# 06a - Annex C: Rabies 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

# 1

# Executive summary

# Rabies Executive Summary (1/2)

**Rabies causes ~13,000-59,000 deaths per year, concentrated among poor and vulnerable populations**

- Burden of disease is highest in Sub-Saharan Africa and South Asia with ~90% in Gavi-eligible countries (2016)
- WHO recommends post-exposure prophylaxis (PEP) for all people exposed to the virus as disease is 100% fatal

**Strong global momentum with Zero by 30 campaign**

- “United Against Rabies” coalition of WHO, Food and Agriculture Organization of the United Nations, World Organisation for Animal Health (OIE) and Global Alliance for Rabies Control (GARC) developed strategy with goal of eliminating dog-mediated human rabies by 2030
- One Health approach* builds awareness and incorporates both human and dog rabies
- Many countries have a Rabies Policy and/or implemented programme in place but the level of functionality is variable

**Key market challenges could be addressed with Gavi investment**

- Currently, the poor quality of demand forecasting combined with lack of vaccine financing results in inadequate supply levels, lack of awareness and/or confidence in health systems amongst target population, and a vicious circle of inadequate supply and/or stockouts and unknown or inaccurate demand
- 15+ manufacturers exist in the market, 2 WHO Pre-Qualification (PQ), 2 under review for WHO PQ in 2018
- Potential for Gavi to unlock existing supply capacity, which is currently unused because of unknown demand which is partially caused by capped country budgets



*'One Health' is an approach to designing and implementing programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better public health outcomes.

# Rabies Executive Summary (2/2)

**Investment in rabies vaccination would supplement existing domestic funding for PEP**

- Catalytic opportunity to shift countries to intradermal dosing in line with WHO recommendations; lower cost would reduce burden on country health systems
- Gavi's learning agenda suggests that existing programs do not currently function well so Gavi's impact would be helping to scale up rather than substituting existing country programmes
- Rabies Immunoglobulin (RIG) and monoclonal antibody (mAb) were considered as part of the vaccination strategy, but deprioritized due to high cost and limited incremental impact

**Different nature of rabies programme suggests some new features required**

- Gavi support traditionally in EPI vaccines; rabies programmes require multisectoral coordination between EPI, primary health care (PHC) and animal health, representing new stakeholders and partners for Gavi
- To enhance probability of successful scale-up of programmes, set of criteria to determine 'country readiness' for Gavi investment to be applied, reflecting country commitment and capacity

**Could avert ~96,000-267,000 deaths between 2021-2035 (~$847-3,161 per death averted)**

- High health impact relative to other VIS vaccines with the range depending on impact of existing country efforts
- As a post-exposure vaccine, very different programme than Gavi typically supports with questions around implementation feasibility, especially concerning supply chain planning, demand education and health care worker training
- Successful implementation dependent on accessibility of public supply (particularly in decentralized areas), improved demand forecasting to unlock existing manufacturing capacity and successful inter-sectoral coordination.

**RECOMMENDATION**

**Provide support for human rabies vaccine for post-exposure prophylaxis, 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

**Shortlisted in 2013 but no decision for long-term investment:**

- Uncertain demand
- Operational challenges of supplemental programme
- Possible misalignment with Gavi model

→ **Decision to invest in a learning agenda to identify burden and feasibility**

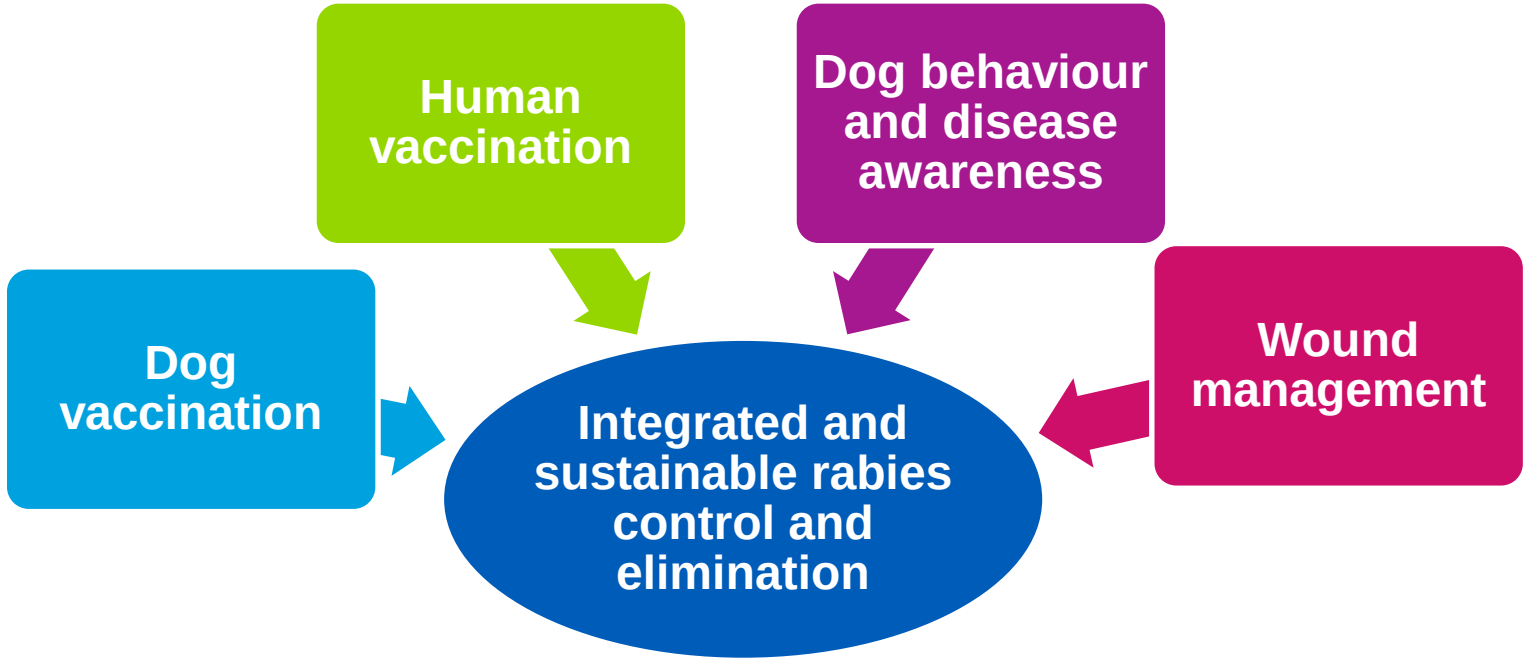
**Several changes since 2013**

- New WHO recommendations endorsed by SAGE in Oct 2017
- Zero by 30: The Global Strategic Plan, coordinated, country-centric strategy – published June 2018
- Establishment of WHO Rabies Modelling consortium in April 2017
- Gavi learning agenda findings – finalisation of study results in 2018. Findings confirm data and operational challenges and possible solutions for human PEP programmes (WHO studies), as well revealing limited information on true incidence of rabid dog bites (Swiss TPH studies)
- A first mAb is licensed and available on the market

# Human rabies vaccine complements other health interventions for comprehensive disease control

**Rabies control is multisectoral:**

- Human rabies vaccine prevents onset of rabies in the event of a dog bite (as main vector of human rabies)
- Incidence of rabies reduced and eventually eliminated through regular vaccination of dogs



# Key vaccine benefits

| Investment framework element | Key benefits | Comments |
|---|---|---|
| Strategic fit | | |
| Outcome and impact | **Potential for high health impact and more equitable access to vaccines; opportunity to support elimination of neglected tropical disease (NTD)** | • Appropriate wound management and prompt access to quality-assured PEP is almost 100% effective in preventing human rabies deaths<br>• Rabies affects the world's most vulnerable populations, majority of cases in Africa & Asia particularly children; support would enable reaching these populations<br>• Access to rabies PEP is limited in public sector, resulting in patients self-purchasing via the private market<br>• Human rabies only vaccine-preventable NTD |
| Value for money | **High value for money relative to other VIS vaccines** | • Due to high ability to prevent disease onset with PEP if vaccine is administered in a timely manner (~$847-3,161 per death averted) |
| Cost | | |
| Feasibility | | |
| Market implications | **Enhanced demand forecasting and improved supply through greater predictability** | • Vicious circle of inaccurate demand and insufficient supply contributing to challenges of existing programmes<br>• Stronger demand forecasting could unlock existing manufacturing capacity and could encourage more vaccines to go through pre-qualification process |

# Key vaccine challenges

| Investment framework element | Key challenges | Comments |
|---|---|---|
| Strategic fit | **Post-exposure non-routine vaccine programme not aligned with Gavi's current vaccine support** | • As a post-exposure vaccine, different from Gavi's current portfolio of support, requiring other resources and stakeholders<br>• Potential policy implications to address the incremental investment aspect of the programme |
| Outcome and impact | | |
| Value for money | | |
| Cost | **Challenge to assess full scope of potential additional programme costs** | • Vaccine procurement cost is low, but could carry additional costs for training, inter-department sectoral coordination, social mobilisation, integration and introduction costs<br>• Switch to ID dose, which brings some cost savings, could carry higher wastage |
| Feasibility | **Non-EPI platform, sectoral inter-dependencies, switch to fractional dose and the risk of displacement of country funds present challenges** | • Potentially a new platform required or coordination with several different existing platforms (eg, animal health, primary health care)<br>• Impact of an investment in human rabies PEP programme dependent on non-Gavi supported activities (ie. dog vaccination) being scaled up<br>• Need to determine and verify current domestic funding at country level to provide incremental support so as not to displace funds currently allocated for existing rabies programmes |
| Market Implications | | |

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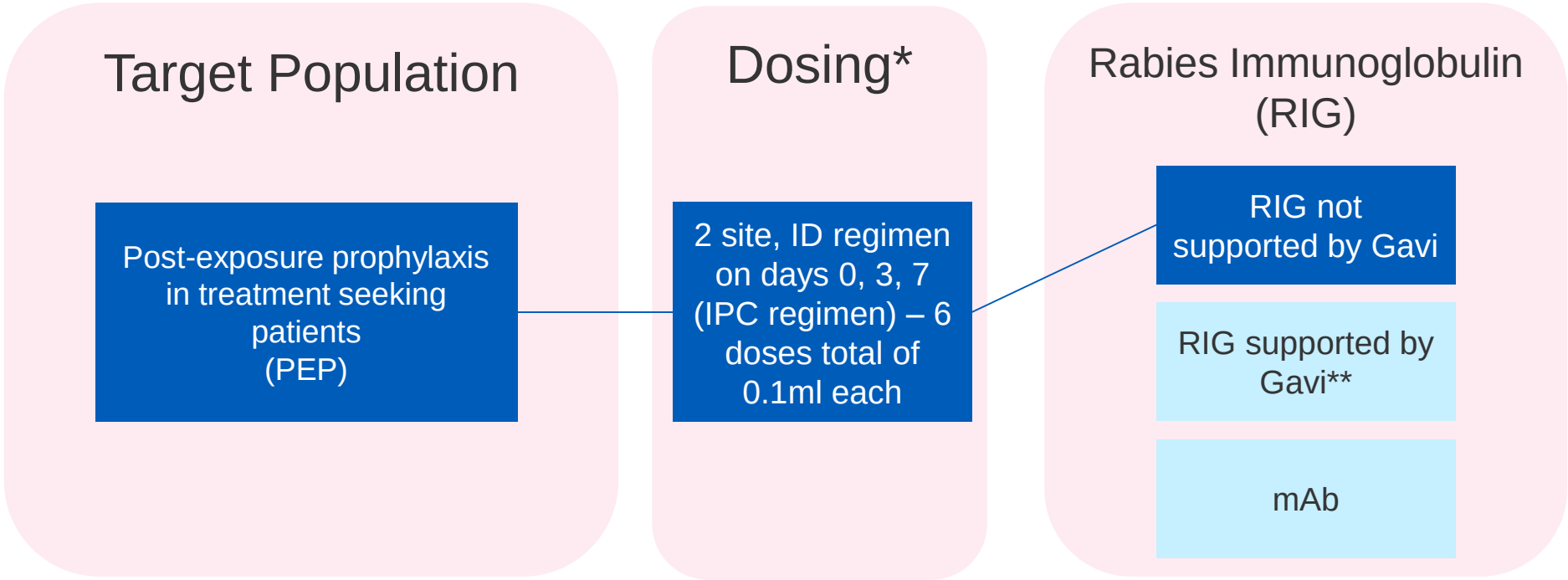
# Policy approach

# Rabies vaccination strategy




Proposed strategy

Excluded

*Aligned with updated WHO recommendations endorsed by SAGE in Oct 2017

**Based on Phase 2 analyses on impact and value for money, and uncertainty around use and cost, scenarios including RIG have been deprioritised. Currently no evidence of RIG benefits when modern vaccines are used (100% effective if administered properly).

# Approach to considering potential programmatic selection criteria

**To enable long term programme sustainability, establishment of programmatic selection criteria to assess 'country readiness' for Gavi support to scale up PEP.**

**The approach would allow for continuous programme improvement to assess feasibility and impact, with ability to apply learnings from higher-performing 'early adopters' to gradually expand support to countries with lower capacity over time**

Principles and illustrative potential programmatic criteria:

1. Demonstration of engagement in global elimination agenda: e.g., country commitment to Global Zero by 30 Plan

2. Level of current commitment to integrated rabies control plan:
   a. Establishment of One Health or other coordinated approach and engagement with animal health sector
   b. Commitment to dog vaccination or other strategy for animal rabies control

3. Status of a country's current commitment & investment in rabies vaccination programme towards human rabies elimination.
   E.g., assessment of:
   a. Whether a human rabies vaccination programme exists
   b. The current vaccination programme platform(s) to determine which integration points are required and what opportunities exist to leverage off an EPI system (if it makes sense to do so)
   c. The current level of PEP vaccine accessibility in the public and private markets
   d. The country's current financial investment into its rabies vaccination programme

# Vaccine introduction grant (VIG) considerations

Gavi's Rabies Learning Agenda (conducted following the VIS 2013) suggests that existing programs do not currently function well so activities linked to introduction would still be required for Gavi's support to have a catalytic impact.

Current approach to vaccine introduction grants (VIG) for existing portfolio of Gavi-supported vaccines: $0.60-$0.80 per infant in the birth cohort*

- Logic: To cover a share of the cost of pre-introduction activities to facilitate a timely introduction
- Birth cohort serves as proxy for population at risk

For rabies, population to be vaccinated is not the birth cohort but individuals bitten by suspected rabid animal.

- However fewer PEP vaccinated individuals does not necessarily mean introduction activities are smaller or less costly than routine immunisation to an entire age cohort and would not need to reach the health system across the entire country
- Smaller number of individuals to be vaccinated with PEP (i.e., bite victims vs birth cohort), however, same number of health care workers to be trained
- Population for social mobilisation outreach is still the wider community to ensure demand education – ie. awareness building, demand creation, awareness of when PEP is required, proper wound washing etc

Proposed approach for Rabies VIG: To apply current policy for calculating VIG: ($0.60-$0.80) x birth cohort

* Or a lump sum amount of USD 100,000, whichever is larger



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# Illustrative approach to incremental support

**Purpose:** To mitigate the risk of displacing domestic funding currently allocated for existing Rabies programmes

**Goal:**

- Gavi investment helps reinforce and strengthen a country's existing rabies programme
- Catalytic support to help close the coverage gap and de-fragmented demand

**Policy considerations:**

- Before or upon country application, assessment of country's current financial investment level in rabies programme to be confirmed/verified
- Policy requirement to maintain current investment level plus additional co-financing requirements
- As part of annual reporting, country to provide actual verifiable domestic funds spent on rabies programme

# 4

# Demand, health impact, cost and value for money

# Rabies key assumptions

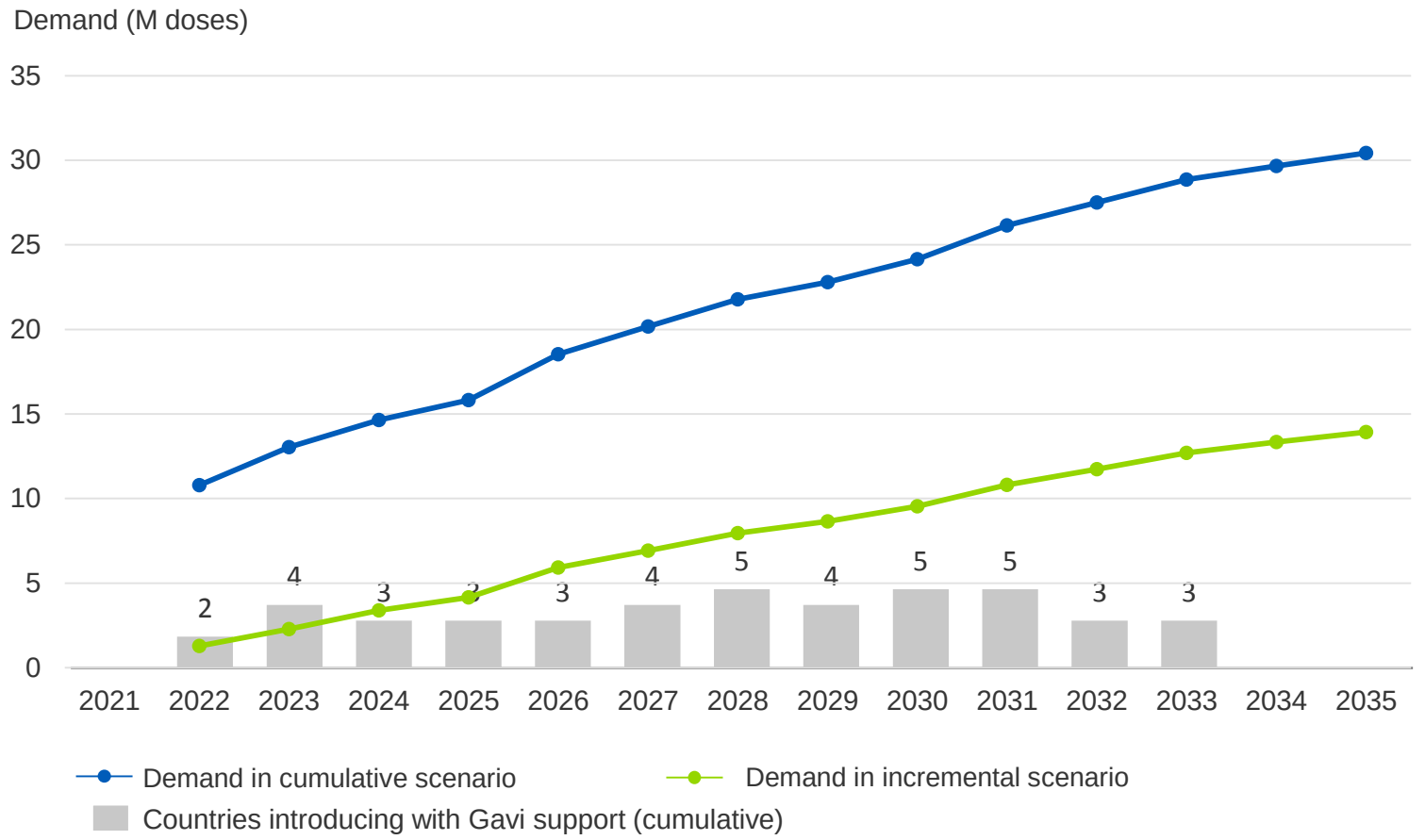
xx: included in model uncertainty range
xx: not included

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

1. Models used in the evaluation only model direct impact;
2. This uncertainty was chosen to reflect the fact that current PEP delivered in countries are mainly OOP costs. Gavi could then envision to take over those programs

Note: IBCM – Integrated Bite Case Management

# Expected cumulative demand 2021-2035 ~304M ID doses[1]




***Nigeria excluded***

**Scenarios:** incremental and cumulative demand, no dog vaccination[2]

**Total demand from countries that introduce with Gavi support (2021-2035)**

**Cumulative demand** **~304M**

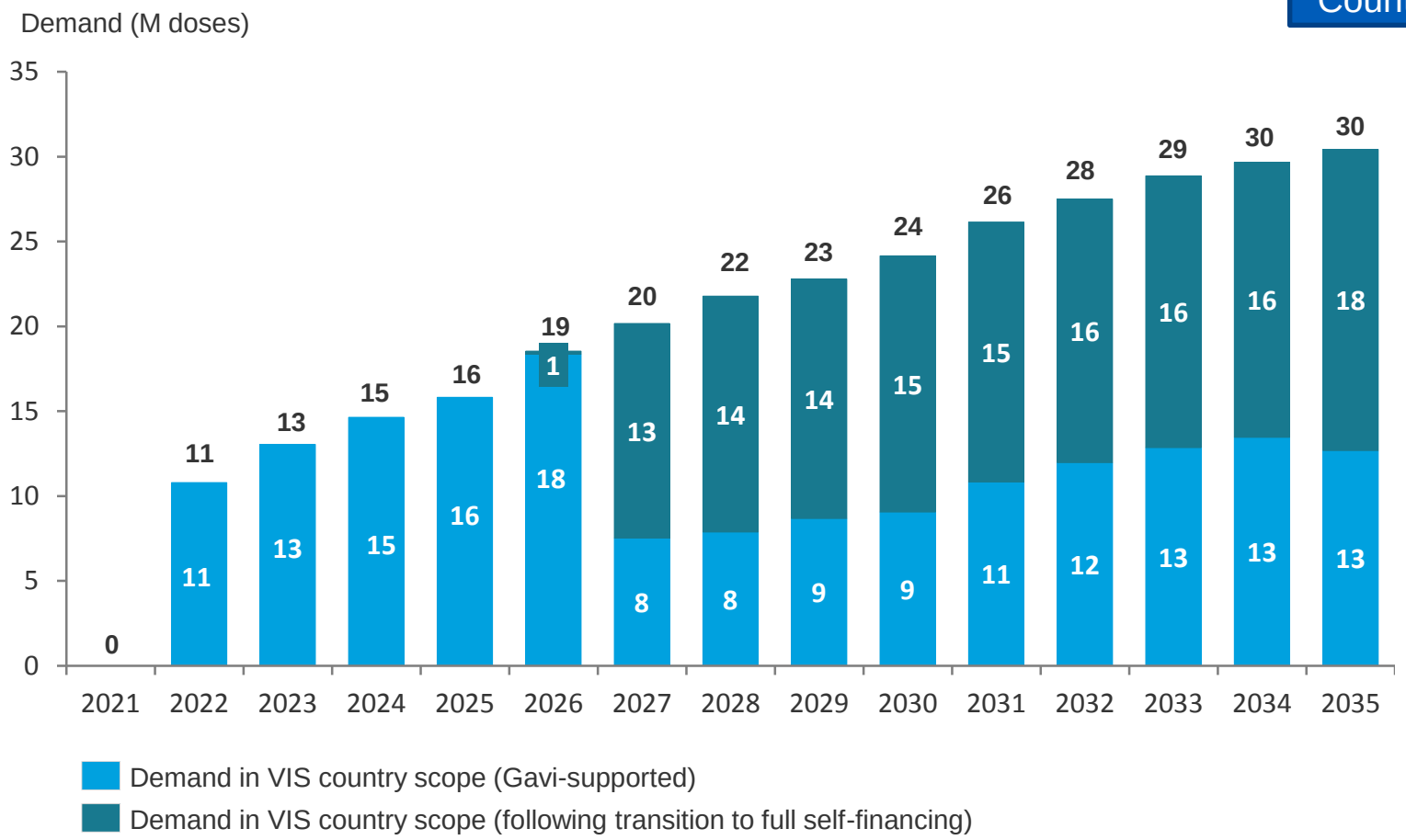
**Incremental demand** **~113M**

1. Based on Gavi's current eligibility and transition policy
2. Cumulative demand takes into consideration what countries already do and would supply themselves (not necessarily for free), whereas incremental demand is what is required on top of existing country provision to meet demand

Incremental and cumulative demand estimated with scenario assuming base share of bite victims seeking (90%), receiving (93%), and completing (80%) treatment and no dog vaccination

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

# Demand in Gavi-supported countries up to ~168M ID doses between 2021-2035[1]




***Nigeria excluded***

Countries supported by Gavi for introduction

**Scenarios:** cumulative demand, no dog vaccination[2]

**Total cumulative demand from countries that introduce with Gavi support (2021-2035)**

**Gavi-supported demand[2]** ~168M

**Post transition demand** ~137M

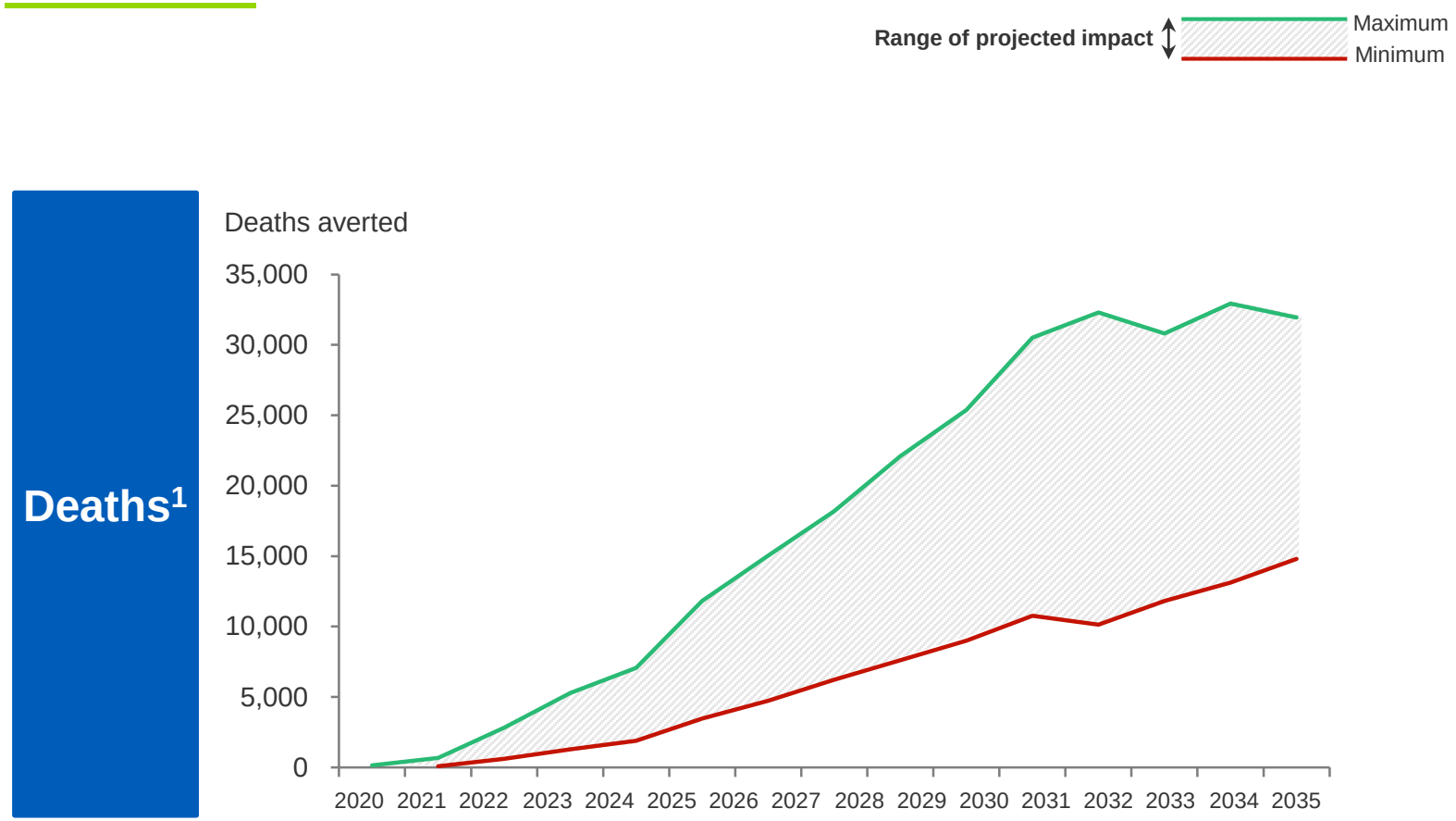
1. Based on Gavi's current eligibility and transition policy
2. This demand is used to calculate 'procurement cost to Gavi and countries', which itself is used in the calculation of 'value for money'

Cumulative demand estimated with scenario assuming base share of bite victims seeking (90%), receiving (93%), and completing (80%) treatment and no dog vaccination

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

Source: University of Glasgow

# Vaccination could avert between ~96K-267K future deaths and cases through 2035




***Nigeria excluded***

**Scenarios:** incremental and cumulative demand, no dog vaccination; variable coverage[2]

| | Total deaths averted (2021-2035) | Deaths averted per 100K vaccinated (k) |
|---|---|---|
| Max | ~267K | ~3.2K |
| Min | ~96K | ~3K |

1: Cases averted and deaths averted are equal

2. WHO Rabies Modelling consortium and IPM (direct impact only) models; Incremental and cumulative demand estimated with scenario assuming variable share of bite victims seeking (85%/90%/95%), receiving (88%/93%/98%), and completing (50%/80%/90%) treatment and no dog vaccination

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 impact driven by challenges in estimating impact estimates

# Summary of health impact, cost, and value for money (2021-2035)

***Nigeria excluded***

**Scenarios:** incremental and cumulative demand, no dog vaccination; variable coverage[2,3]

***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 rabies PEP introductions.***

| | | Primary modelled scenario |
|---|---|---|
| **Impact** | Fully vaccinated persons | ~8.5M |
| | Total future deaths averted | ~96-267K |
| **Cost[3]** | Gavi procurement costs | $91M |
| | Gavi operational costs | $27M |
| | Total Gavi cost | $118M |
| | Country procurement costs | $178M |
| | Country operational costs | $86M |
| | Country recurrent delivery costs | $94M |
| | Total Country cost | $358M |
| | *Total cost* | *$477M* |
| **Value for money** | Cost per death averted[1] | ~$847-3,161 |

Note: 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 rabies PEP introductions
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

1. Calculated using procurement cost only
2. WHO Rabies Modelling consortium direct impact only model; Incremental and cumulative demand estimated with scenario assuming variable share of bite victims seeking (85%/90%/95%), receiving (88%/93%/98%), and completing (50%/80%/90%) treatment and no dog vaccination
3. Cumulative demand scenario used to estimate all costs

# Assessment of uncertainty in demand and impact analyses

| | Comments |
|---|---|
| Demand | • Surveillance is challenging and estimates of disease burden are model-based only<br>• Baseline values for demand and coverage based on available data from existing PEP use in countries and from Gavi learning agenda studies<br>• Timing of introductions based on Global Zero by 30 Strategic Plan, adjusted to estimate 'readiness' to introduce with Gavi support based on proposed programmatic criteria |
| Price | • Forecast based on market intelligence, not historical trends |
| Health impact | • Uncertainty around burden data for rabies. Estimates are model projections, but outputs were validated against burden estimates<br>• Uncertainty in decision tree model structure for capturing impact, but approach was vetted by WHO<br>• Disease burden is modelled as a function of bite incidence from rabid dogs, with approximately 1 in 6 individuals bitten by a rabid dog developing rabies in the absence of PEP |



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 | ~7-10% |
| Deaths averted | ~31-37% |
| Cost | 10% |



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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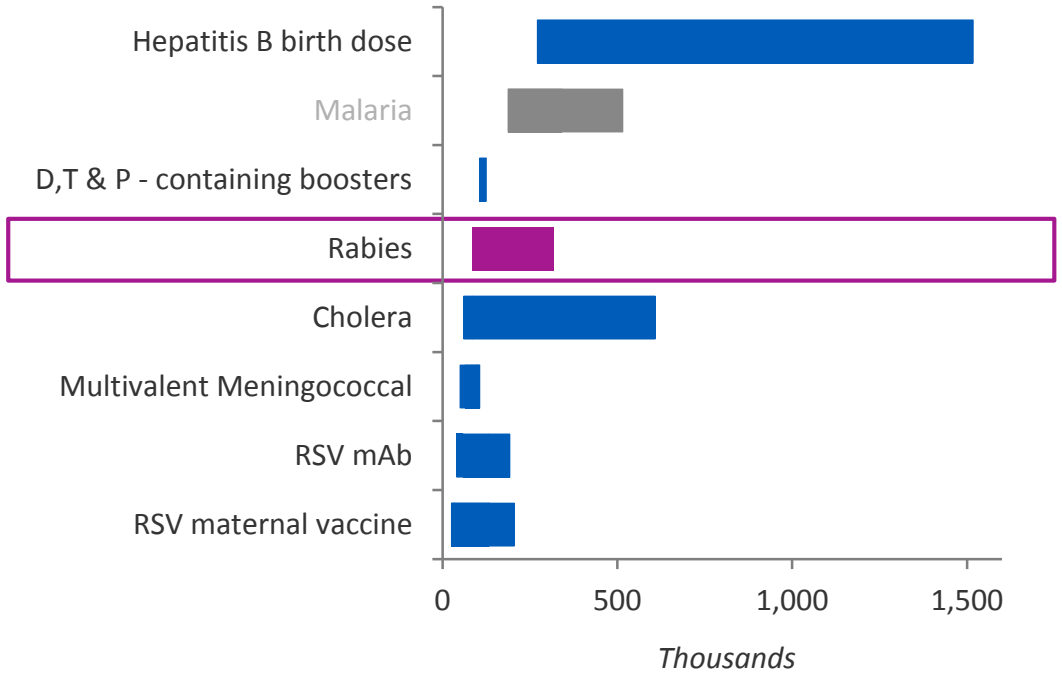
# Impact and value for money compared to VIS candidates

# Health impact compared across VIS candidates

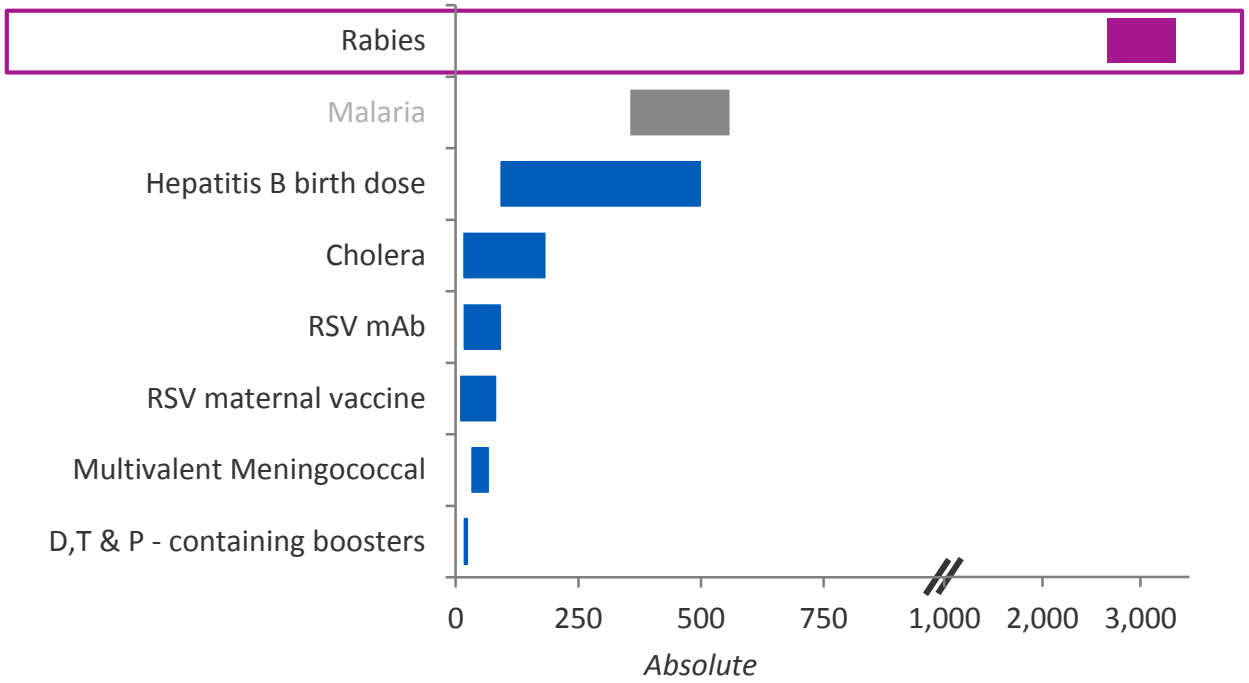
***Nigeria excluded***

**Scenarios:** incremental and cumulative demand, no dog vaccination; variable coverage[1]

## Total future deaths averted (K), 2021-2035




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




1. WHO Rabies Modelling consortium and IPM (direct impact only) models; Incremental and cumulative demand estimated with scenario assuming base share of bite victims seeking (90%), receiving (93%), and completing (80%) treatment and no dog vaccination
Range of impact driven by challenges in estimating impact estimates
Note: Multivalent meningococcal represents the risk based scenario

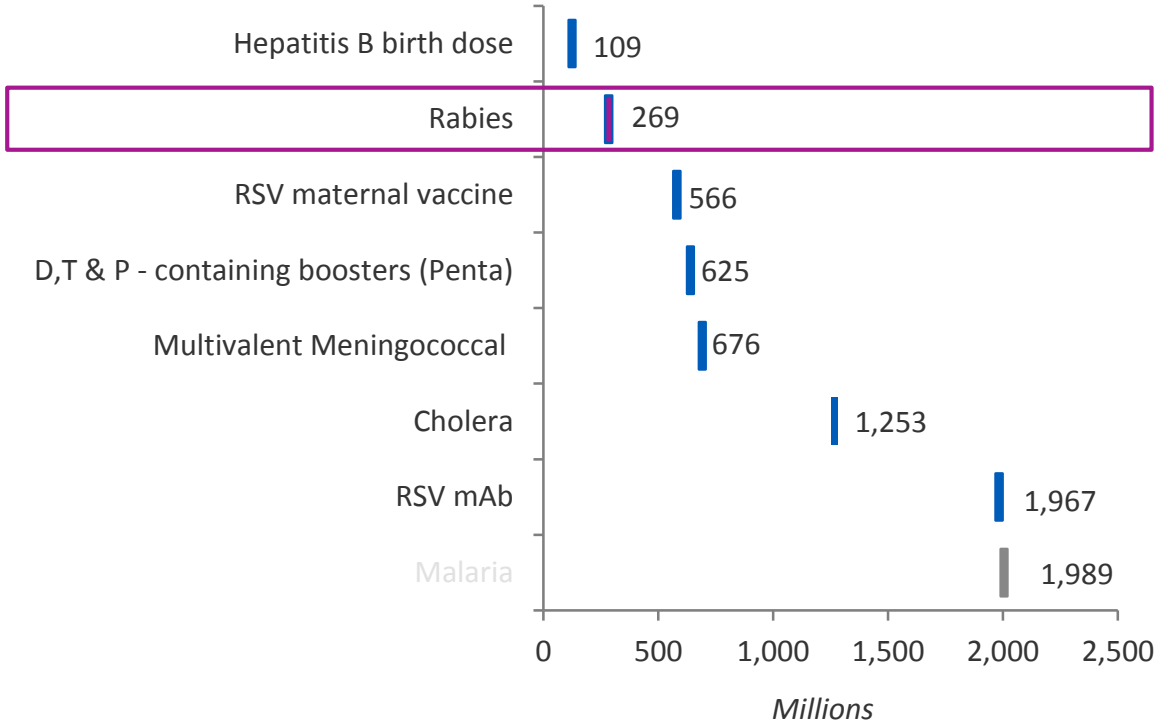

Range of projected impact

# Procurement cost and cost per death averted compared across VIS candidates

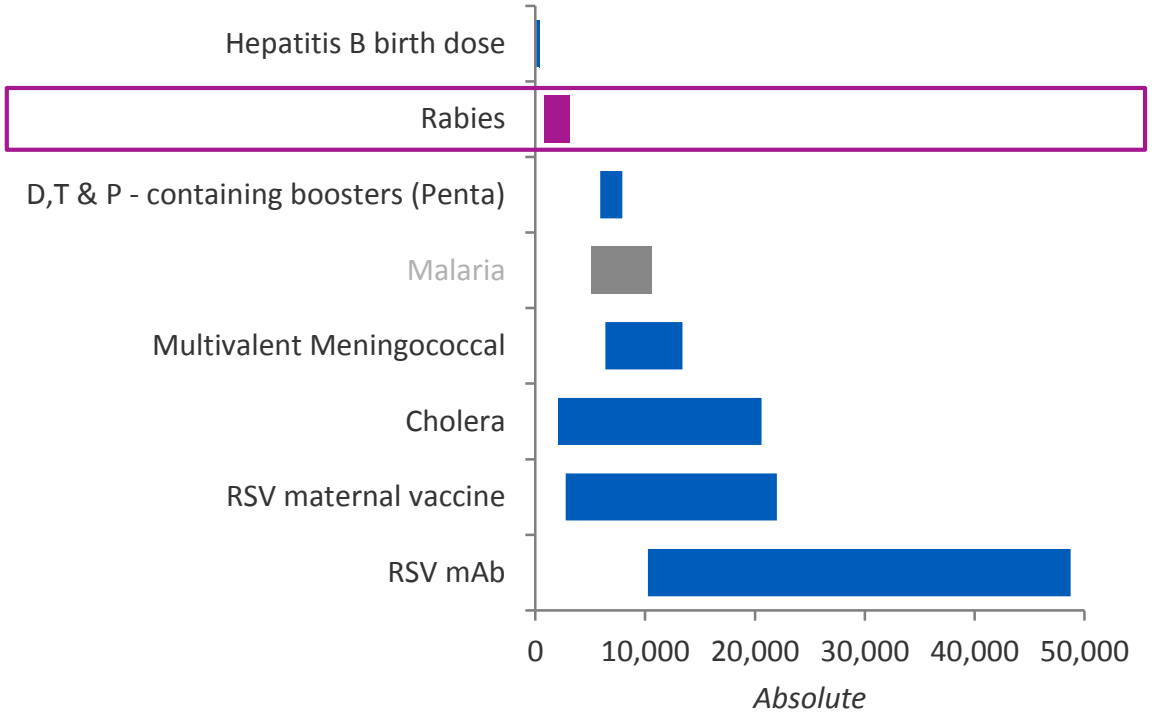
**Nigeria excluded**

**Scenarios:** cumulative demand, no dog vaccination; variable coverage[1]

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




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




***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 rabies PEP introductions.***


1. WHO Rabies Modelling consortium and IPM (direct impact only) models; Incremental and cumulative demand estimated with scenario assuming base share of bite victims seeking (90%), receiving (93%), and completing (80%) treatment and no dog vaccination
Range of impact driven by challenges in estimating impact estimates
Note: Multivalent meningococcal represents the risk based scenario; D,T&P –containing boosters represent Penta as first booster

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# Country perspective

# Interviews with country stakeholders revealed that most countries have weak, fragmented programmes

**Priorities and approach**

- High priority for many countries as burden is significant or increasing in young children and results in death
- Many countries have weak and fragmented programmes mainly in the private sector resulting in high out of pocket expenditure for patients
- Some countries using non-PQ human rabies vaccine, though quality is not assured
- Mixed responses on prioritising dog vaccination, though might have other approaches to animal control

**Integrated disease control and coordination**

- Rabies post-exposure prophylaxis (PEP) is not coordinated through EPI
- Sometimes a separate cold chain, though at district 2 level could be same
- Animal control/dog vaccination housed in different ministry though some respondents unsure of which ministry
  - However one country highlighted existing One Health function to coordinate different components of comprehensive programme
- Some countries feel public rabies PEP programme could be built on existing public health system infrastructure (eg, integrated in primary health care)

**Challenges**

- Demand fragmentation and supply raised as significant challenges, leading to stockouts and lack of confidence in availability of the vaccine
- Animal control could be logistically difficult in terms of reaching all stray dogs, as well as coordination with another ministry
- Misalignment in roles and training: vaccinators not trained to give rabies PEP but have access to it; emergency department personnel trained to give rabies PEP but can't access vaccine
- Building community awareness would cost more than social mobilisation for traditional vaccine introduction
- Could be some challenges with switching to a prequalified vaccine and intradermal administration
- Logistics of vaccine storage unclear: vaccine needs to be made available at which level of health facility?

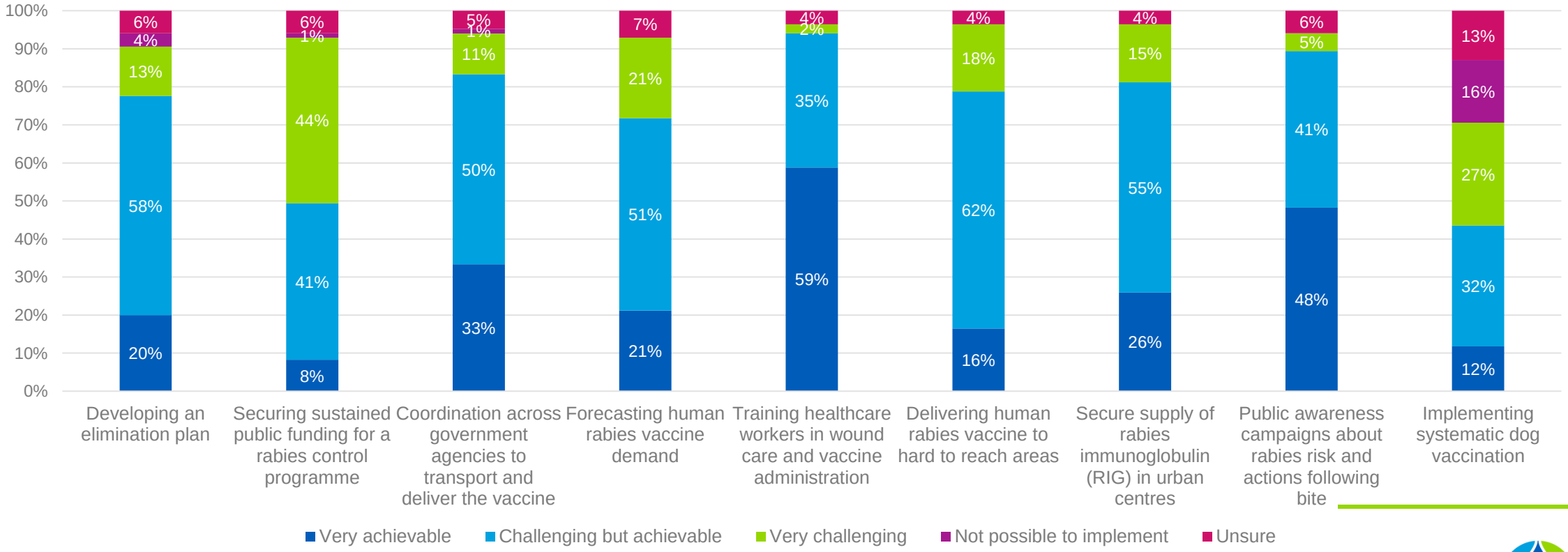


Source: VIS Phase III in-depth country interviews

# Public funding a particular challenge, but multisectoral coordination could help achieve success

*In your opinion, how challenging do you think each of the following activities related to rabies elimination are?*

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





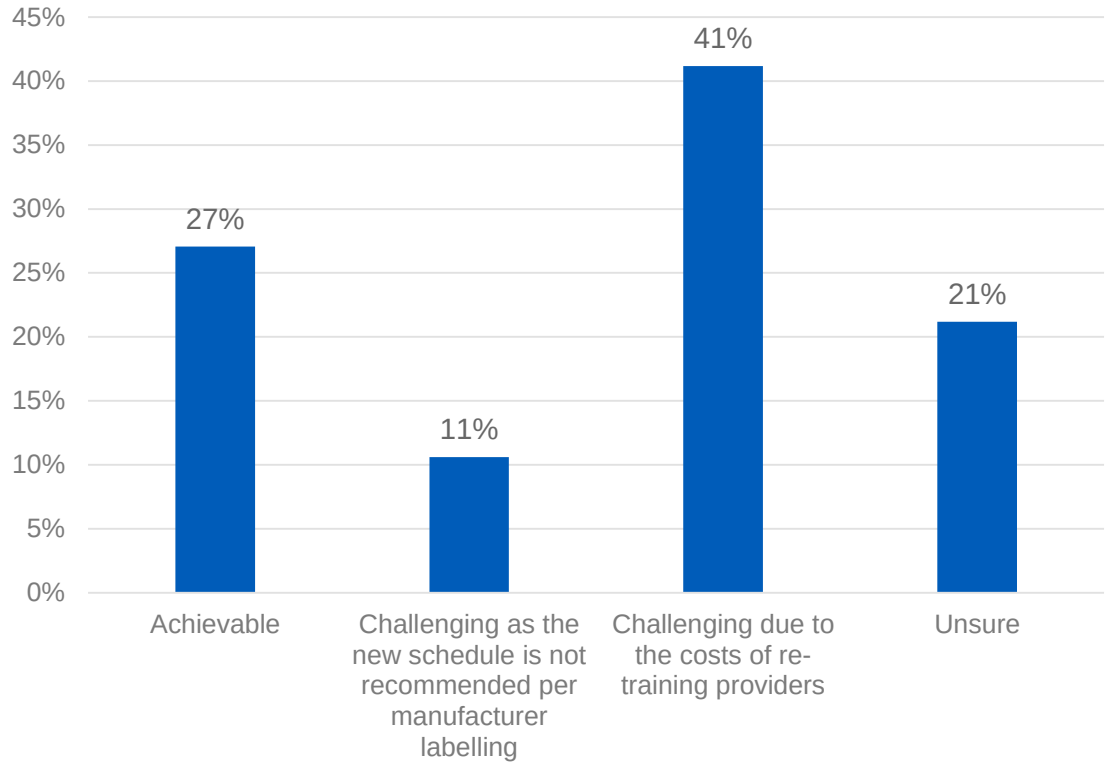

Source: VIS Phase III country survey

# Respondents would find implementing the new WHO recommendations challenging due to costs of training

*The updated WHO recommendation is to administer a 1-week, 2-site intradermal post-exposure prophylaxis schedule (2-2-2-0-0), of a total 6 doses of 0.1 ml vaccine injected intradermal vaccination during 3 visits over the course of 7 days, rather than a 5 dose intramuscular post-exposure prophylaxis schedule of a total of 5 ml vaccine injected during 5 visits over 28 days.*

*The new recommendation requires fractionating intramuscular doses as the volume per dose delivered is lower. How challenging do you think it would be to implement this new recommendation?*

% respondents answers regarding new WHO recommendation






Source: VIS Phase III country survey

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# Implementation requirements

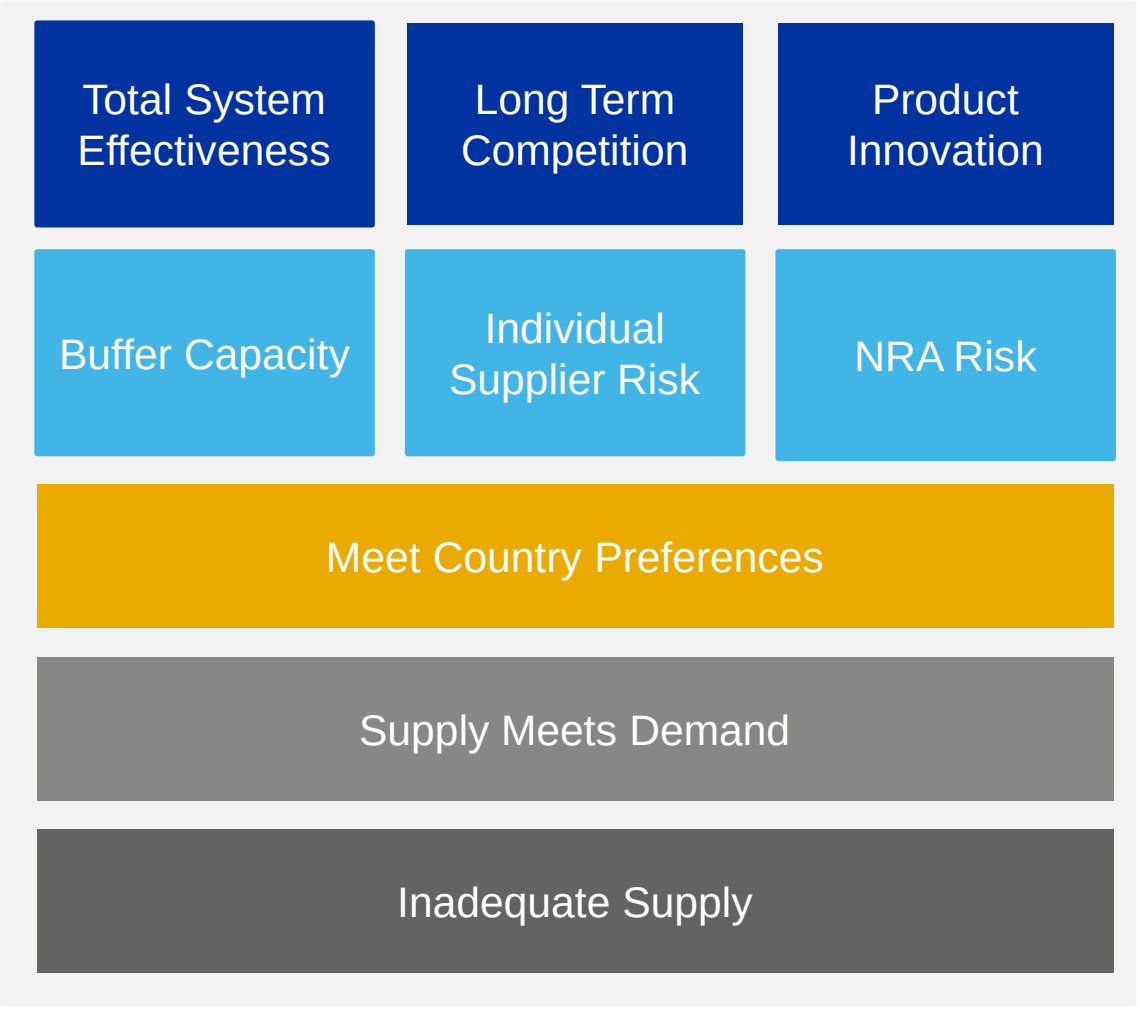
# Unique implementation requirements

| | Area of focus | Unique implementation requirements | Associated costs |
|---|---|---|---|
| **Global level** | Policies and processes | • Incremental support, not displacing existing domestic financing<br>• Identification of programmatic criteria to assess 'country readiness'<br>• Coordination with United Against Rabies collaboration | • Verification of country's current rabies investment<br>• Technical assistance to develop broader plans |
| | Supply | • WHO: Global Characteristics of the Rabies Biological Market in 2017 report indicates potential for existing manufacturers to increase production | |
| **Country level** | Planning, coordination, integration | • Implementation of robust demand forecasting<br>• Coordination with animal health sector to scale up dog vaccination<br>• Platform not easily identifiable; might need to be unique/need to be tailored for each country | • Country level intersectoral coordination |
| | Supply chain infrastructure and logistics | • Logistical coordination across sectors; potentially can use EPI and PHC supply chain but vaccine administration would be through PHC | |
| | Health workforce | • Comprehensive training for: intradermal administration, identification of when vaccines are required and when not, wound management | • Training for vaccine and wound management |
| | Social mobilization, education, communication | • Broad awareness campaigns for behavior around animals and awareness of when a vaccine is required and when not<br>• Synergy with Zero by 30 scale-up of dog vaccination and corresponding awareness campaigns | • Additional training and awareness materials |
| | Surveillance | • Hospital and community based surveillance (dog bites, clinical rabies, PEP)<br>• Integrated Bite Case Management (IBCM) systems implementation, provides primary surveillance data (high risk bites)<br>• Reliance of quality data on dog vaccination/disease burden in dog population | • Improved surveillance and data management |



Most challenging | Unique but manageable | Few unique implementation requirements

# A number of manufacturers with collective capacity to meet demand in Gavi market




High number of manufacturers could ensure good level of competition on the long term, pending WHO prequalification

Manufacturers are developing new delivery devices facilitating the administration of rabies vaccine

**Rabies vaccine:** 15+ manufacturers of which 2 are WHO pre-qualified and 2 are currently under WHO PQ review in 2018

**Human RIG:** 10+ manufacturers in 7 countries, WHO PQ process does not yet exists

**Rabies mAb:** 1 manufacturer with two formulations available, WHO PQ process does not yet exist

Poor quality of demand forecasting results in inadequate supply levels and a vicious circle of inadequate supply and unknown or inaccurate demand

Potential for Gavi to unlock existing supply capacity, which is currently unused because of unknown demand which is partially caused by capped country budgets

Existing supply capacity could be sufficient to meet projected demand in Gavi-supported countries, but most manufacturers are not prequalified

# Gavi Learning Agenda: WHO studies confirm data and operational challenges

## Study Objectives

- Strengthening the understanding of rabies burden and potential vaccination impact in Gavi-eligible countries (VIS 2013 Challenge 1)[1, 2]
- Understanding the feasibility and logistical requirements of increasing access to PEP through decentralized delivery systems (VIS 2013 Challenge 2 & 3)[1]

## Scope

- **Survey on procurement, distribution & delivery of PEP:** 25 countries surveyed
- **Country specific activities:** Bhutan, Cambodia, India, Kenya, Vietnam

## Select Findings

- Demand forecasting challenges
  - Budgets capped/ 100% budgeted/forecasted is ultimately consumed
- PEP procurement separate from EPI; 50% use EPI cold chain, 90% use non-EPI system for distribution
- Gavi-eligible countries have limited to medium accessibility of PEP
- Advocacy and awareness of proper PEP treatment needed for patients and health care workers
- Diverse opportunities for integration with other existing delivery platforms
- Investments at the district level would have significant impact



1. Scope of WHO study: Survey on procurement, distribution & delivery of PEP: 25 countries surveyed; country specific activities: Bangladesh, Bhutan, Cambodia, India, Kenya, Vietnam
2. Scope of Swiss TPH study: Survey of ~25,000 households in Chad, Cote d'Ivoire, Mali,

# Gavi Learning Agenda: Swiss TPH Study reveals limited information on true incidence of rabid dog bites

## Study Objectives

Estimation of the burden of rabies and vaccination impact in West and Central Africa (VIS 2013 Challenge 1)

1. Establish the incidence of rabies exposure, rabies mortality burden and its risk factors
2. Establish risk factors of exposure, suspected exposure and levels of current PEP in vaccination coverage, compliance, current vaccination costs, sources of funding and unmet demand
3. Estimate the health impact of PEP with regard to timing and number of doses received

## Scope

- Survey of ~25,000 households
- Countries specific studies: Chad, Cote d'Ivoire, Mali, Liberia

## Select Findings

- Estimated 153'000 (95% CI 106'000 – 226'000) dog bites per year in Chad, Cote d'Ivoire, and Mali, with slightly higher incidence in urban settings
- Less than 60% of victims seek help in a health centre
- Health personnel likely significantly overestimate rabies incidence amongst dog bites
- Lack of information of the true rabies status of the animal vector likely results in overuse of PEP; highlights importance of identifying rabies status of animal
- Low proportion of dog vaccination and variable coordination between human and animal health sectors

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# Risks and mitigation

# Risks of inaction (Gavi investment not approved)

| Strategic concern | Risk |
|---|---|
| **Financial** | • Vaccine costs to countries remain high without reliable and efficient bulk procurement resulting in potentially continued use of intramuscular (IM) regimens and continued stock-outs and use of poor quality vaccines<br>• Government investment in rabies remains low resulting in patients shouldering the cost burden |
| **Market** | • Demand remains uncertain due to lack of access and confidence in availability of vaccine. Existing production capacity remains underutilised due to lack of confidence in demand forecasts |
| **Programmatic** | • Bite victims are unable to access PEP due to vaccine stock-out and/or high costs at point of care<br>• No incentive to switch to ID vaccination as costs fall directly to patients<br>• Momentum built from learning agenda impeded; data gathered could be unused |
| **Reputational** | • Gavi viewed as out of alignment with momentum of Global Zero by 30 goals<br>• Missed opportunity for health systems strengthening that goes beyond EPI<br>• No catalytic effect on improved programmes and vulnerable populations continue to experience high mortality |

# Risk and mitigation plan if Gavi investment approved

| Strategic concern | Risk | Mitigation plan |
|---|---|---|
| **Financial** | • As a rabies programme is in place in some countries, Gavi support could displace existing domestic financing | • Country assessment of current funding levels should provide information on incremental needs |
| **Market** | • Continued fragmented demand; existing capacity remains under-utilised | • Improved surveillance and demand forecasting capacity should add predictability<br>• Continued engagement with manufacturers for improved presentations |
| **Programmatic** | • Gavi investment does not achieve impact due to programmatic constraints<br>• Lack of integration between human and animal health sector stalls or inhibits coordinated approach<br>• Delays in implementation of dog vaccination programme will have a direct spill-over effect on human PEP vaccination programme | • Programmatic criteria intended to ensure country 'readiness' to scale up with Gavi support<br>• Gavi and partners will work with countries to ensure introductions are planned and resourced to address bottlenecks<br>• Country PEP applications include demonstrated commitment to integrated approach<br>• Learnings from early adopters applied to future introductions to improve programme |

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# Investment recommendation

# Recommended investment scenario

No Gavi support for Rabies vaccine

Limited interventional studies (national in select countries)

**Provide support for human rabies vaccine for post-exposure prophylaxis, beginning in 2021**

**Recommendation**



**vaccination consists of vaccine procurement and operational costs for introduction*

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# Illustrative components of a research agenda for rabies post-exposure prophylaxis

| Objective | Key questions | Indicative cost |
|---|---|---|
| Lessons learned of an integrated rabies control programme | • Assessment of programmatic criteria for successful roll-out<br>• Identification of opportunities to overcome additional barriers and gaps | $1 million/year for 3-4 early introducing countries for ongoing assessment and outcomes monitoring |
| Feasibility of Integrated Bite Case Management | • Assessment of capacity needs and approach to implementing IBCM | $1-2 million for multi-site pilot 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

# Rabies: key experts

| Experts consulted |
| --- |
| Bernadette Abela Ridder (WHO)<br>Lea Knopf (WHO)<br>Emily Wootton (WHO)<br><br>*(in consultation with WHO collaborating centres, SAGE working group on rabies, rabies-endemic countries implementing Gavi Learning Agenda)* |
| Katie Hampson (University of Glasgow)[1]<br>Caroline Trotter (University of Cambridge)[1] |
| Terri Hyde, Ryan Wallace, Anyie Li, Nandini Sreenivsan (CDC) |
| Erin Sparrow (WHO) |
| Julien Potet (MSF) |

1. VIS 2018 Modeller



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

# Rabies: sources

## Sources

- WHO Publication: Summary of 2017 Updates – Rabies vaccines and immunoglobulins: WHO Position
- Rabies WHO Position Paper, 2010 and 2018
- Zero by 30: The Global Strategic Plan to End Human Rabies from Dog-Mediated Rabies by 2030
- Swiss Tropical and Public Health Institute – 2017 Mid-Year Progress Report for Gavi: Estimation of the Burden of Rabies and Vaccination impact in West and Central Africa
- WHO: Rabies Post-Exposure Prophylaxis Provision, Distribution & Delivery Assessment – Report to Gavi
- WHO: Global Characteristics of the Rabies Biological Market in 2017
- WHO Rabies Modelling Consortium: Modelling the potential impact of improved provision of rabies post-exposure prophylaxis in Gavi-eligible countries (August 2017)
- Hampson K et al. Estimating the Global Burden of Endemic Canine Rabies. PLoS Negl Trop Dis 9(4), 2015
- Global Burden of Disease, Institute for Health Metrics and Evaluation (IHME), 2016

# 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

# Phase II scorecard: Rabies *(June 2018)*

## Modelled strategy: Vaccination as part of PEP in treatment-seeking patients, 2 sites, total 6 doses

| VIS criteria | Indicator | Results | Evaluation[1] |
|---|---|---|---|
| Health impact | Total impact averted | ~300-720K future deaths averted, ~300-720K future cases averted, 2020 – 2035 | |
| | Impact averted per 100K | ~5,790-6,930 future deaths and cases averted, 2020 – 2035, per 100K vaccinated population | |
| Value for money | Procurement cost | ~$ 330-380 procurement cost per death and per case averted | |
| Equity & social protection impact | Impact on vulnerable groups | Burden concentrated among low socioeconomic groups, rural poor | |
| | Benefits for women and girls | No special benefits of vaccination for women and girls | |
| Economic impact | Direct medical cost averted | High average consumption per capita averted in out-of-pocket medical costs | |
| | Indirect cost averted | ~$ 1,810-2,860 productivity loss averted, 2020 – 2035, per vaccinated person | |
| Global health security impact | Epidemic potential | Not IHR notifiable, unless it crosses borders; shift to new hosts possible, but currently no indication | |
| | Impact on AMR | Low impact of vaccination on AMR (1.1/10 points in expert consultation) | |
| Vaccine cost | Total procurement cost | ~$ 110-260 million total procurement cost to Gavi and countries, 2020 – 2035 | |
| Relevant second. criteria | Implementation feasibility / Add. costs for introduction | Large packed volume, new platform; learning agenda confirming feasibility challenges | |

**Additional considerations**

- Strong political momentum with global Zero by 30 campaign
- Gavi's Learning Agenda suggest challenges with existing programs, so Gavi's impact would be additive rather than substituting existing country programs

Note: PEP – Post-exposure prophylaxis

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: Rabies *(June 2018)*

## Modelled strategy: Vaccination as part of PEP in treatment-seeking patients, 2 sites, total 6 doses

| VIS criteria | Indicator | Results | Evaluation[1] |
|---|---|---|---|
| Other impact | U5 deaths averted, total | ~30-71K U5 deaths averted, 2020 – 2035 | |
| | U5 deaths averted, per 100K | ~571-684 U5 deaths averted, 2020 – 2035, per 100K vaccinated population | |
| | DALYs averted (cost per DALY) | ~11-35 million DALYs averted, 2020 – 2035, ~$ 9-13 procurement cost per DALY | |
| | DALYs averted, per 100K | ~210-336K DALYs averted, 2020 – 2035, per 100K vaccinated population | |
| Gavi comp. advantage | Vaccine market challenges | Some potential to influence the market (e.g., support demand forecasting) | |
| | Catalytic investment | High potential to catalyse additional investments (e.g., dog vaccination) | |
| Implementation feasibility | Ease of supply chain integration | Packed volume of 20-174cc; 24-48 months shelf life at 2-8°C; VVM = 30 | |
| | Need for HCW behaviour change | Strong need for HCW change: Training of new HCW group required, use of primary and secondary health facilities for delivery, change in HCW practices for intradermal administration | |
| | Feasibility of vaccination time point | Ad-hoc vaccination, not aligned with other schedules | |
| | Acceptability in target population | Ranked 3/9 in country stakeholder survey, but need for demand education | |
| | Long-term financial implications | Falls within the category of price per course >$ 5 | |
| Alt. interventions | Alternative interventions | Alternative interventions: Pre-exposure prophylaxis, dog vaccination | |
| Broader health system impact[2] | Broader health system impact | Ability to test and establish innovative supply chains, health systems strengthened by increased HCW training, enhanced surveillance of acute encephalitis syndromes | |
| Operational cost[3] | Incremental costs per vac. person | High incremental cost per vaccinated person | |
| Implementation costs | Additional costs for introduction | High: Different program needs; challenging to establish surveillance systems, need to promote switch from i.m. -> i.d.; need for demand education among both HCWs and general pop. | |

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 | IPC Regimen: 2 site Intradermal, 6 x 01.ml doses (interval: 0, 3, 7 days) | WHO, January 2018: 'Rabies vaccines and immunoglobulins: WHO position. Summary of 2017 Updates'. |
| Target Population | Bite victims seeking treatment | |
| RIG | Modelled but not used in VIS assessment | WHO, January 2018: 'Rabies vaccines and immunoglobulins: WHO position. Summary of 2017 Updates'. Indicates that RIG should be used prudently and is indicated for "severe category III exposures", i.e. prioritization option if in short supply and now only intramuscular |

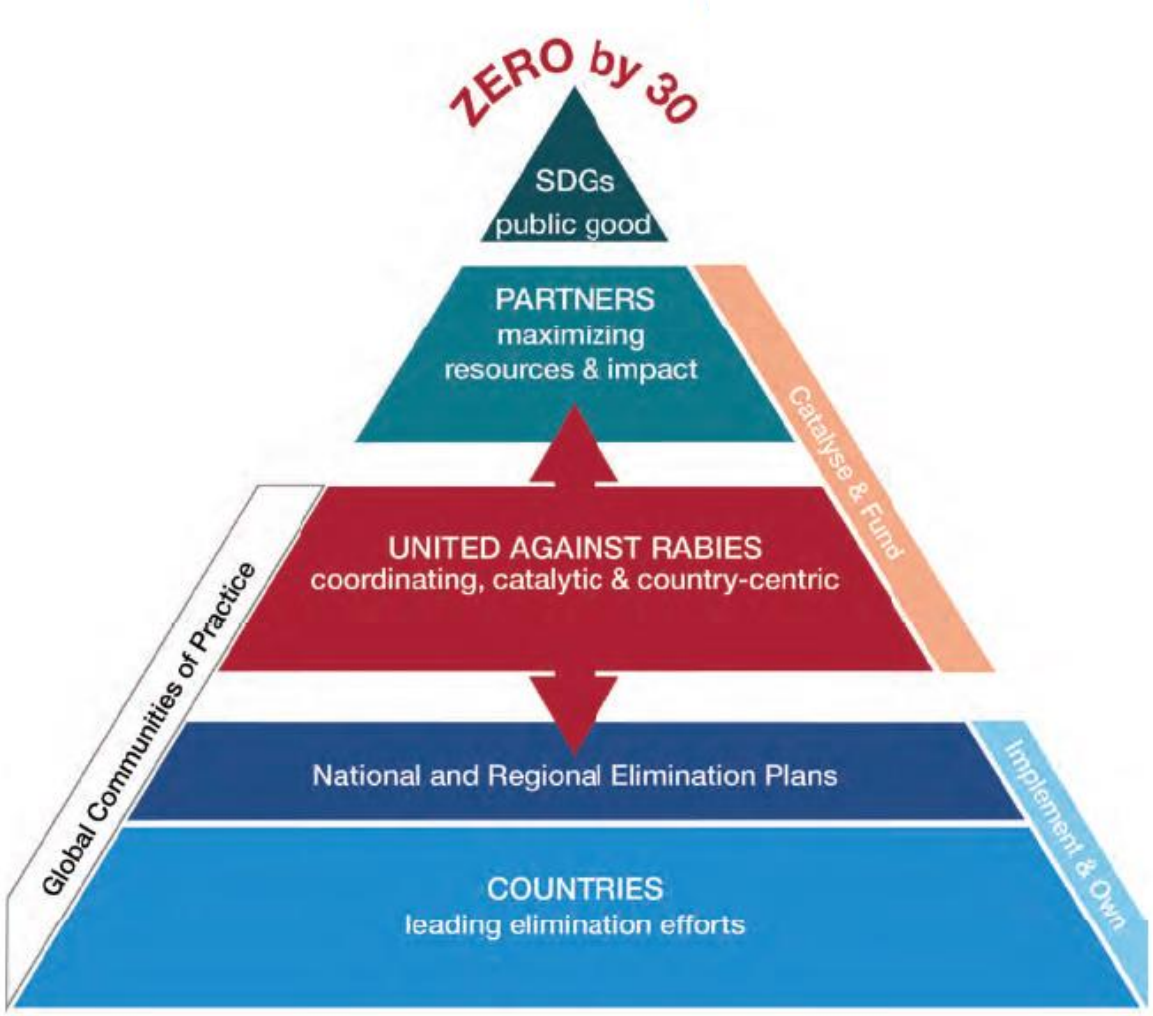
# Demand forecasting assumptions

| Element | | Assumptions | Rationale / Source |
|---|---|---|---|
| Country scope | | Gavi 73 where rabies is endemic | |
| Target population | | Incremental support: Bite victims that are not currently receiving treatment in Gavi-eligible countries (Cambridge model also taking into account those already receiving RIG)<br>Cumulative support: All bite victims in Gavi-eligible countries | Gavi would not replace existing funding; all support would be additive<br>Since it is difficult to measure existing levels of support, the full target population was used as the upper limit for demand |
| Delivery Strategy | | Clinics – treatment-seeking patients | |
| Introduction dates | | First introduction: 2021<br>Country introductions to be phased according to the WHO Global Business Plan & other input variables | Vaccine already on the market and pre-qualified |
| Vaccine uptake | | n/a | Rabies vaccination infrastructure already in place in most Gavi-eligible countries |
| Coverage | Baseline | *(Reflects average values; country specific values will be used)*<br>% rabies exposed patients seeking treatment: 67.5%<br>% patients that seek treatment that receive PEP: 67.2%<br>% completing treatment: 60.9% | Values based on available data from existing PEP use in countries |
| Coverage | Gavi-support | % rabies exposed patients seeking treatment:<br>• Base: 10% increase in yr.1; subsequent 3%/yr. to max. 90%<br>• High: 15% increase in yr.1; subsequent 3%/yr. to max. 95%<br>• Low: 5% increase in yr.1; subsequent 3%/yr. to max. 85%<br>% patients that seek treatment that receive PEP:<br>• Base: 10% increase in yr.1; subsequent 3%/yr. to max. 93%<br>• High: 15% increase in yr.1; subsequent 3%/yr. to max. 98%<br>• Low: 5% increase in yr.1; subsequent 3%/yr. to max. 88%<br>% completing treatment:<br>• Base: 10% increase in yr.1; subsequent 3%/yr. to max. 80%<br>• High: 15% increase in yr.1; subsequent 3%/yr. to max. 85%<br>• Low: 5% increase in yr.1; subsequent 3%/yr. to max. 75% | Values based on data from non Gavi-eligible LMICs & from Gavi learning agenda studies in select countries reflecting scale-up of government supported programmes with fully subsidised PEP to individuals |
| Products | | Intradermal schedule: IPC Regimen<br>Presentation: 10 doses from 1ml vials using Insulin syringes | January 2018: Summary of 2017 Updates to Rabies vaccines and immunoglobulins WHO position and expert input |
| Logistics | | Wastage Factor: 1.12 in urban settings (0.67 vials/patient) to 3.7 in rural settings (2.2 vials/patient)<br>Buffer stocks = 25% | Back-calculated<br>Buffer stocks assumption consistent across antigens |

# Impact modelling assumptions

| Element | Assumptions | Rationale / Source |
|---|---|---|
| **Efficacy** | 100% for fully vaccinated persons<br>98.5% for partially vaccinated persons | Manufacturer package labels<br>Efficacy studies |
| **Duration of protection** | PEP treats people who are already infected; extension of protection to subsequent bites not modelled | Immunogenicity and boost-ability data following vaccination long lasting, > 20 years |
| **Burden of disease** | Rabies incidence model outputs, parameterized from published studies and validated against published estimates (Hampson et al, 2015)<br>Scenario including dog vaccination and thus lower burden of disease is being modelled<br>Projected burden takes into account published or inferred dog populations based on human:dog ratios | Supplemented with Gavi Learning Agenda study results |

# Multi-sectoral approach: United Against Rabies – Zero by 30 Plan




**WHO, OIE and FAO already coordinate efforts to advance the One Health approach for several priority diseases, including rabies, within the Tripartite collaboration *(9)*.**

**The World Health Organization, established in 1946, is tasked to build a better, healthier world for all.**

- Global leadership for public health development to meet needs of disadvantaged populations.
- Nexus for governments, international organizations, NGOs, private sector and civil society.
- Provides technical support to countries and catalyses capacity-building.

**The Food and Agriculture Organization of the United Nations, established in 1945, aims to eliminate hunger and food insecurity worldwide.**

- Advocates for improved social and economic status of all people worldwide.
- Engages partners and stakeholders including governments, civil society and the private sector.
- Links what happens in local communities to regional and global initiatives.

**The World Organisation for Animal Health, established in 1924, aims to improve animal health and welfare.**

- Develops evidence-based international standards, guidelines and recommendations for disease control and animal welfare.
- Manages the OIE World Animal Health Information System (WAHIS) for animal disease notification.
- Promotes strengthening of Veterinary Services worldwide.

**The Global Alliance for Rabies Control, established in 2007, is dedicated to eliminating deaths from rabies.**

- Develops information, surveillance and training tools to increase country capacity for rabies control.
- Provides training and capacity building to countries and coordinates regional intersectoral rabies networks.
- Undertakes advocacy, education and communication campaigns (World Rabies Day, End Rabies Now).



Source: Zero by 30 – The Global Strategic Plan to End Human Deaths from Dog-mediated Rabies by 2030