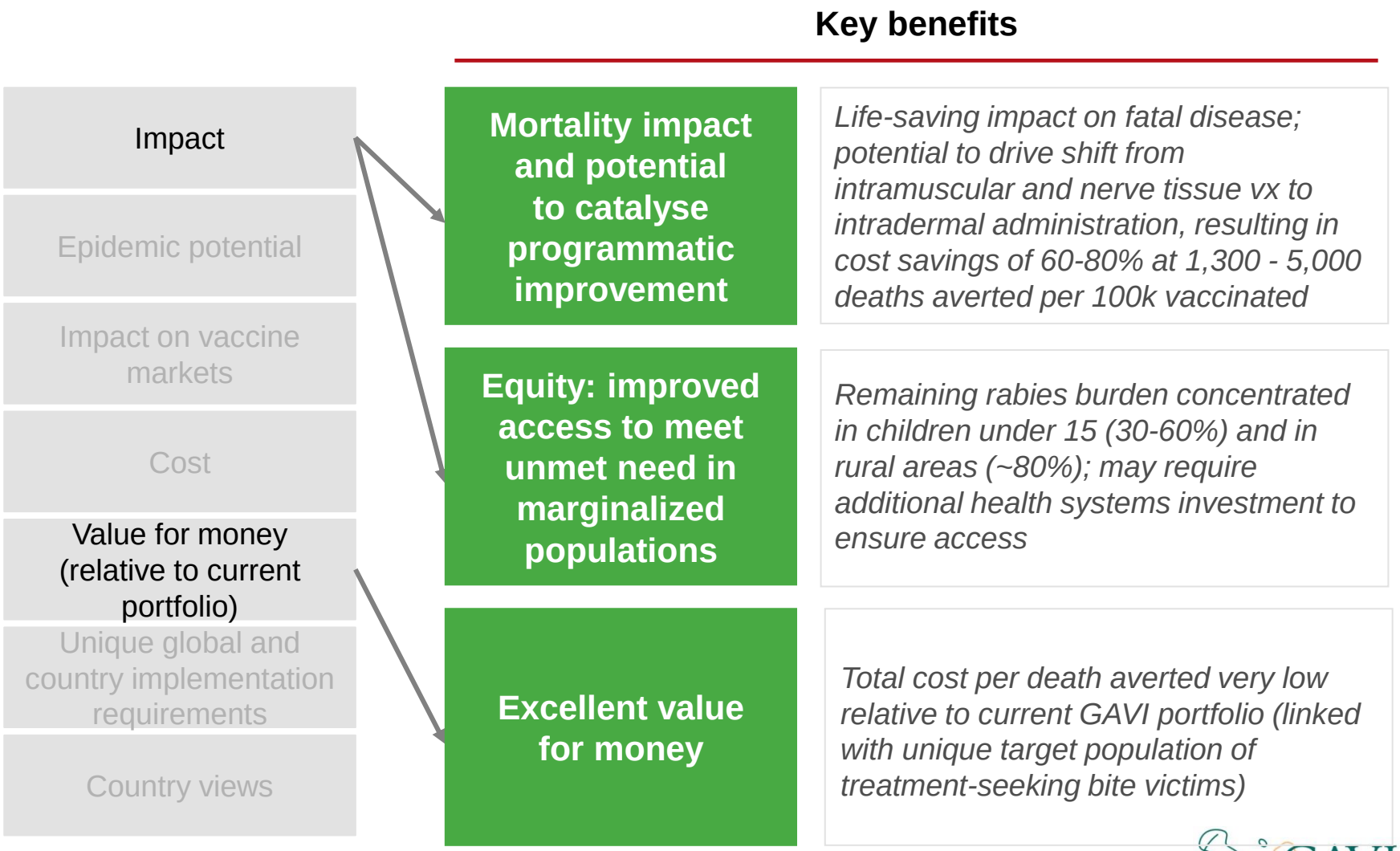
**Recommendation: conduct an assessment of the feasibility of GAVI support for rabies vaccines (to be evaluated in the next Vaccine Investment Strategy process)**

- Operational difficulties, uncertainty around demand and impact, and required changes to GAVI business model outweigh potential benefits of opening funding window
- Observational study to understand uncertainties around implementation feasibility so that rabies vaccine support can be appropriately considered in the future

GAVI ALLIANCE

# Key rabies vaccine benefits:

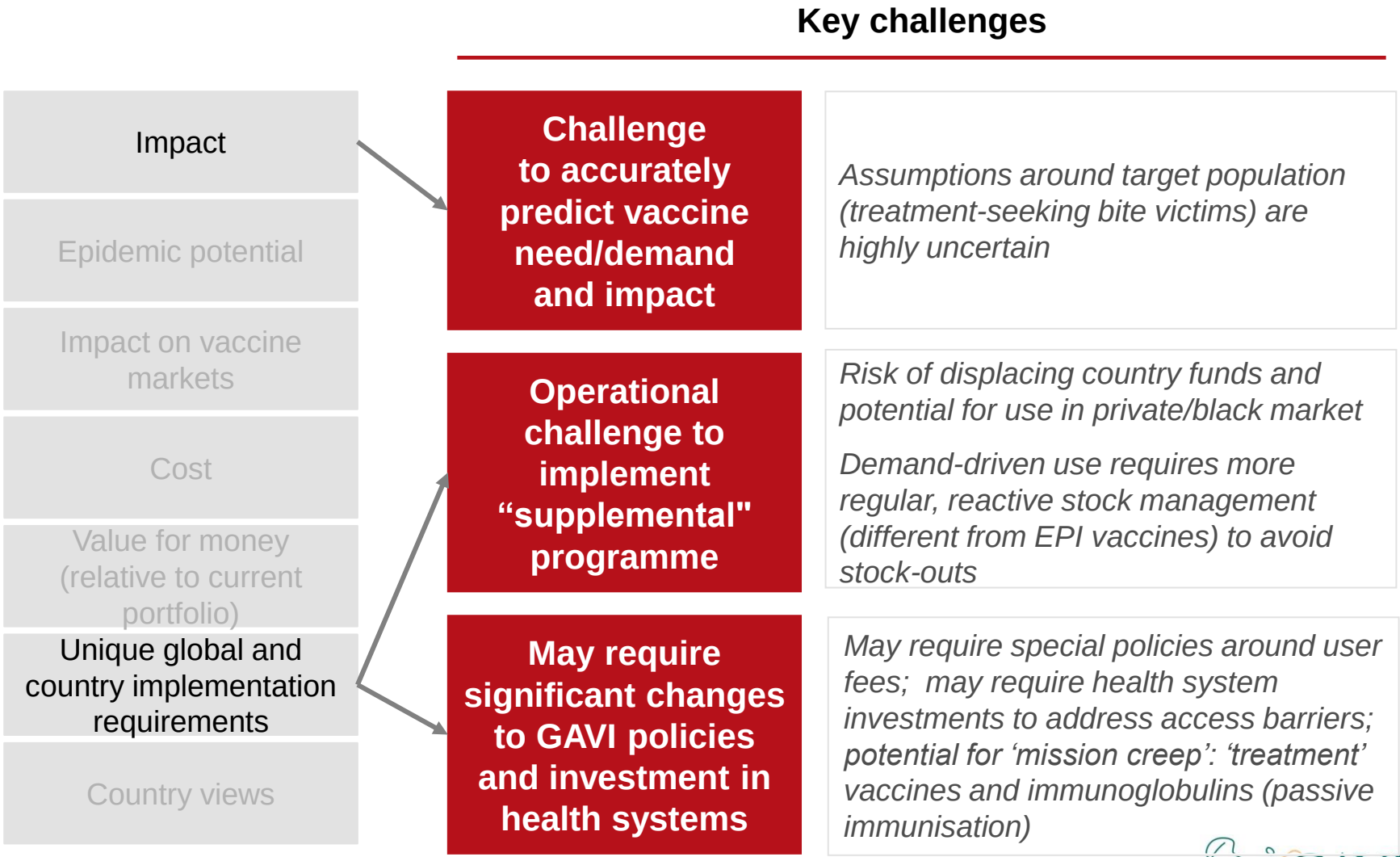
## Severe disease, value for money, opportunity to drive programmatic improvement




GAVI ALLIANCE

# Key rabies vaccine challenges:

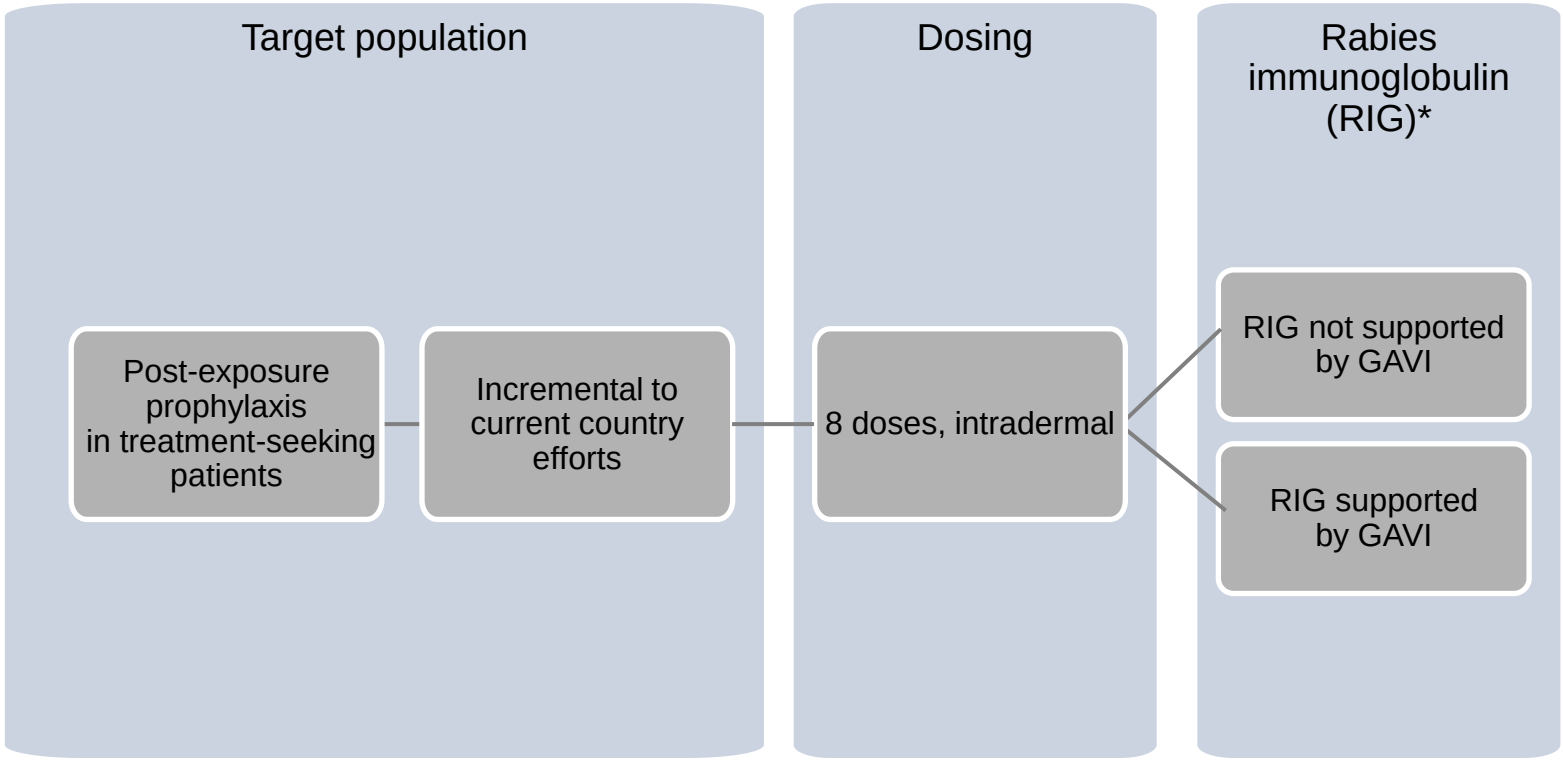
## Uncertain need, operational challenges, possible misalignment with GAVI model



# Rabies vaccine investment scenario:

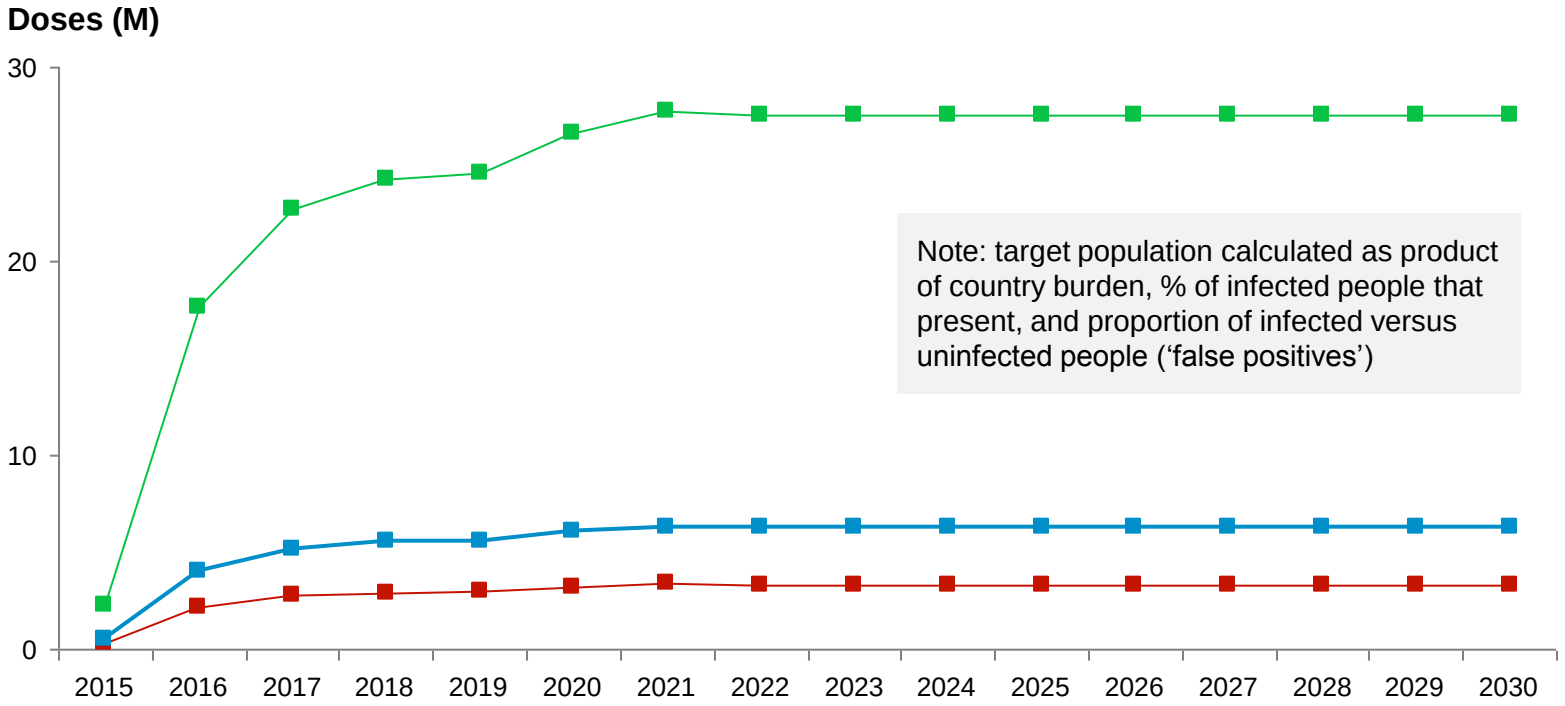
## Supplemental support for post-exposure vaccination (2 options)

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




*See slide 26 for details on rabies immunoglobulins as part of rabies post-exposure prophylaxis

# Cumulative demand estimated to be 48M - 393M doses through 2030 (intradermal use assumed)




| *# countries introducing* | *10* | *12* | *8* | *3* | *4* | *4* | *4* | *0* | *0* | *1* | *0* | *0* | *0* | *0* | *0* | *0* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

Upper bound of demand forecast[1] Lower bound of demand forecast[2] Point estimate[3]

1. Upper bound assumes 80% treatment completion, 99% treatment seeking, 1 in 75 PEPs prevent a death
2. Lower bound assumes 60% treatment completion, 45% treatment seeking, 1 in 20 PEPs prevent a death
3. Point estimate assumes 60% treatment completion, 85% treatment seeking, 1 in 20 PEPs prevent a death

Note: includes demand from countries that graduate from GAVI support during 2015-2030 (following GAVI supported introduction)
Source of ranges: Global Alliance for Rabies Control; Knobel et al.; expert consultations

# Potential to avert 198,000 deaths at total cost of $154M - $207M over 2015-2030

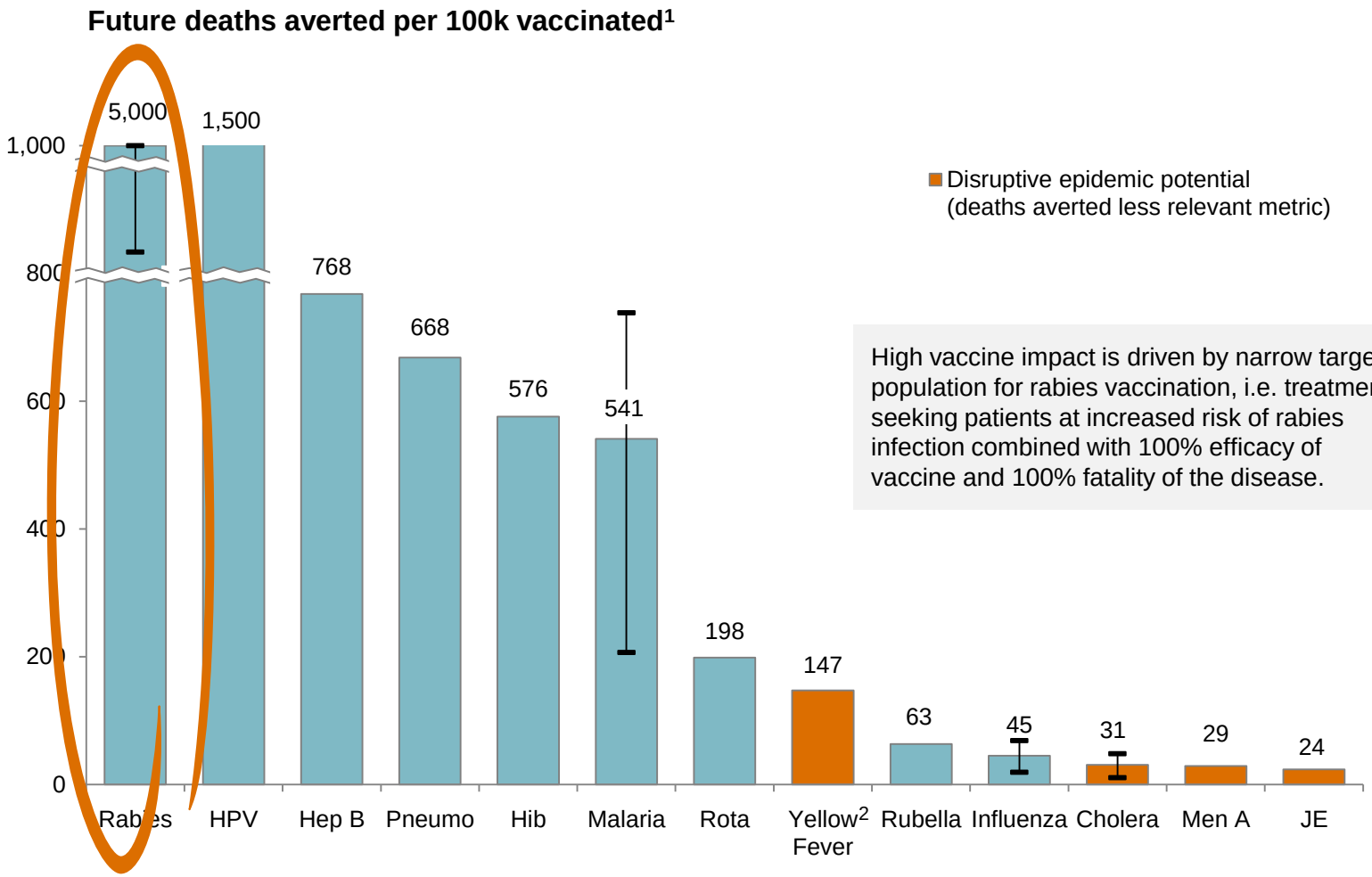
| | | Vaccine only[1] | Vaccine and rabies immunoglobulin[2] |
|---|---|---|---|
| Impact | Fully vaccinated persons | Vaccine: 4M | Vaccine: 4M<br>RIG: 2.6M |
| | Total future deaths averted | 198,000 | 198,000 |
| | Deaths averted per 100k vaccinated | 5,000 | 5,000 |
| Cost[1] | GAVI procurement cost | $112M | $164M |
| | GAVI introduction grant | $5M | $5M |
| | Total GAVI cost | $116M | $169M |
| | Country procurement costs | $29M | $29M |
| | Country operational costs | $9M | $9M |
| | Total cost | $154M | $207M |
| Value for money | Total cost per death averted | $780 | $1050 |

1. Assumes all fully completed rabies vaccination courses are effective in preventing rabies; 2. assumes midpoint of RIG coverage estimates modelled (40% of patients who present for treatment require and receive RIG), see slide 25

Note: counterfactual assumes countries continue their current level of rabies support; impact estimates assume no impact from partially completed courses of treatment or from extension of protection to additional rabies bites; cost estimates assume intradermal administration of rabies vaccine and use of equine rabies immunoglobulin

GAVI ALLIANCE

# High vaccine impact due to special 'target' population (not population-based)

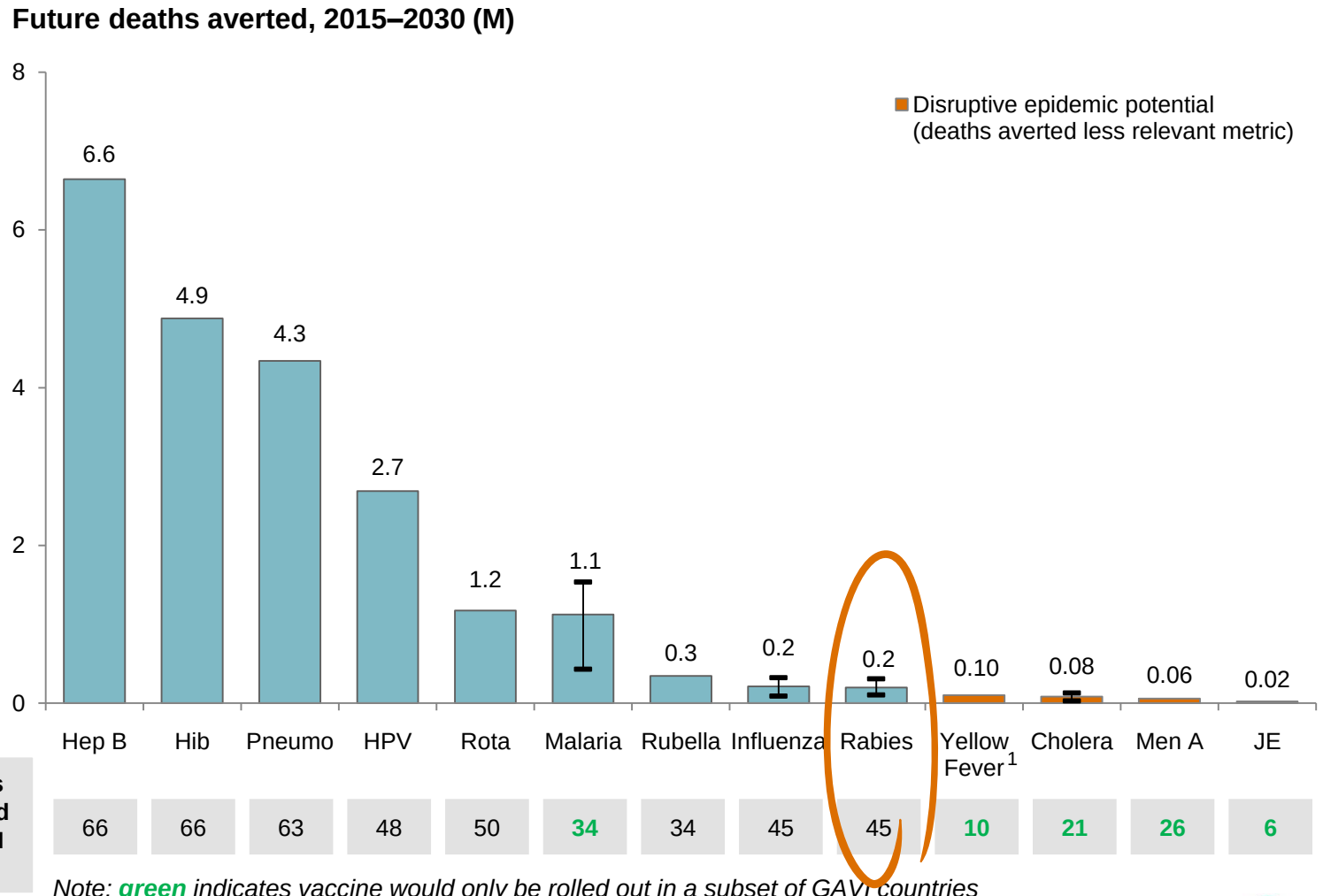



High vaccine impact is driven by narrow target population for rabies vaccination, i.e. treatment-seeking patients at increased risk of rabies infection combined with 100% efficacy of vaccine and 100% fatality of the disease.

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

Note: model outputs shown for intradermal administration; error bars show highest and lowest value generated by sensitivity analyses and are driven by assumptions on patient treatment seeking behavior; source: VIS analysis

# Low overall impact relative to existing programmes due to comparatively small global disease burden



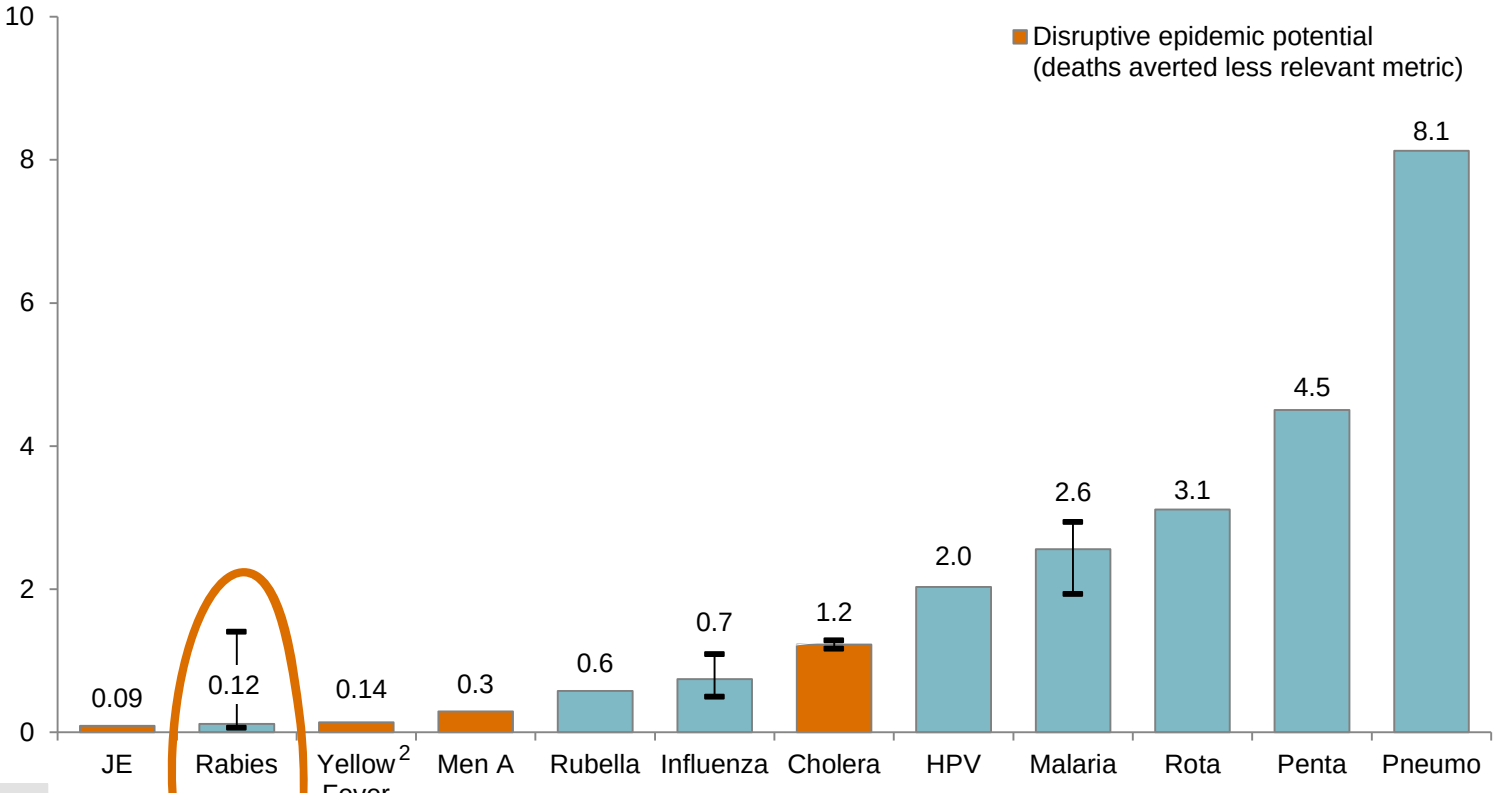

1. VIS only

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

Note: model outputs shown for intradermal administration; error bars show highest and lowest value generated by sensitivity analyses and are driven by patient treatment seeking behavior. Source: VIS analysis

# Cost to GAVI highly variable based on method of administration and treatment seeking behavior

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

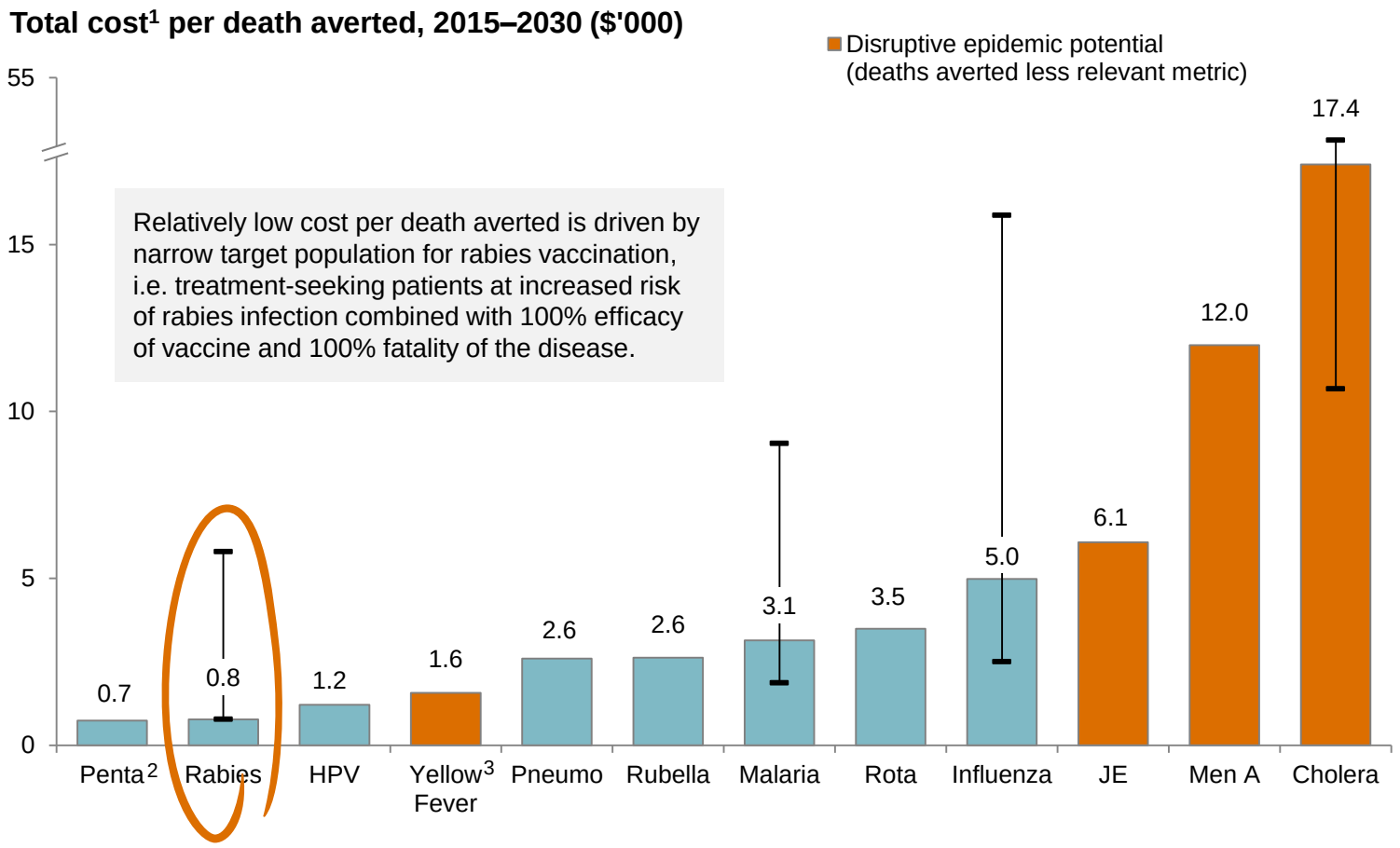



| Countries introduced with GAVI support | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 6 | 45 | 10 | 26 | 34 | 45 | 21 | 48 | 34 | 50 | 66 | 63 |

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

1. Includes GAVI procurement cost + vaccine introduction grants + GAVI operational cost grants; 2. VIS only
Note: model outputs shown for intradermal administration (vaccine only); error bars show highest and lowest value generated by sensitivity analyses and are driven by patient treatment seeking behavior and route of administration (intradermal vs intramuscular)
Source: GAVI Financial Forecast v7.0Fb as of July 2013, VIS analysis

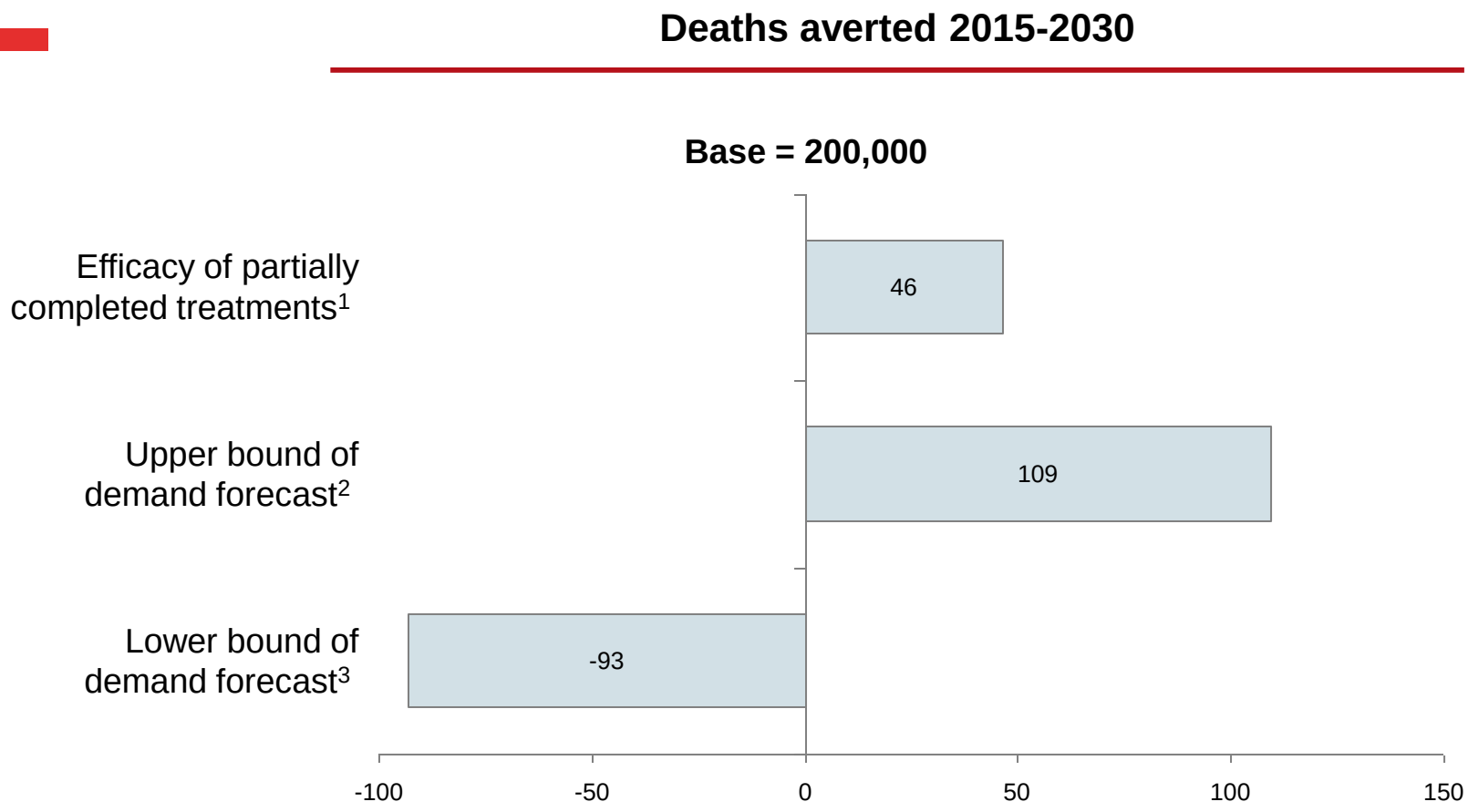
# Value for money also variable based on method of administration and treatment seeking behavior




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 intradermal administration (vaccine only); error bars based on highest cost / lowest impact and lowest cost / highest impact as generated by sensitivity analyses. Source: GAVI Financial Forecast v7.0Fb as of July 2013, VIS analysis

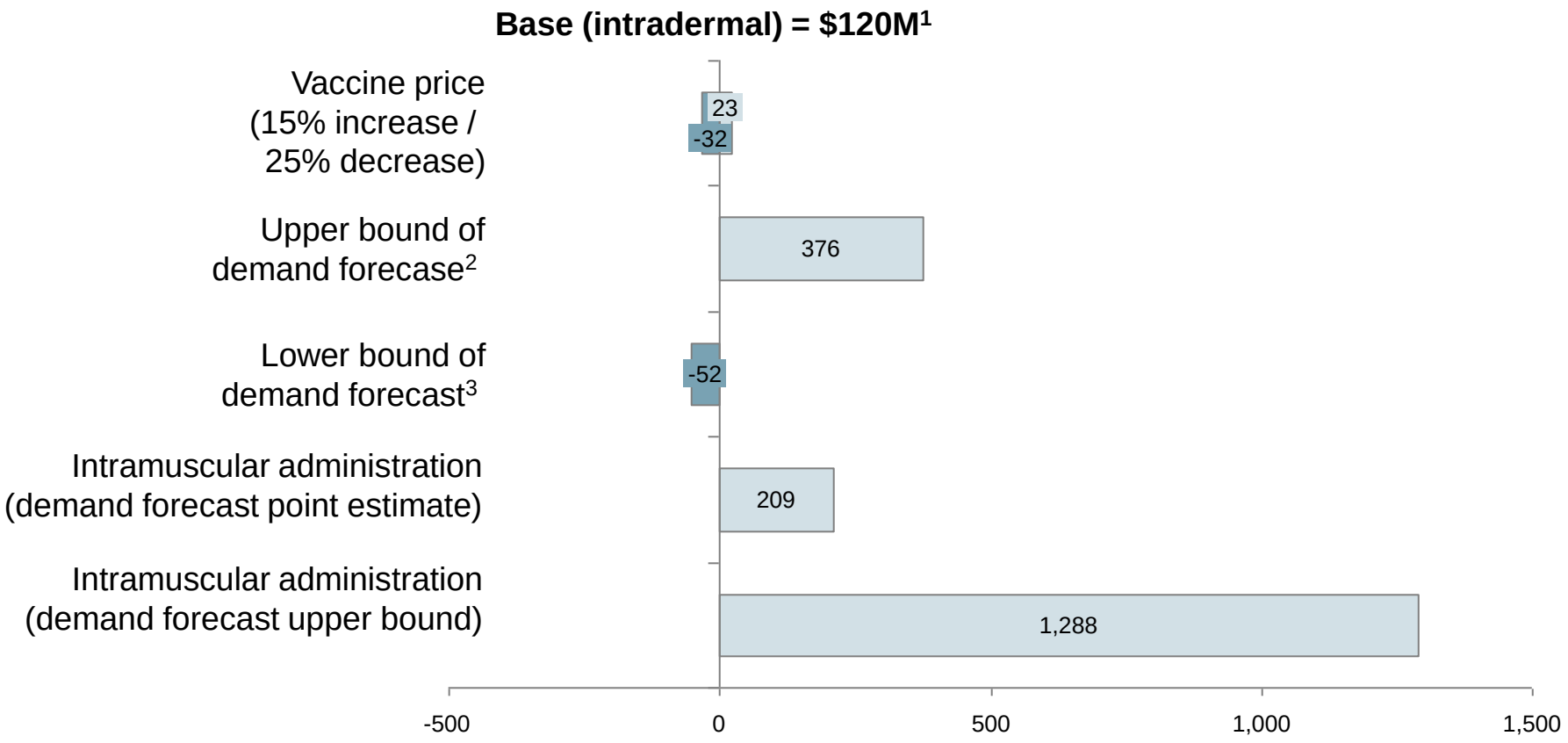
# Key uncertainty in impact is patient treatment seeking behavior




1. Models additional future deaths averted potentially driven by partially completed treatment, assuming 0% efficacy for 1 visit, 33% efficacy for 2 visits, and 100% efficacy for 3 visits; 2. Upper bound assumes 80% treatment completion, 99% treatment seeking, 1 in 75 PEPs prevent a death; 3. Lower bound assumes 60% treatment completion, 45% treatment seeking, 1 in 20 PEPs prevent a death

# Key uncertainties underlying cost are treatment seeking behavior and method of administration

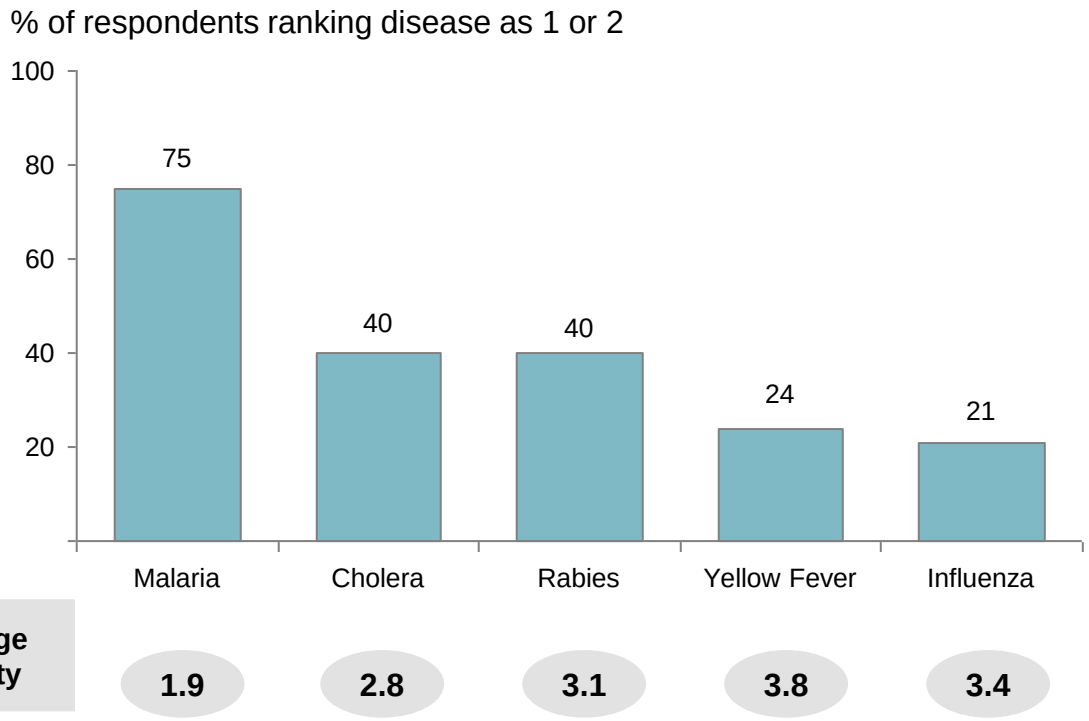
## Cost to GAVI




1. Total cost to GAVI 2. Upper bound assumes 80% treatment completion, 99% treatment seeking, 1 in 75 PEPs prevent a death 3. Lower bound assumes 60% treatment completion, 45% treatment seeking, 1 in 20 PEPs prevent a death

# About half of all country respondents indicated rabies as a priority

## Survey respondents: rabies ranked as second highest priority




## Quotes from in-depth country interviews

**"Rabies vaccine is very expensive"**

**"It's a serious problem in my country. No availability in most districts."**

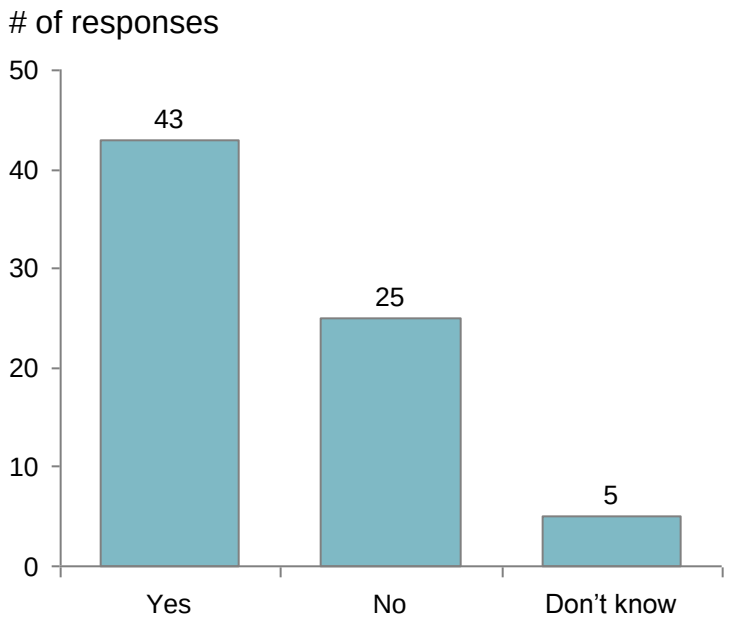
**"Bite victims go to the health facility (HF), then they need to go to the veterinary, who needs to write a report, then back to the HF. HF often does not have the vaccine. So they then need to go to hospital, get the vaccine vial, then back to the HF for administration"**

Source: 2013 GAVI country consultation survey, total responses = 182, 130 from countries in scope for GAVI support of rabies
Question: please rank all of the following vaccines in terms of prioritisation for future introduction in your country

# Mixed responses reflect diversity and/or lack of clarity on rabies programme

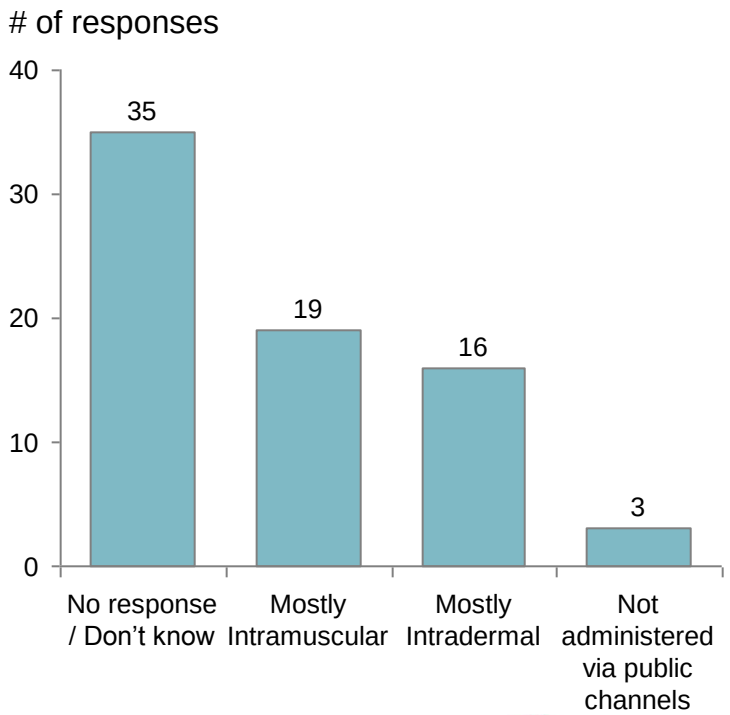
## Majority of respondent countries had rabies control program in place

***Question: Is there currently a rabies control program in place in your country?***




## Respondents split on method of vaccine administration

***Question: How is rabies vaccine typically administered via public channels in your country?***

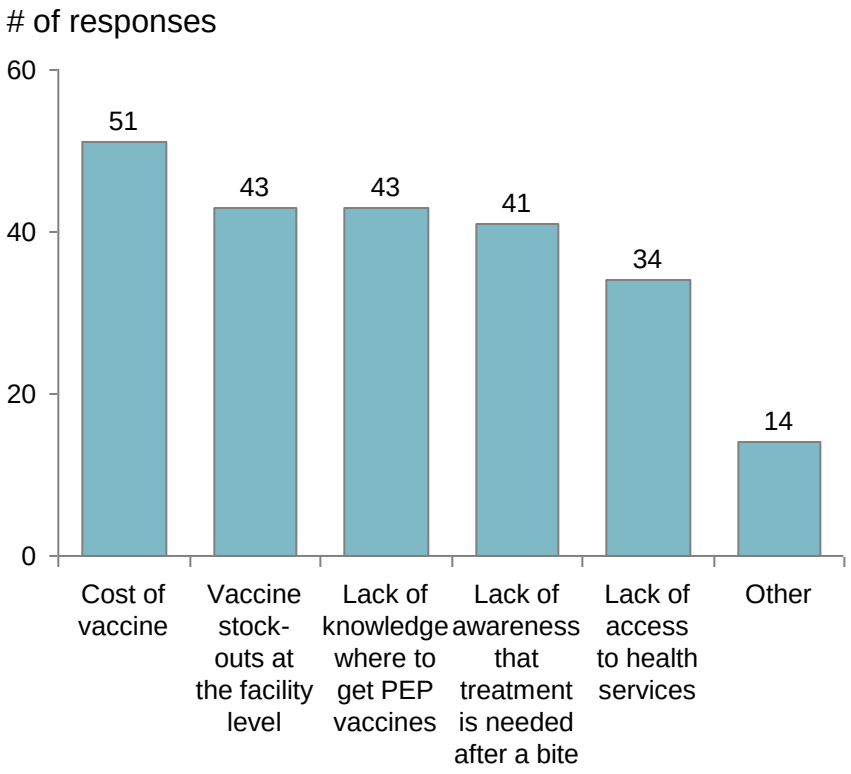



Source: 2013 GAVI Phase II country consultation survey, total n = 182; rabies-specific questions asked only to the respondents ranking rabies as a first of second priority for introduction in their countries

# Price is leading barrier to post-exposure prophylaxis vaccination

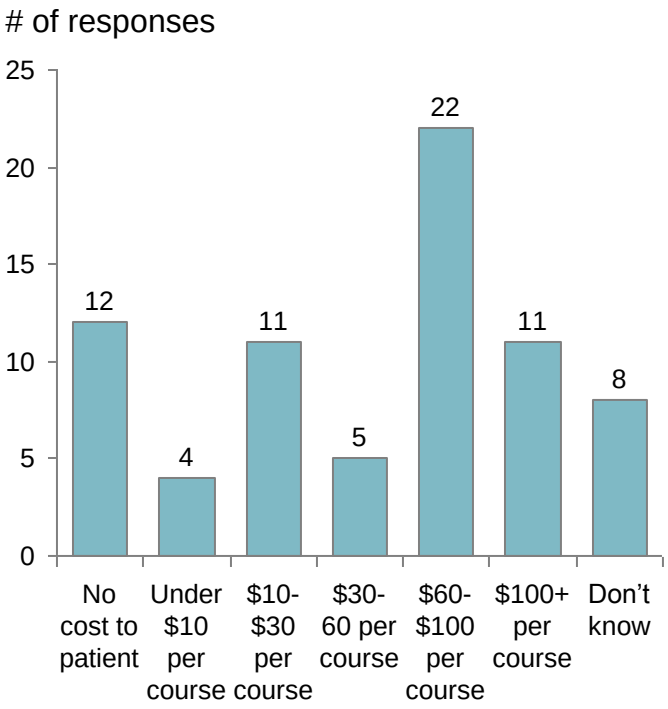
**Multiple barriers to getting treatment**

***Question: What are the key barriers for bite victims to access rabies post- exposure prophylaxis vaccines in your country?***




**Most common cost to patient is $60-$100 per course**

***Question: What are currently the avg costs to a patient in your country to receive a full treatment with rabies PEP vaccines?***




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

# Several unique implementation requirements, some may be significant risks

| | Area of focus | Unique implementation requirements | Cost |
|---|---|---|---|
| Global level | **Policies and processes** | ▪ Policies to prevent replacement of country funds<br>▪ Policies to manage integration of GAVI vaccine in existing market/programme where needed<br>▪ Policies to support provision of rabies immunoglobulin?<br>▪ Requirement that countries administer intradermal instead of intramuscular? | ▪ Cost TBD (further research needed) |
| Country level | **Supply** | ▪ Limited RIG supply | ▪ No direct costs |
| | **Health workforce** | ▪ Train health workers on intradermal administration | ▪ Cost accounted for in operational costs[1] |
| | **Social mobilisation, education, communication** | ▪ Inform population on how to access potentially complex vaccine provision network (public and private channels)<br>▪ IEC activities to raise awareness of risk and increase treatment seeking behavior in bite victims | ▪ Cost accounted for in operational costs[1] |
| | **Supply chain infrastructure and logistics** | ▪ Stock management (EPI restocking strategies may not be appropriate for rabies vaccine)<br>▪ Manage risk of vaccine 'leaking' to private market<br>▪ New rabies bite centers may be required (in addition to better supplying existing centers and use of existing facilities for PEP) to ensure coverage in hard to reach populations | ▪ Cost TBD (further research needed to define program) |
| | **Surveillance** | ▪ Policies and surveillance to prevent black market development | ▪ Cost TBD (further research needed) |
| | **Planning, coordination, integration** | ▪ Regulatory approval needed for intradermal administration in many countries | • Focused organisational effort |

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

Unique but manageable

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

# Options for a rabies investment

| Open funding window to support rabies PEP vaccination and RIG | Open funding window to support rabies PEP vaccination only | Do not open funding window; invest in assessment of feasibility of GAVI support for rabies vaccines (to be evaluated in the next Vaccine Investment Strategy process) | Do not to support rabies vaccine |
|---|---|---|---|

***Recommended option***

# Implications of no GAVI support

**Slower reduction in rabies burden due to funding constraints and fewer advocates for programmatic improvements; rabies remains a neglected tropical disease**

# Rabies: experts and sources consulted

## Sources

- IHME Global Burden of Disease Study 2010
- WHO rabies 2010 position paper
- Evaluate Pharma product reports
- Manufacturer vaccine data
- GAVI 2008 VIS rabies analysis
- Mortality Survey: Rabies in India, Suraweera et al.[1]
- WHO Neglected Tropical Diseases report
- PAHO newsletter February 2012 (pricing)
- Hampson et al., " Rabies Exposures, Post-Exposure Prophylaxis and Deaths in a Region of Endemic Canine Rabies,"
- Knobel et al., "Re-evaluating the burden of rabies in Africa and Asia"

## Experts consulted

- Francois Meslin (WHO)
- Anastasia Pantelias (BMGF)
- Sanofi Pasteur
- Serum Institute of India
- Deborah Briggs (GARC)
- Bernadette Abela Ridder (WHO)
- Martin Friede (WHO)
- Erin Sparrow (WHO)
- Lea Knopf (GARC)
- Katie Hampson (University of Glasgow)
- Charles Rupprecht (GARC)
- Betsy Miranda (GARC)
- Stanley Plotkin
- Julien Potet (MSF)

# Appendix

# Detailed demand forecasting assumptions (1 of 2)

## Base scenario

| Element | Assumptions | Rationale |
|---|---|---|
| Country scope | • 53 countries in scope<br>• 46 forecasted to introduce with GAVI support in 2015-2030 | • Burden concentrated in Africa, Asia |
| Target population | Bite victims that are not currently receiving treatment in GAVI countries<br>• % of infected bite victims that would present for treatment: 85%<br>• Victims receiving PEP that were infected: 1 in 20 | GAVI would not replace existing funding; all support would be additive |
| Introduction dates | First available: 2015<br>Timing of subsequent introductions based on disease burden and timing of penta intro | Vaccines already on the market and prequalified |
| Uptake | N/A | Rabies vaccination infrastructure already in place in most GAVI countries |
| Coverage | Demand met : 100%<br>Fully vaccinated population: 60% | Per expert consultations and Tiembre (2008 & 2009) |
| Products | ID Schedule: Thai Red Cross (2x2x2x0x2)<br>Presentation: single-dose vial for IM administration | ID dosing offers significant cost savings over IM (less vaccine required); would reduce burden on country health systems |
| Logistics | Wastage factor: 1.67<br>No buffer due to flat target population | WHO indicative wastage rates for 10 to 20 dose presentations that must be discarded at the end of session or max 6 hours from opening |

# Detailed demand forecasting assumptions (2 of 2)

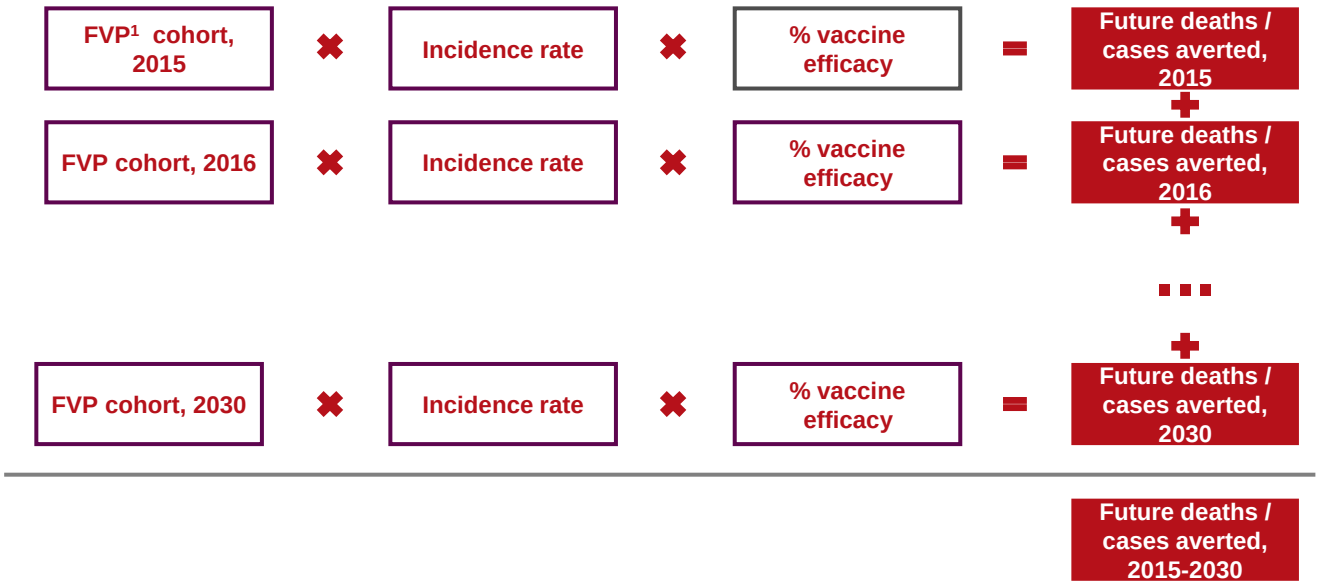
## Alternative high and low scenarios

| Element | Assumptions | Rationale |
|---|---|---|
| **Country scope** | Idem | idem |
| **Target population** | % of infected bite victims that would present for treatment:<br>• High: 99%<br>• Low: 45%<br>Victims receiving PEP that were infected:<br>• High: 1 in 75<br>• Low: 1 in 20 | Significant uncertainties surrounding target population assumptions. Range created based on expert consultations, Knobel et al., and Hampson et al. |
| **Introduction dates** | idem | idem |
| **Uptake** | idem | idem |
| **Coverage** | Demand : idem<br>Fully vaccinated population:<br>• High: 80%<br>• Low: 60% | Significant uncertainties surrounding target population assumptions. Range created based on expert consultations |
| **Products** | idem | idem |
| **Logistics** | idem | idem |

# Rabies impact modelling assumptions

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

## Modelling approach




## Key assumptions

- **Deaths / cases:** 55,000 global deaths per year (source: Knobel et al and WHO position paper, within range established in the literature)
- **Duration of protection:** Post-exposure prophylaxis treats people who are already infected; extension of protection to subsequent bites not modelled
- **Death rate if untreated:** 100% (rabies is 100% fatal)
- **Incidence rate:** 1 in 20 to 1 in 75 (common to seek treatment for non-infected bites; extrapolated from Hampson et al. and expert consultations)
- **Efficacy:** 100% (source: manufacturer package labels)
- **Treatment completion:** 60-80% (extrapolated country case studies and expert consultations); impact estimates assume no impact from partially completed courses of treatment

1. Fully vaccinated persons

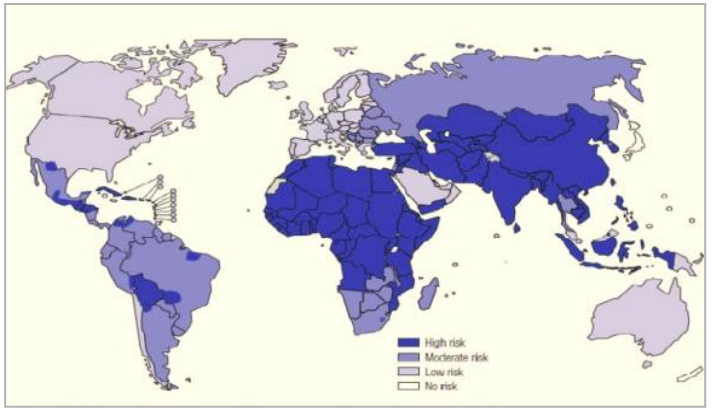
# Treatment-seeking assumptions used to estimate incremental population in scope

**Incremental* vaccinated population**

| | |
|---|---|
| **Global rabies deaths per year[1]** | 55,000 |
| **% of infected people who will present[2]** | 45% - 99% |
| **Number of PEP per averted death[2]** | 1 in 20 to 1 in 75 |
| **Total new global demand (courses)** | 500,000-3.5M |

***~15M people currently treated with post-exposure prophylaxis**

**Incremental vaccinated population allocated across countries**




***Distributed using IHME weighting of rabies deaths per country***

1. Knobel et al. 2. Knobel et al., Hampson et al., consultations with rabies experts
Source: Global Alliance for Rabies Control , Knobel et al., expert consultations, IHME GBD 2010 study

# Need to determine whether GAVI support would include rabies immunoglobulin

## WHO recommends support for RIG in addition to vaccine for some bite victims

**Rabies immunoglobulin provides antibodies against rabies virus for passive protection before post-exposure vaccination triggers bite victims to produce their own**

- Administered during first visit to bite clinic following exposure (category III)

**WHO recommends administration of RIG in all people with category III exposure and to those with category II exposure who are immunodeficient[1]**

- Human RIG is the preferred product, but price is very high and supply is limited
- Equine RIG should be used in instances where human RIG is unavailable or unaffordable
- Monoclonal antibody (lower cost) may be available as a replacement as early as 2014
- Price point for equine RIG is ~$20 per course

## $14M-$346M of rabies investment would be RIG

| Scenario | RIG lower bound cost (20% who present) | RIG upper bound cost (60% who present) |
|---|---|---|
| **Lower bound** | $14M | $42M |
| **Point estimate** | $26M | $79M |
| **Upper bound** | $115M | $346M |

1. Category II exposure: nibbling of uncovered skin, minor scratches or abrasions without bleeding; Category III – single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks, licks on broken skin, exposures to bats. Note: Based on consultations with global rabies experts, assumed use of equine rabies immunoglobulin in 20%-60% of GAVI-supported cases for modelling purposes, at average cost of $20 per course

# Examples of rabies programs in select African countries

| Country | PEP vaccinations in 2008 | ERIG available? | Coverage | # of prevention centers | Source |
|---|---|---|---|---|---|
| Algeria | 80,000 | Yes | Free in most sectors (Vx+ RIG) | >100 (most emergency depts) | Dodet et al. |
| Benin | 440 (60% incomplete) | Yes | Patient pays | 21 | Dodet et al. |
| Burkina Faso | 985 | Yes | Vaccine subsidized, RIG pays | 2 (public sector) | Dodet et al. |
| Cameroon | 859 | Yes | Patient pays | 3 | Dodet et al. |
| Cote d'Ivoire | 1131 (rupture of public sector stock) | No rupture of stock | Patient pays | 25 (public sector) | Dodet et al. |
| Gabon | 128 | Since Jan 2008 | Patient pays | 2 (public sector) | Dodet et al. |
| Madagascar | 25,000 | Only at Institut Pasteur | Free | 25 | Dodet et al. |
| Mali | 380 | No | Patient pays | 1 | Dodet et al. |
| Morocco | 50,000 | Yes | Free (Vx+ RIG) | 147 | Dodet et al. |
| Niger | 15 (60% incomplete) | No | Patient pays | 1 | Dodet et al. |
| CAR | 979 | 100 doses from MSF | Free (Vx + RIG) | 4 (private only) | Dodet et al. |
| Rep. Congo | 1582 | No | Patient pays | 2 (public sector) | Dodet et al. |
| Senegal | 842 | Since Mar 2008 | Patient pays | 1 (Institut Pasteur Dakar) | Dodet et al. |
| Togo | >2000 | Yes | Patient pays | Lome + main towns | Dodet et al. |
| Tunisia | 34,784 | Yes | Free (Vx + RIG) | 206 (public) | Dodet et al. |

GAVI-eligible
Not GAVI eligible

Source: Dodet et al., "The fight against rabies in Africa: from recognition to action"