# Annex C: Hepatitis B Birth Dose Investment Case

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

Gavi
The Vaccine Alliance

# 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

# Hepatitis B Birth Dose Executive Summary (1/2)

**Hepatitis B causes ~800,000 deaths per year globally and ~330,000 deaths in Gavi-supported countries**

- Deaths are concentrated in South Asia (160,000) and Sub-Saharan Africa (90,000) and in older population segments (92% of total deaths in population over age 30), due to chronic infection causing liver cancer and cirrhosis, with resulting high indirect cost for patients

**Perinatal infection can be prevented with a highly efficacious (>95%) and low-cost vaccine**

- WHO recommends all infants should receive their first dose of hepatitis B (Hep B-BD) as soon as possible after birth, preferably within 24 hours
- The risk of developing chronic Hepatitis B virus (HBV) infection varies inversely with age: 80-90% of infants infected during their first year of life develop chronic infections, as opposed to 30-50% of children infected before the age of 6 years and 1-5% of adults
- 38 Gavi-supported countries currently not delivering Hep B-BD; only 4 Gavi-supported countries have independently introduced Hep B-BD since 2013 despite WHO recommendation, yet vaccine is consistently highly ranked for prioritisation by country stakeholders
- Prevalence of infection is highest in Sub-Saharan Africa and Hep B-BD is not in current schedule in majority of countries in region
- If well executed, Hep B-BD could interrupt the majority of vertical transmission within a generation, thereby closing the gap in immunity between birth and primary series

**Hepatitis B birth dose strategy would extend Gavi's existing investment support on pentavalent vaccine, finishing the hepatitis B vaccination series**

- Opportunity to support life-course vaccination and integrate health services (Expanded Programme on Immunization [EPI] & Maternal, Neonatal and Child Health [MNCH]), potential to drive additional health system benefits such as demand for and investment in facility births, strengthening birth-delivery platform (alongside BCG vaccine)
- Introduction would be aligned with the Global Health Sector Strategy on Viral Hepatitis goal of eliminating viral hepatitis by 2030 and would contribute to reaching SDG indicators and support the NCD agenda
- However, the investment would be atypical in that Gavi has not historically invested in low cost vaccines

# Hepatitis B Birth Dose Executive Summary (2/2)

**Gavi support could avert 0.3 – 1.2M perinatal infection-related deaths and 1.2 - 1.5M cases from 2021-2035**

- A key driver of uncertainty in impact modelling is estimated coverage rates for vaccination within 24 hours of birth and disease progression to death
- Proposed strategy includes both in-facility and out of facility births; the latter have high implementation barriers; use of compact pre-filled autodisable devices (cPADs), such as Uniject, is an option but there is limited information on impact and significantly higher price

**Cost per dose (~$0.20) is near current co-financing thresholds so Gavi's strategy would consider non-traditional investments that address platform establishment or strengthening to catalyse country introduction**

- ~$72 - $403 per death averted

**RECOMMENDATION**

**Provide support to establish platform as catalytic support for intro of hepatitis B administered at birth, beginning in 2021[1]**



1. In line with current co-financing policy, Gavi would not fund procurement of hepatitis B vaccine as the price is below the minimum country co-financing level. cPADs are only supported through the learning agenda.

2

# Key benefits / challenges and strategic rationale

# Strategic rationale for consideration of investment case

**VIS 2013 decision and changes to vaccine context since**

**Not put forward for investment**

- Intermediate impact and low on under 5 mortality, which was a driving criterion
- Low vaccine price raised questions about Gavi's role
- Key driver of uncertainty in impact modelling is estimated coverage rates for vaccination within 24 hours of birth

**Few changes to context since VIS 2013**

- Improvements in impact modelling techniques but continued challenges in projecting coverage rates in and out-of-facility
- No changes in vaccine characteristics or vaccination strategy described in WHO Position Paper
- WHO's Controlled temperature chain Working Group has prioritised hepatitis B and one manufacturer has now updated labelling allowing out of cold chain (OCC) use for 28 days at up to 37ºC
- WHO established Global Health Sector Strategy on Viral Hepatitis goal of eliminating viral hepatitis by 2030
- Only 4 Gavi countries, Afghanistan, Mauritania, Senegal & Timor-Leste[1], have independently introduced Hep B-BD since 2013



1. Angola has it in schedule but does not report coverage data); those 31 countries that had introduced prior to 2013 are mainly in WPRO & SEARO

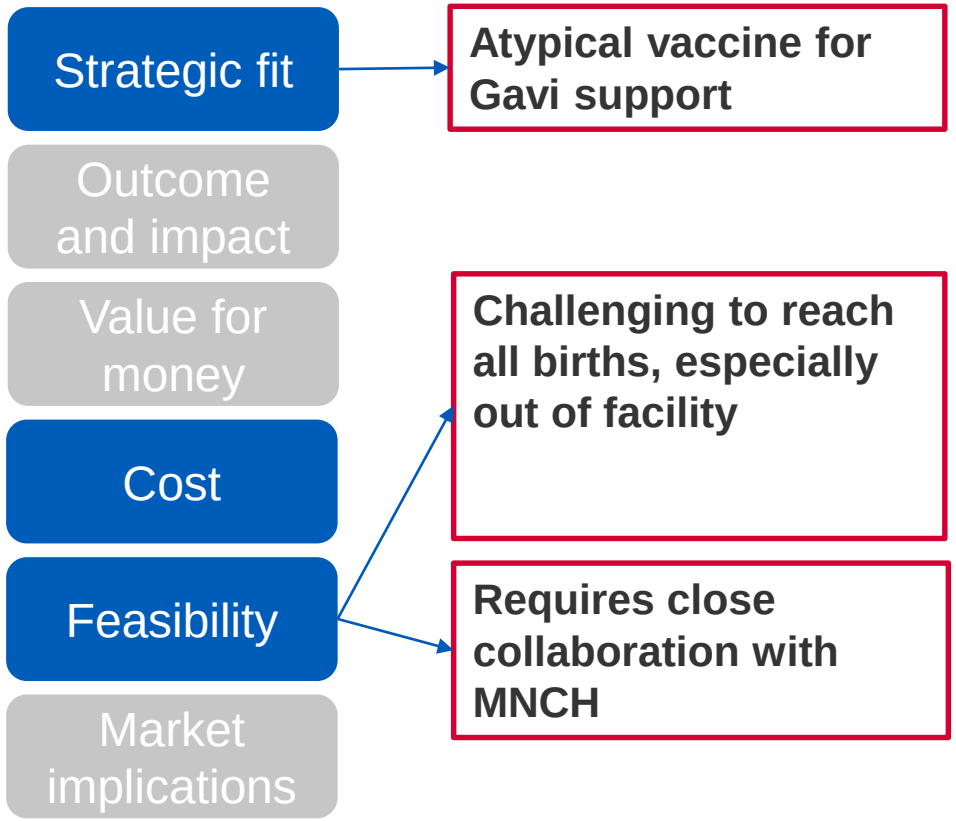
# Key vaccine benefits

| Investment framework element | Key benefits | Comments |
|---|---|---|
| Strategic fit | **Completes primary series supported by Gavi & global agenda for elimination** | • Represents expanded investment to Gavi's existing support for the pentavalent vaccine; closing the gap in protection between birth and primary series<br>• Gavi role to accelerate introduction of available vaccines; only 4 Gavi-eligible countries have independently introduced Hep B-BD since 2013 despite WHO recommendation<br>• Each WHO region has specific hepatitis B-related targets to achieve by 2030 |
| Outcome and impact | **Very high direct impact on mortality and morbidity** | • Gavi support could avert 0.3 – 1.2M perinatal infection-related deaths from 2021- 2035; those countries that have not introduced have the highest burden<br>• High potential to drive additional health system benefits such as demand for and investment in facility births, strengthening birth-delivery platform (alongside BCG vaccine) and integration with MNCH services |
| Value for money | **Low overall cost to Gavi compared to other VIS candidates and high value for money** | • $72-$403 per death averted<br>• Low overall total cost to both Gavi (~$25M in platform establishment support) and countries ($63-586M depending on whether in and/or out of facility births targeted) |
| Cost | | |
| Feasibility | **Very high country interest** | • Hep B-BD a high priority based on country consultations |
| Market implications | | |



Note: Does not consider Gavi support for cPADs e.g. Uniject

# Key vaccine challenges




Comments

- Low cost vaccines have not historically been where Gavi invests
- Limited market shaping role, unless cPADs e.g. Uniject, are considered

- Ideally, vaccine should be delivered within 24hrs of birth, which poses logistical challenges
- Less accessible births taking place outside of health facilities make up a significant subset of the population in some countries (40% of Gavi-eligible countries that have not introduced Hep-B BD have >30% such births); these are much harder to reach as there are few established best practices to do so

- Requires strong collaboration between MNCH and EPI to ensure success
- New platform for all countries, however MNCH can and should be leveraged as the touch-point already exists



Note: Does not consider Gavi support for cPADs e.g. Uniject

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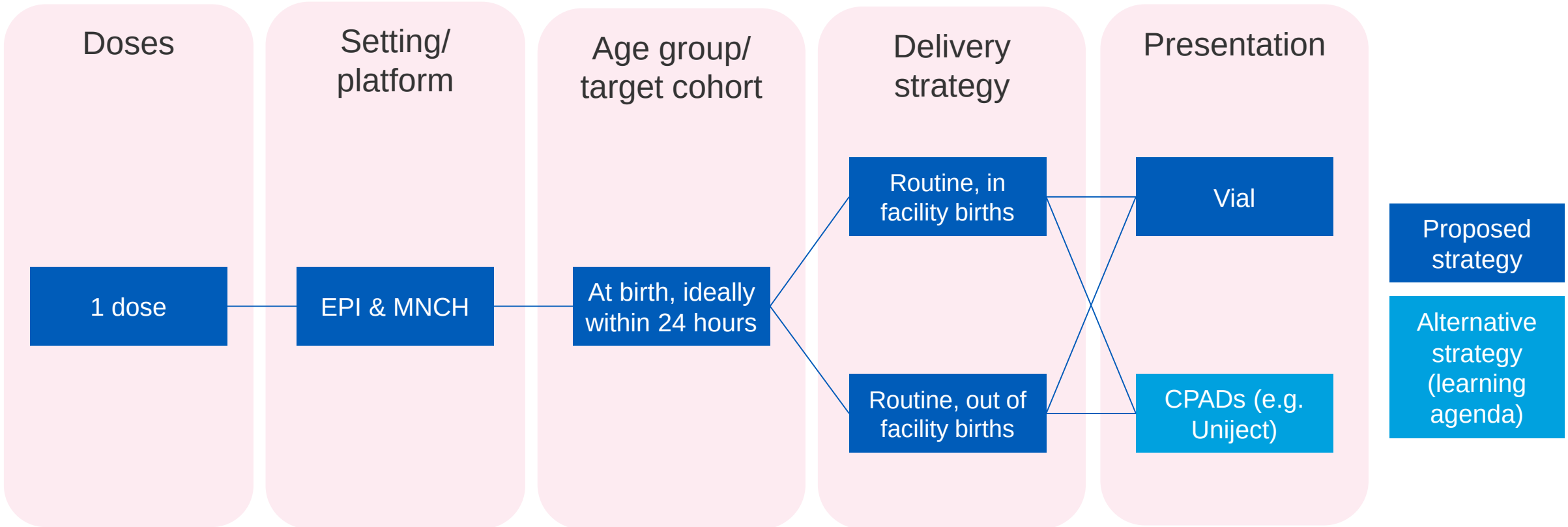
# Policy approach

# Proposed vaccination strategies






CPAD = compact pre-filled auto- disposable injection system

# In accordance with the current co-financing policy, countries would fully finance vaccine

## Gavi support based on current co-financing policy

- **According to current co-financing policy, there would be no support for HepB-BD given the price is below the minimum country co-financing level for low income countries ($0.20)**

## Considerations

- Some countries noted that vaccine **cost is a barrier to introduction**, however this is in the **context of HepB birth dose being part of a broader set of immunisation costs** for the country across all vaccines in the schedule
- The **co-financing policy will be reviewed 2019-2020**, which may lead to updates that would be applicable to VIS 2018 vaccines including Hepatitis B birth dose (if investment approved)



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# Platform strengthening support is required for introducing hepatitis B birth dose

## Approach for platform establishment and strengthening support

- Lack of a strong or established immunisation timepoint poses a **barrier to introduction of hepatitis B birth dose**
- To enable high coverage of these vaccines, **supplementary Gavi support** provided to countries would aim to strengthen or establish the necessary immunisation **timepoint** within the broader, **integrated service delivery platform**
- This supplementary funding would **complement a country's broader package of health systems strengthening support** and aim to improve delivery of all antigens
- The types of activities that could be executed with the platform strengthening support could include:
  - Identifying key issues driving low immunisation coverage in existing immunisation timepoints
  - Expansion of existing EPI data systems to new immunisation timepoints (e.g. targeting a wider age range) for data recording, reporting and analysis
  - Additional training to ensure effective task sharing among HCWs and across sectors (e.g. EPI & MNCH)
  - Social mobilisation activities targeting new age groups
  - Identification of the appropriate setting for administering vaccine (e.g. outside health facilities) and establishing this delivery point
  - Effective integration with other health care sectors (e.g., MNCH)
- This would be the **sole support Gavi offers to countries for hepatitis B birth dose** due to low cost of vaccines

***The HSIS Support Framework will be reviewed and updated in 2019-2020. Gavi's support modality for platform establishment and strengthening would be defined as part of that process, which would also take into consideration other types of Gavi support including for longer term systems strengthening.***

# 4

# Demand, health impact, cost and value for money

# Hepatitis B birth dose key assumptions

xx: included in model uncertainty range
xx: not included

| | | | |
|---|---|---|---|
| **Models** | CDA, Imperial, Goldstein | | |
| **Vaccination strategies** | Routine 1 dose, all live births (no use of cPADs e.g. Uniject) | Routine, all live births (no use of cPADs e.g. Uniject) | Routine, all live births (all cPADs e.g. Uniject) |
| **Uncertainty analysis driving ranges** | Variation in parameters<br>• Efficacy (high, medium, low)[2]<br>• Transmission risks (high, medium, low) | | |
| **Other key assumptions** | Duration of protection:<br>Between administration and 1st dose of Penta | Coverage:<br>Percent of births in a health facility discounted by 7.69%[1] | |

1. Average difference between Hep B-BD coverage and % facility births for Gavi countries with Hep B-BD already introduced
2. Not included because those uncertainties analysis were modeled with variation of pentavalent vaccine efficacy as well and thus not exploitable
3. Cases data from Goldstein not included in the range as the case definition was not comparable with other VIS candidates and the 2 other models



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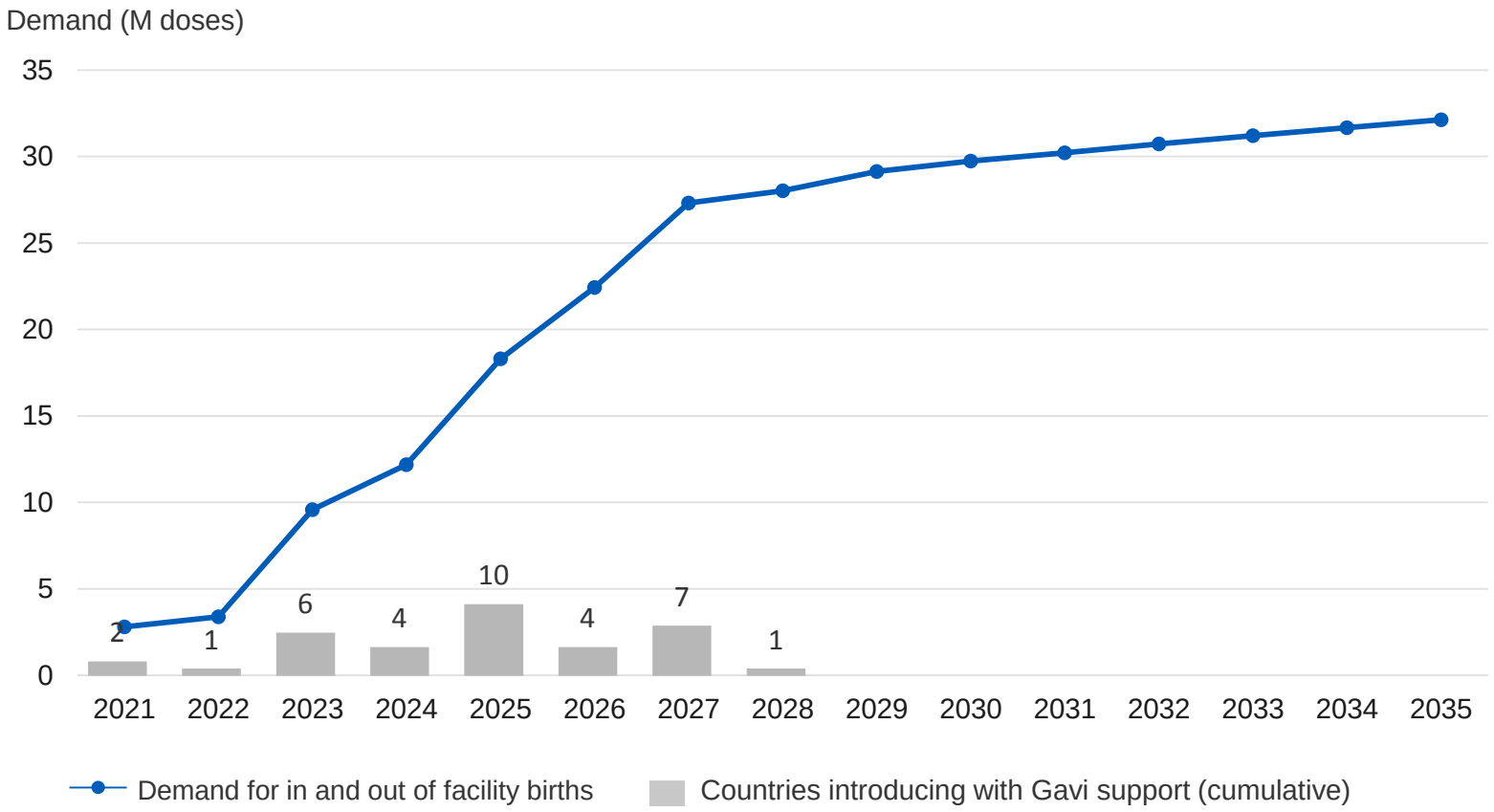
# Expected cumulative demand 2021-2035 ~353M doses[1]




***Nigeria excluded***

**Scenario:** Both in and out of facility births with a traditional vial[2]

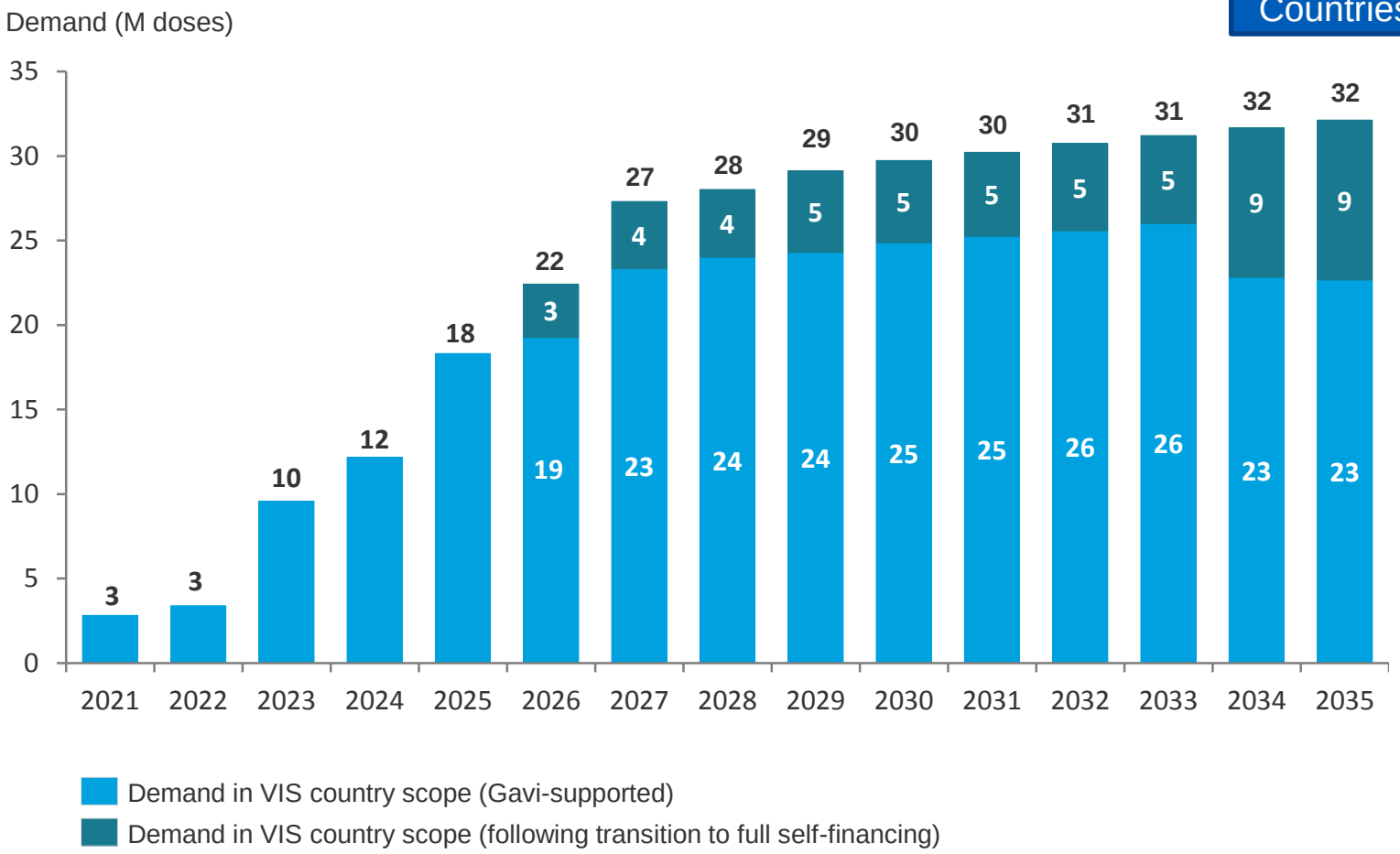
**Total cumulative demand from countries that introduce with Gavi support (2021-2035)**

**Primary scenario (in and out of facility births)**

**~339M**

1. Based on Gavi's current eligibility and transition policy
2. Gavi VIS forecast; demand forecast of both in and out of facility births using a traditional vial
Consideration for Gavi support to Nigeria for VIS candidates would be considered separately through the Nigeria-specific strategy which was approved by the Gavi Board in June 2018

# Gavi anticipates supporting up to ~284M doses between 2021-2035[1]




***Nigeria excluded***

**Countries supported by Gavi for introduction**

**Scenario:** Both in and out of facility births with a traditional vial[2]

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

**Gavi supported demand[2]** ~284M

**Post transition demand** ~55M

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'

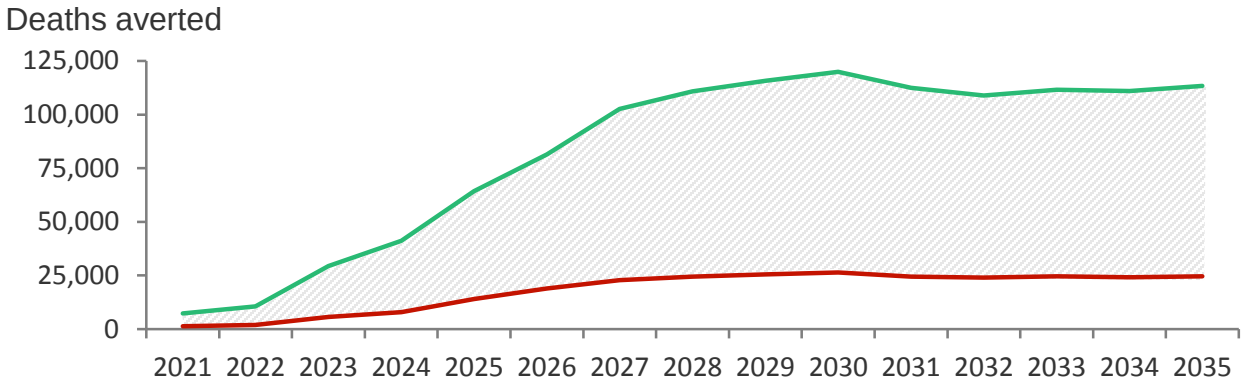
Source: Gavi VIS forecast; Gavi VIS forecast; demand forecast of both in and out of facility births using a traditional vial
Consideration for Gavi support to Nigeria for VIS candidates would be considered separately through the Nigeria-specific strategy which was approved by the Gavi Board in June 2018

# Vaccination could avert between ~0.3M-1.2M future deaths and ~1.2M-1.5M future cases through 2035

***Nigeria excluded***

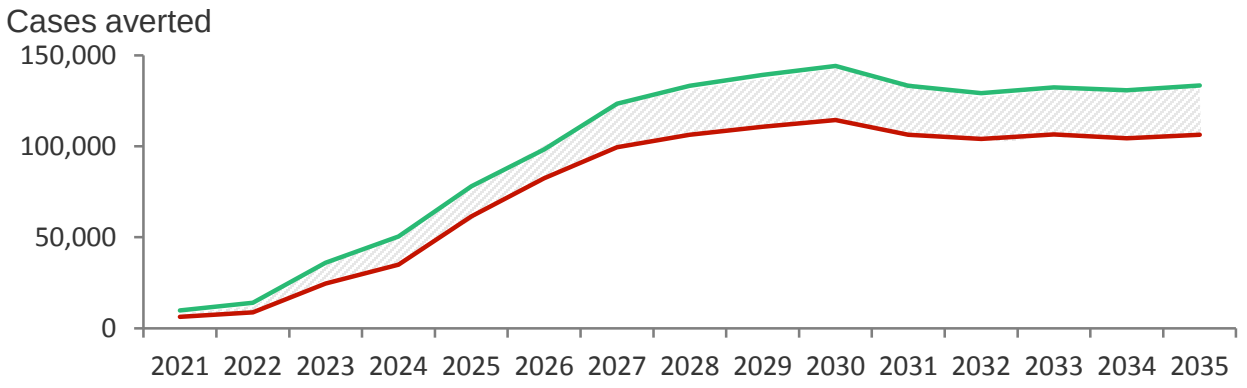
**Scenario:** Both in and out of facility births with a traditional vial; variable transmission rate[1]

## Deaths




| | Total deaths averted (2021-2035) | Deaths averted per 100K vaccinated |
|---|---|---|
| Max | ~1.2M | ~240 |
| Min | ~0.3M | ~52 |

## Cases




| | Total cases averted (2021-2035) | Cases averted per 100K vaccinated |
|---|---|---|
| Max | ~1.5M | ~287 |
| Min | ~1.2M | ~227 |

1. Goldstein, CDA and Imperial models, assuming both in and out of facility delivery and including sensitivity analysis on rate of vertical transmission (low/medium/high)
Range in impact outcomes driven by differences in burden assumptions, larger range in cases driven by difference in disease progression estimates used by different modelling groups
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

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

***Nigeria excluded***

***Cost projections are unconstrained. Values do not account for anticipated introduction of current portfolio and other VIS candidate vaccines that may reduce the number of planned Hepatitis B birth dose introductions.***

**Scenario:** Both in and out of facility births with a traditional vial; variable transmission rate[1]

| | | Primary modelled scenario |
|---|---|---|
| **Impact** | Fully vaccinated persons | ~518M |
| | Total future deaths averted | ~0.3 – 1.2M |
| **Cost** | Gavi procurement costs | $ 0 |
| | Gavi operational costs | $25M |
| | Total Gavi cost | $25M |
| | Country procurement costs | $109M |
| | Country operational costs | $75M |
| | Country recurrent delivery costs | $63-586M[2] |
| | Total Country cost | $247-770M |
| | *Total cost* | *$273-795M* |
| **Value for money** | Cost per death averted[3] | ~$72 - 403 |

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 hepatitis B birth dose introductions
1. Goldstein, CDA and Imperial models, assuming both in and out of facility delivery and including sensitivity analysis on rate of vertical transmission (low/medium/high)
2. Delivery cost range dependent on delivery strategy employed (i.e. in-facility only vs. in and out of facility delivery)
3. Calculated using procurement cost only
Consideration for Gavi support to Nigeria for VIS candidates would be considered separately through the Nigeria-specific strategy which was approved by the Gavi Board in June 2018

# Assessment of uncertainty in demand and impact analyses

| | Comments |
|---|---|
| Demand | • Uncertain coverage data for timely Hep B-BD and out-of-facility<br>• Unclear if coverage for cPADs e.g. Uniject would differ from traditional vaccine if used in-facility |
| Price | • High confidence for Hep B-BD vials in facility which are based on historical trends<br>• Medium confidence in cPADs e.g. Uniject which are based on market intelligence with limited historical trends to validate<br>• Costs dependent on packaging and volume scenarios |
| Health impact | • High uncertainty around true burden data<br>• Dynamic models both fit (calibrate) to prevalence and number of women of child bearing age, improving reliability<br>• Bias likely to be towards lower estimates as herd immunity not considered |



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 | 0% |
| Deaths averted | 0% |
| Cases averted | 0% |
| Cost | 0% |

*No difference as Nigeria has already introduced hep b birth dose independently*



Consideration for Gavi support to Nigeria for VIS candidates would be considered separately through the Nigeria-specific strategy which was approved by the Gavi Board in June 2018

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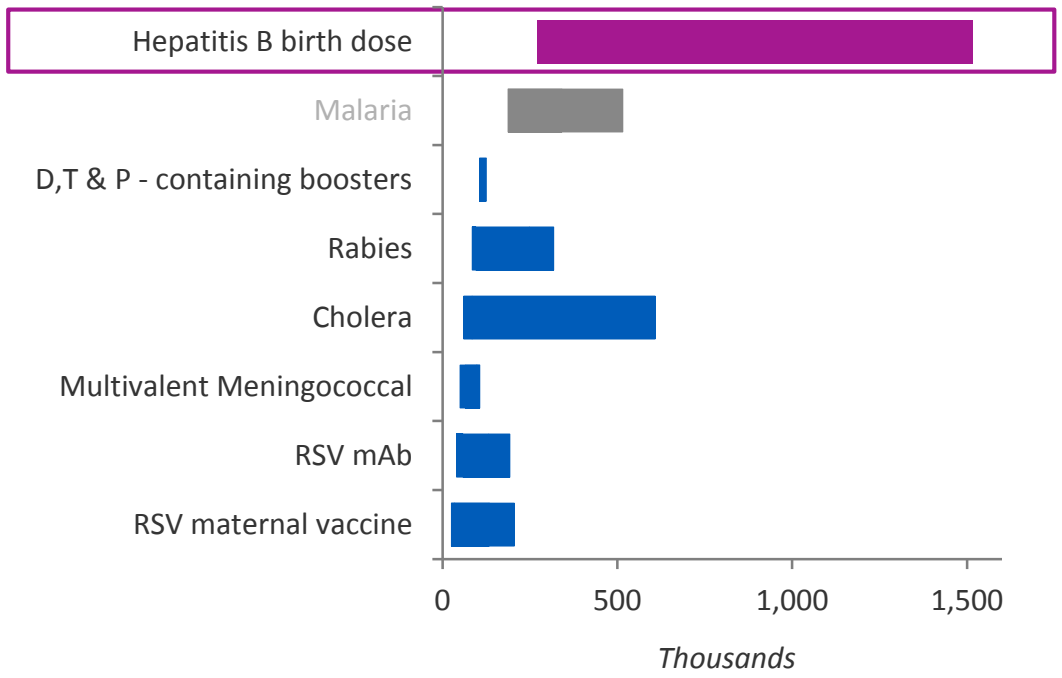
# Impact and value for money compared to VIS candidates

# Health impact compared across VIS candidates

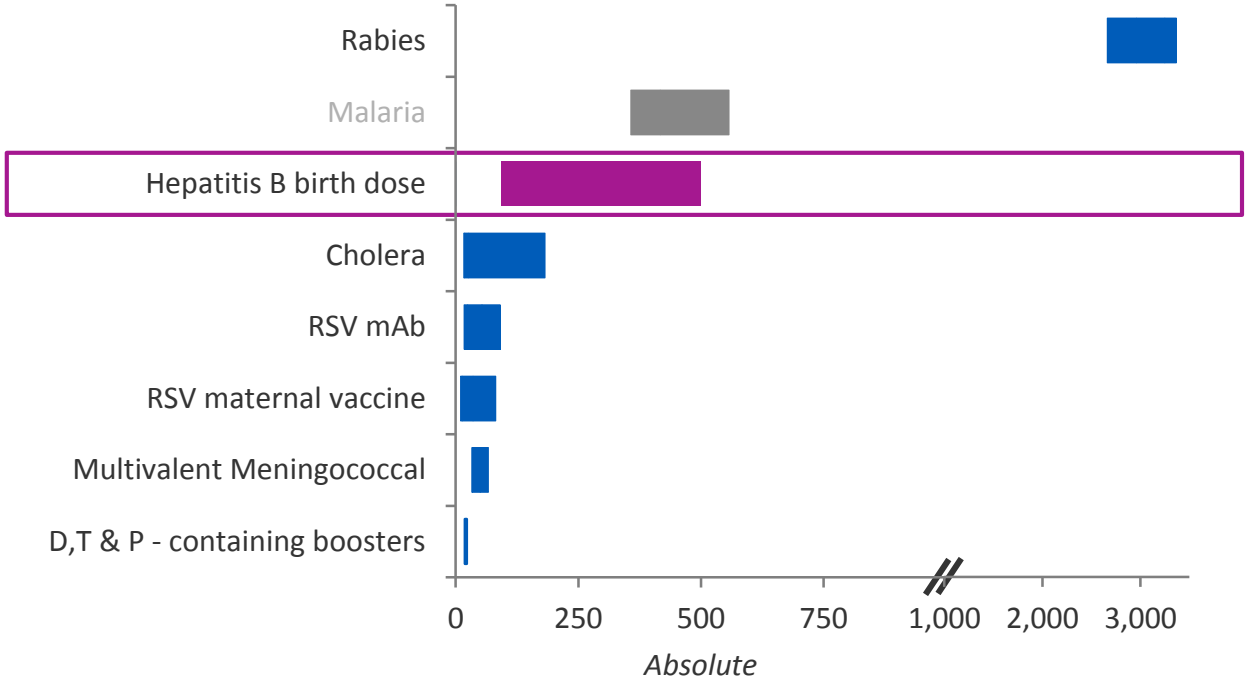
**Nigeria excluded**

**Scenario:** Both in and out of facility births with a traditional vial; variable transmission rate[1]

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




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




1.Goldstein, CDA and Imperial models, assuming both in and out of facility delivery and including sensitivity analysis on rate of vertical transmission (low/medium/high)
Range in impact outcomes driven by differences in burden assumptions
Consideration for Gavi support to Nigeria for VIS candidates would be considered separately through the Nigeria-specific strategy which was approved by the Gavi Board in June 2018

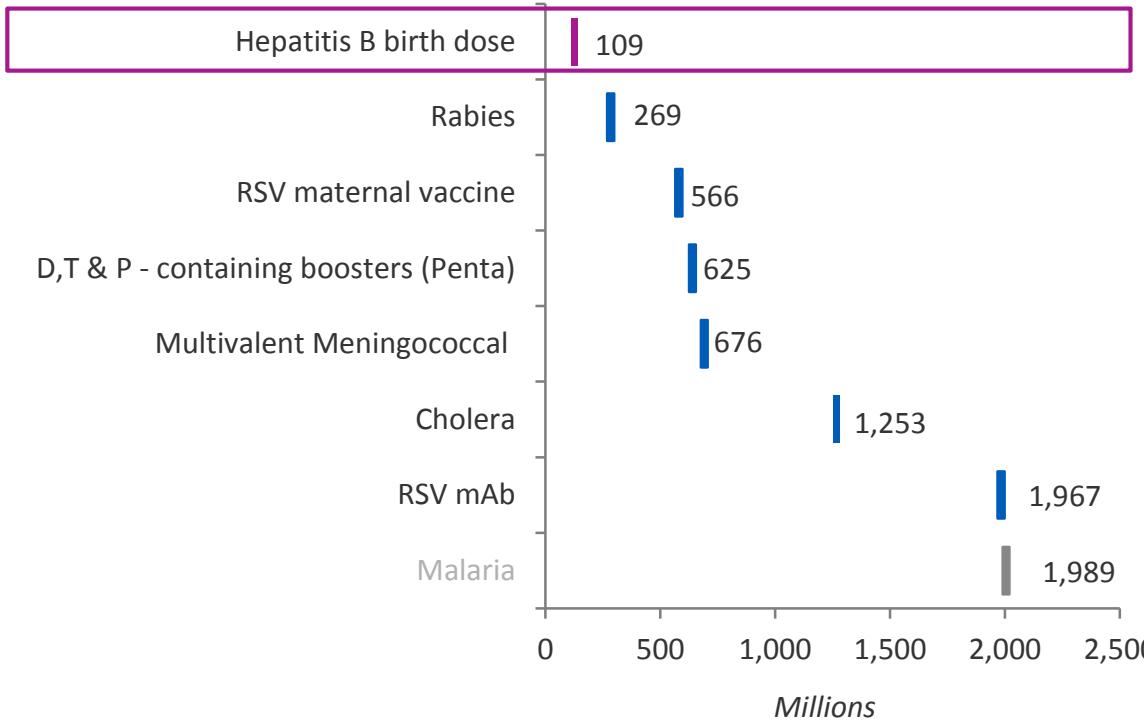

Range of projected impact

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

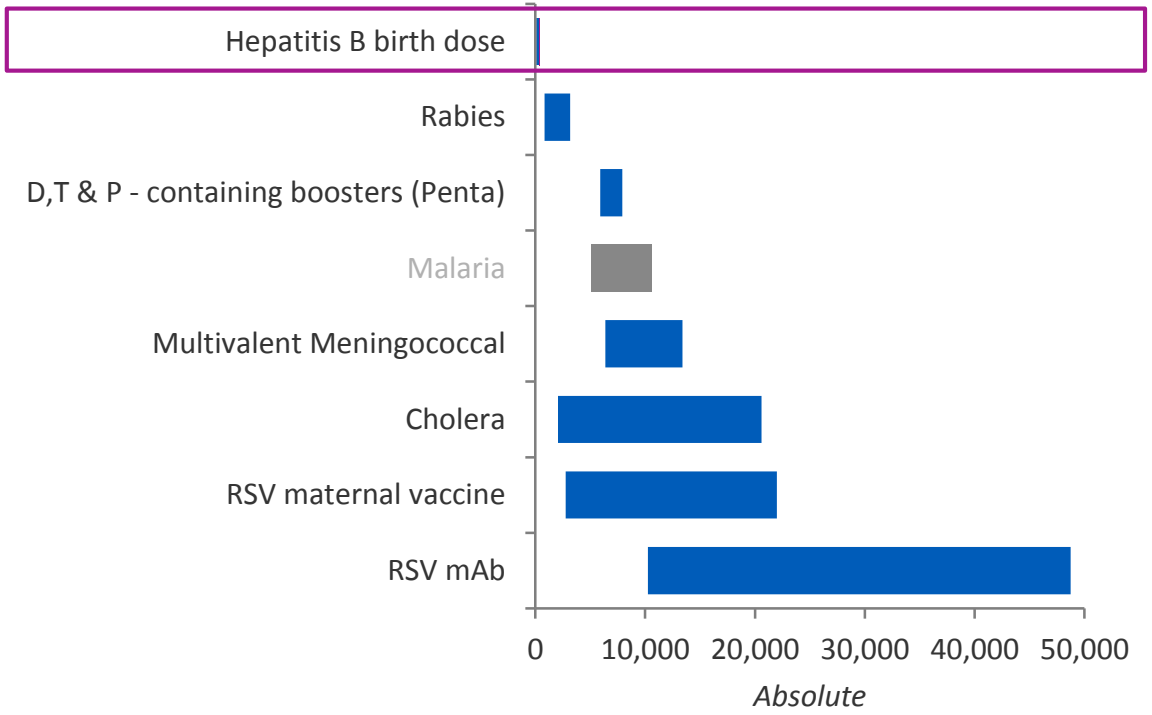
**Nigeria excluded**

**Scenario:** Both in and out of facility births with a traditional vial; variable transmission rate[1]

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




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




1. Goldstein, CDA and Imperial models, assuming both in and out of facility delivery and including sensitivity analysis on rate of vertical transmission (low/medium/high)
Range in impact outcomes driven by differences in burden assumptions
Note: D,T&P –containing boosters represent Penta as first booster
Consideration for Gavi support to Nigeria for VIS candidates would be considered separately through the Nigeria-specific strategy which was approved by the Gavi Board in June 2018


Range of projected impact

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# Country perspective

# Interviews with country stakeholders revealed that reaching out of facility births would be challenging

**Priorities and approach**

- Regional priority (eg, SEAR countries), but some countries mixed as would like to see burden data
- Some countries exploring subnational introductions first, targeting high risk populations
- Not viewed as similar to BCG vaccine due to different time component (eg, longer time period for vaccination with BCG)
- Some countries using traditional vials out of cold chain, seeing improvement in coverage; other countries express interest in cPADs e.g. Unject but cautious on price and cold chain requirements

**Coordination and expanding to new platforms**

- Leveraging maternal and newborn care platform seen as feasible, but mixed views on costs
  - Some respondents noted training midwives could carry higher costs, others felt overall costs should be similar to other vaccine introductions as touchpoint already exists
- Coordination of supply will need to be addressed – should vaccine be stored in maternity wards or using EPI storage facilities?

**Challenges**

- Some confusion over use of vaccine, eg, administration after 24 hours (recommended time frame) or to babies born with low birth weight
- Out of facilities births seen as significant challenge to reach due to distance and lack of skilled birth attendants present
  - Some countries delaying introducing Hep B-BD until institutional birth rate increases
  - Some respondents expressed desire for global guidance on how to access this population
- Midwives can be trained to give Hep B-BD even for out of facility births, but sometimes difficult in administering within 24 hours if birth is unattended (midwife sometimes doesn't arrive for baby check within that timeframe)
- Single dose vials are preferred as midwives cannot carry multi-dose vials, but they would be more expensive presentation
- Some concerns about higher transportation costs to deliver vaccines to district facilities

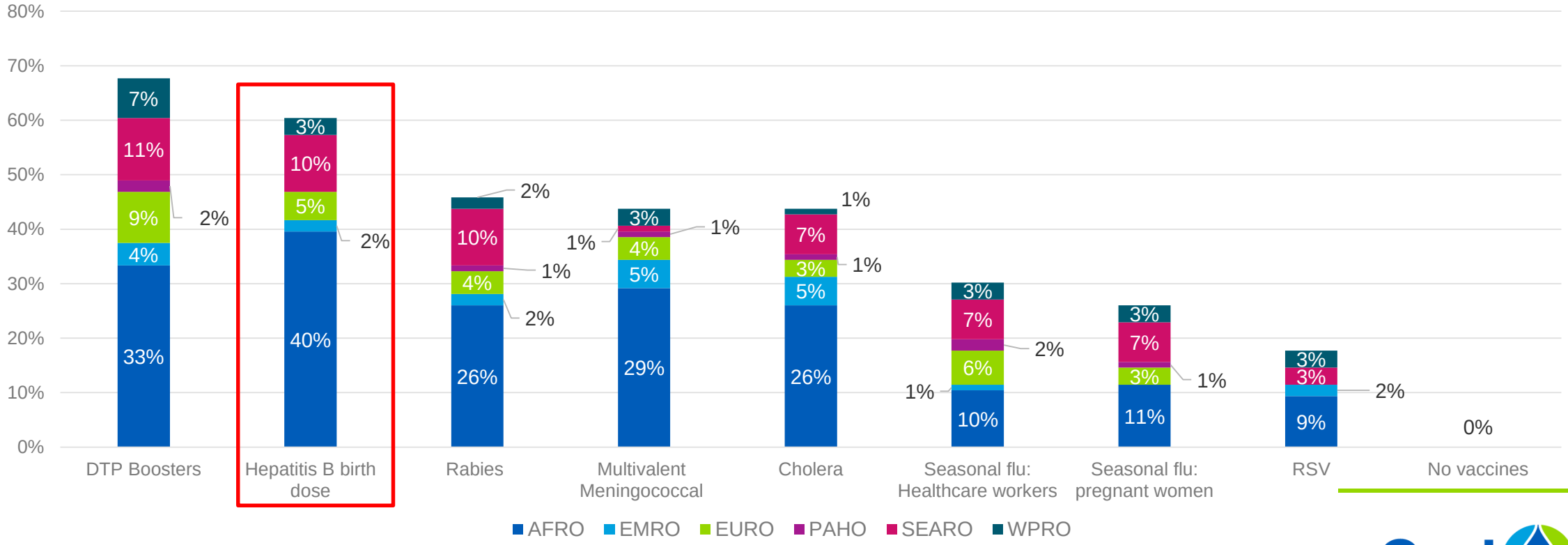


Source: VIS Phase III in-depth country interviews

# Hepatitis B birth dose was prioritised by the majority of respondents (60%)

*Taking into consideration the cost of co-financing/ financing each of these vaccines, the expected impact and your capacity to introduce new vaccines, which would you prioritise over the next 10 years?*

% of respondents indicating they would prioritise each vaccine in next 10 years




*Given limited or regional disease burden, not all vaccines are of relevance for all Gavi-supported countries*

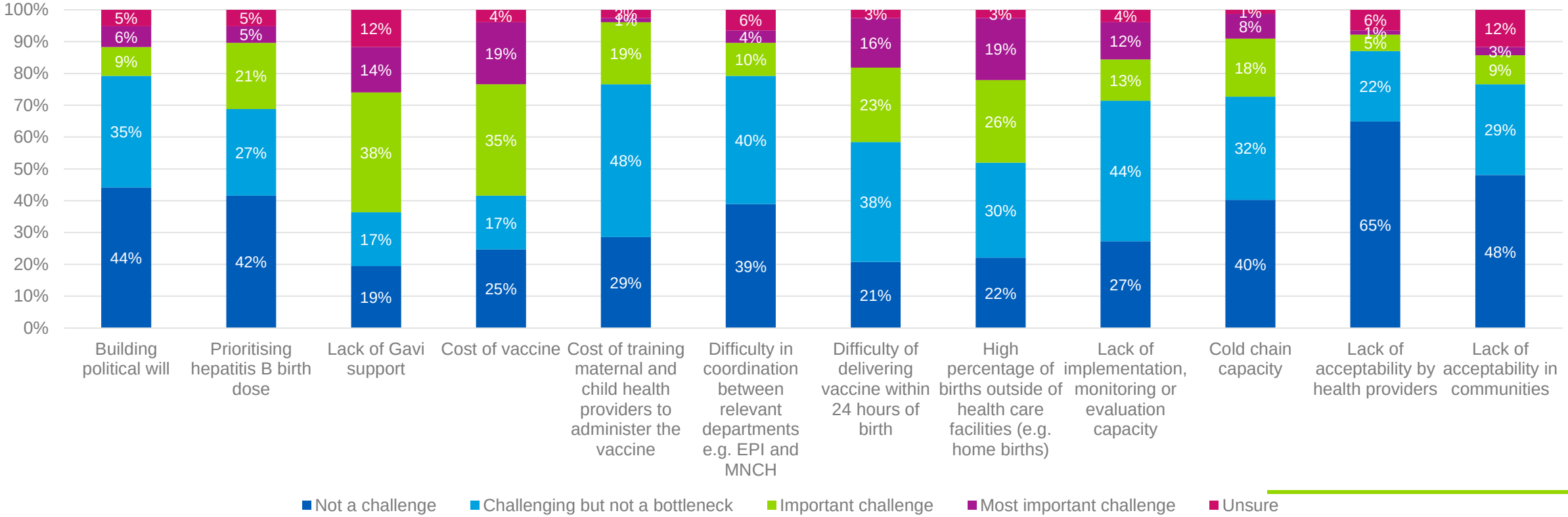


Source: VIS Phase III country survey

# Cost of vaccine, out of facility births and timeliness of administration amongst challenges for introduction

*What are the main challenges faced in introducing and successfully scaling-up coverage of the vaccine?*

% respondents indicating level of challenge for each birth dose-related activity



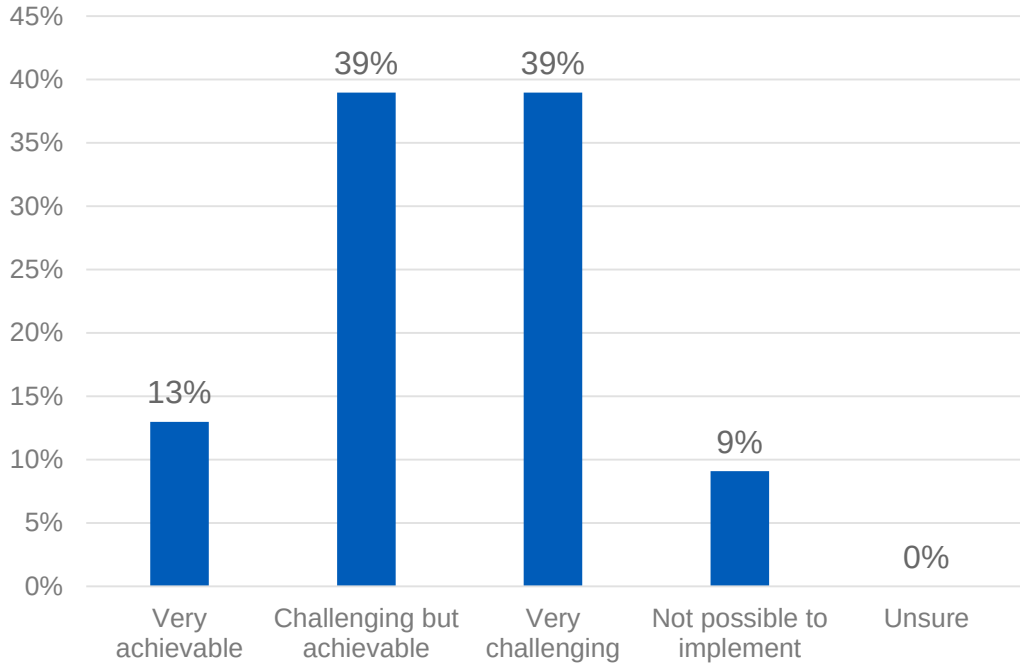



Source: VIS Phase III country survey

# Most respondents indicate that reaching newborns born outside of facilities would be challenging

*For newborns born outside of health facilities, would it be possible to conduct outreach to deliver hepatitis B birth dose within 24 hours?*

% respondents indicating level of challenge to reach newborns outside of health facilities




## Comments regarding delivering birth dose outside of facilities

- Difficulty in reaching remote areas
- Could be integrated into routine outreach activities, but not within 24 hrs of birth
- Lack of reporting of births
- Cost of transport for health care worker (HCW) or family
- Traditions that keep mother and baby at home for post-natal period
- Community HCWs not authorised to vaccinate
- Need for single-dose cPADs and controlled temperature chain to assist HCWs
- Outreach strategy likely expensive to implement, as well as security concerns
- Shortage of human resources
- Acceptability of parents
- Lack of integration between MNCH and EPI

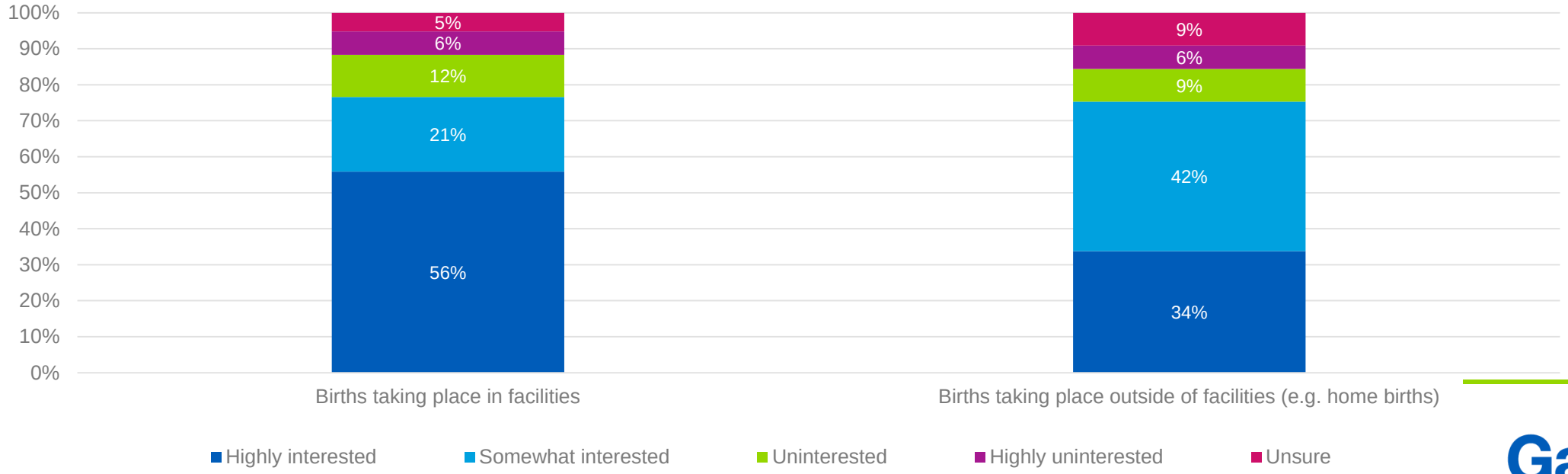


Source: VIS Phase III country survey

# Respondents are interested in using Uniject in facilities and for births taking place outside of facilities

*Uniject is single-use auto-disposable delivery technology which has been pre-qualified for hepatitis B vaccine. Use has been shown to increase coverage, especially in outreach settings, and administrators have found it easier to use, however it is more expensive and requires more cold chain space than multi-dose vials. Would there be an appetite for this product to support hepatitis B birth dose administration if it was offered by Gavi under the usual co-financing arrangement?*

% respondents who would be interested in using Uniject in different delivery settings






Source: VIS Phase III country survey

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# Implementation requirements

# Unique implementation requirements

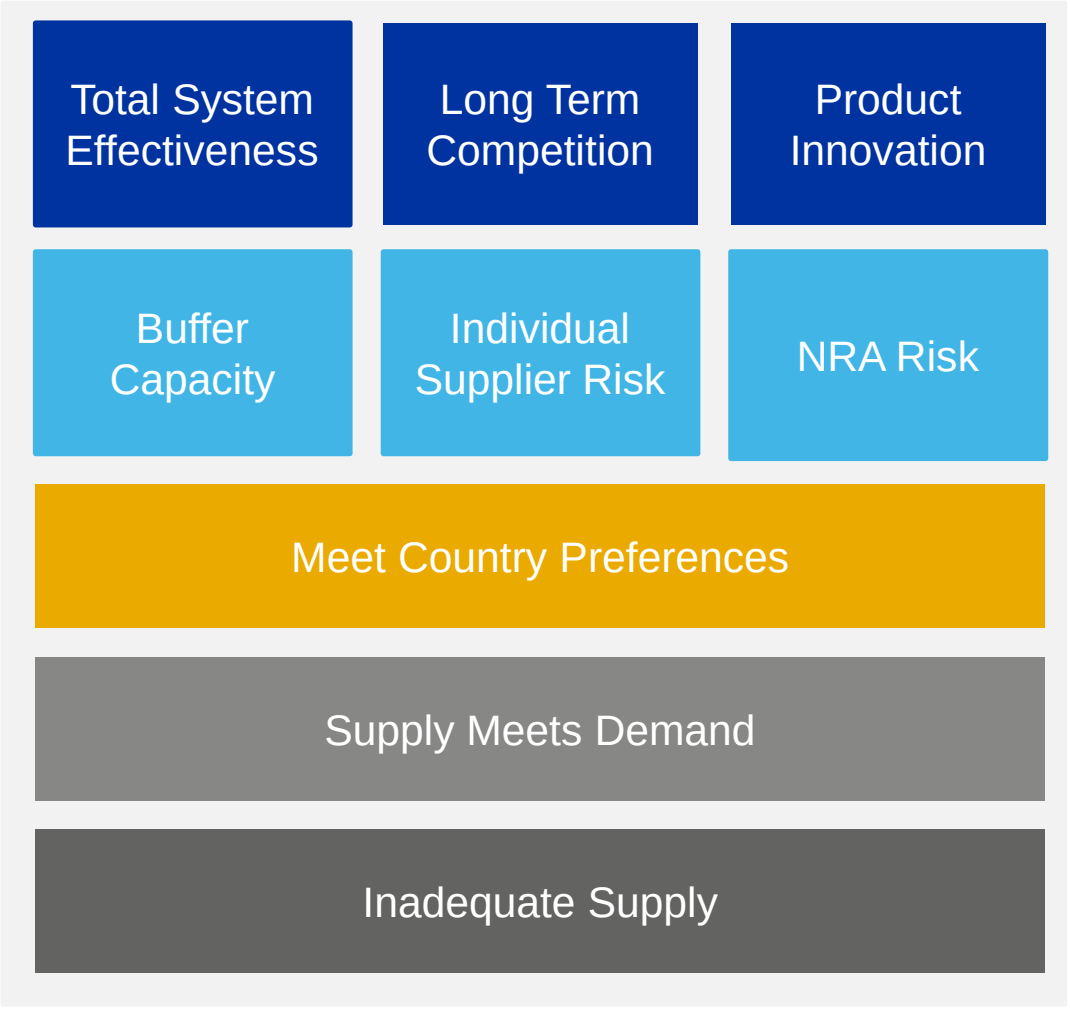
| | Area of focus | Unique implementation requirements | Associated costs |
|---|---|---|---|
| **Global level** | Policies and processes | • n/a | |
| | Supply | • Ensure sufficient supply of monovalent hepatitis B vaccine, within a healthy market framework for both hep b-bd and pentavalent production | |
| **Country level** | Planning, coordination, integration | • Task-shifting to midwives or nurses who deliver babies could be politically challenging in some places<br>• Coordination between MNCH and EPI departments to ensure alignment and appropriate division of labour | • Policy creation and ensuring all stakeholders have ownership<br>• EPI-MNCH coordination |
| | Supply chain infrastructure and logistics | • Vaccine delivered to facilities through EPI, requires cold chain in maternal wards<br>• Vaccine delivered through outreach requires new logistics to be developed | • Cold chain equipment for maternity facilities |
| | Health workforce | • Health workforce already in place, both EPI and MNCH staff would be able to administer<br>• Training MNCH staff in data recording and Hep B-BD vaccination | • Training of MNCH staff |
| | Social mobilization, education, communication | • Educating mothers about necessity of Hep B-BD and empowering them to request it from health providers<br>• Advocacy and awareness campaigns for Hep B-BD | • Social mobilisation costs to ensure strong introduction and continued parental support |
| | Surveillance | • Hepatitis B surveillance is limited and would require specific serosurveys to understand the burden and potential impact | • Serosurveys to measure burden and potential impact |



Most challenging | Unique but manageable | Few unique implementation requirements

Note: Does not consider Gavi support for cPADs e.g. Uniject

# Healthy market framework analysis shows few risks




**Cost-effectiveness of cPADs e.g. Uniject** under the total systems effectiveness lens is yet to be determined

**Future cPADs** could be other contenders for delivering monovalent hepatitis B

**Low supplier and NRA risk** as PQ'd manufacturers are in different countries with established regulatory agencies, and tend to be large manufacturers

Both 1 and 10-dose vials of monovalent hepatitis B are available, however, there is currently **no supply of the only available cPAD, Uniject**, if Gavi were to support this presentation significant market shaping efforts would be required

Forecast demand would double UNICEF procurement of hepatitis B vaccine. As hepatitis B is a component of pentavalent vaccine, **there is little risk that expanded demand could not be met** given the capacity of pentavalent manufacturers

# Countries have faced barriers in introducing Hepatitis B birth dose

## Planning, coordination and integration

**38 Gavi-eligible countries have not introduced HepB-BD despite low cost of vaccine (~$0.20) and clear WHO recommendation**

**Barriers have included:**

- Lack of understanding of burden
- New platform for vaccination requiring close ties with EPI and MNCH
- Low % of facility births in some countries may result in low Hep B-BD coverage
- Logistical challenges of vaccinating infants not born in healthcare facilities and task-shifting to community healthcare workers
- Extra cold chain requirements
- Prioritising funding for establishing the Hep B-BD timepoint vs. introducing other vaccines as the birth dose is not Gavi-supported and therefore not viewed as important by countries

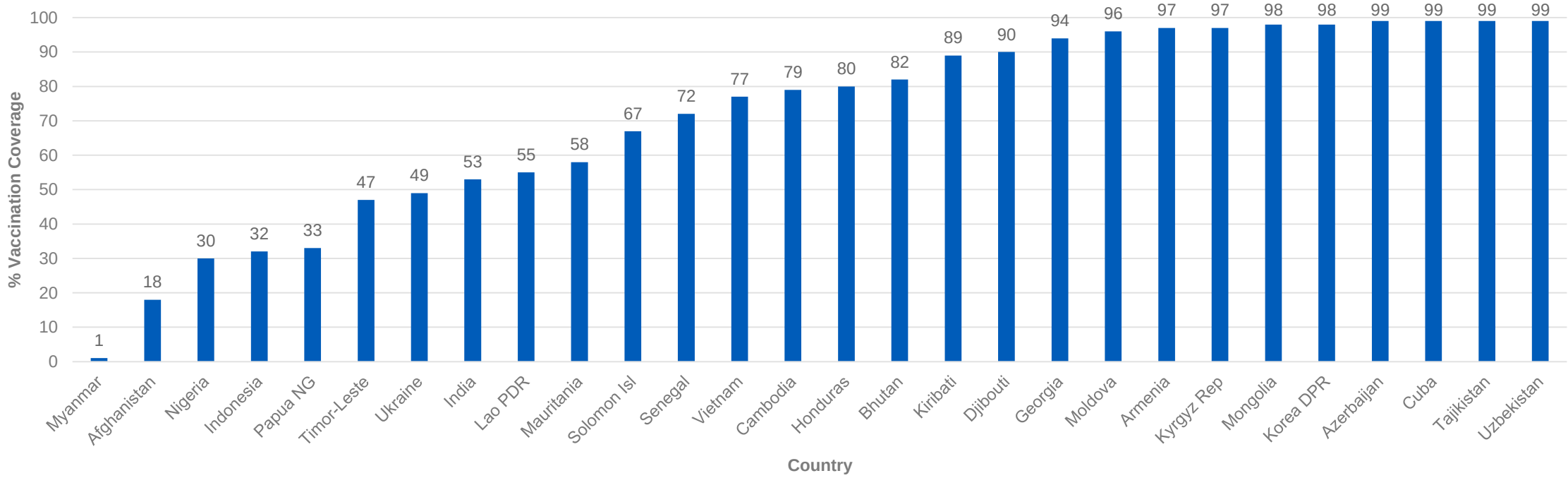
# Strengthening delivery of vaccines at birth will have benefits for other timepoints

| | Antenatal care | Birth | Postnatal care |
|---|---|---|---|
| **Potential vaccines at timepoint** | • Seasonal flu<br>• Td<br>• *Future: RSV, hepatitis E* | • **Hepatitis B birth dose** (<24hrs)<br>• BCG | • n/a |
| **Illustrative examples of other interventions at timepoint** | • Counselling (e.g. about vaccines, breastfeeding, healthy eating)<br>• Vitamin supplementation<br>• Blood testing for anaemia, HIV, diabetes | • Vitamin K<br>• Cord care<br>• Oxytocin (mother) | • Family planning<br>• Counselling about danger signs<br>• Growth monitoring |

*Establishing a timepoints for immunisation is an opportunity to strengthen other interventions*

# In the 29 Gavi countries that have already introduced, coverage ranges greatly

## Gavi 73 – 2017 HepB-BD Coverage






Source: 2017 WUENIC estimates; most countries had Hep B-BD prior to 2013, only Afghanistan, Angola, Mauritania, Senegal ,Timor-Leste. No values reported for Angola.

# MNCH birth systems can be leveraged to drive uptake of hepatitis B birth dose

## Planning, coordination and integration

| MNCH Birth Systems | MNCH system components and interventions* | Relevance for Hepatitis B birth dose |
|---|---|---|
| **Birth protocols** | Understand what to do in each **birth setting** to address all birth complications. Ensure robust linkages between health system levels. | Ensure standard **birth protocols include administering Hep B-BD to the neonate** before discharge or midwife departure from home |
| **Midwife mentoring** | Establish **hands-on mentoring** system to train Skilled Birth Attendants (SBAs); ensure that SBAs are available to attend all births | Ensure that mentoring for midwives include **reminders for Hep B-BD administration and counseling** |
| **Logistics** | Ensure **reliable delivery of all the tools and drugs** necessary to diagnose and treat complications **wherever they arise** | Leverage existing inventory management practices to **ensure availability of Hep B-BD** in delivery facilities |
| **Referral systems** | **Transportation and communication mechanisms** available for cases; specialized care must be received at hospitals and health centers | Leverage **referral systems** that bring mothers in for emergency care to bring neonates in within 24 hours to receive Hep B-BD |
| **Hospital systems** | Midwives, nurses and doctors properly trained; with all health service delivery tools and equipment readily available | Ensure midwives', nurses' and doctors' training includes understanding the **importance of administering within 24 hours** and how **to administer/counsel Hep B-BD** |
| **Management systems** | **All births tracked;** all mentoring, supply chain and referral systems overseen and supported | Leverage **birth tracking systems to send HCWs** within 24 hours of birth to deliver Hep B-BD to neonate |

*Other non-birth MNCH systems could also be valuable for the Hep B-BD program, such as guidance provided during ANC visits for expectant mothers

# Uniject has been considered as a tool to aid the implementation of Hepatitis B birth dose in out of facility births

**Uniject is a compact pre-filled auto-disposable injection device that is currently prequalified for use with Hep B-BD, Tetanus toxoid & pentavalent vaccines as well as oxytocin and Depo Provera (long-acting contraception)**

## Benefits of Hep B-BD Uniject Use

- ✓ Healthcare workers can be trained in less than 2hrs
- ✓ May be used by traditional birth attendants, midwives, or community-based health care workers, depending on local policies
- ✓ Lower risk of contamination & no risk of needle reuse
- ✓ Accurate dosage, lower wastage, no reluctance to open vials
- ✓ Time-saving
- ✓ Pilots in China and use in Indonesia showed increased coverage of out-of-facility Hep B-BD*, especially in rural regions
- ✓ Out of cold chain use supported by WHO Position Paper and operational guidelines in some regions

## Barriers to Hep B-BD Uniject Use

- ✗ Country hesitancy to use non-trained healthcare workers and task-shift
- ✗ Hesitancy to support out-of-facility births in some countries due to mixed messaging
- ✗ Unclear if feasible for Gavi-eligible countries, as only scaled example is Indonesia
- ✗ Lack of WHO approval for HepB-BD out-of-cold-chain use (via CTC)
- ✗ Relative large packed volume vs. 10-dose vial
- ✗ Cost per dose is high
- ✗ Lack of available supply



**Pilots conducted used out-of-cold chain strategy*

# Controlled Temperature Chain could be leveraged in the future to deliver hepatitis B birth dose

## Supply chain, infrastructure & logistics

*"The controlled temperature chain (CTC) is an innovative approach to vaccine management allowing vaccines to be kept at temperatures outside of the traditional cold chain of +2°C to +8°C for a limited period of time under monitored and controlled conditions, as appropriate to the stability of the antigen.*
*A CTC typically involves a single excursion of the vaccine into ambient temperatures not exceeding +40°C and for duration of a specific number of days, just prior to administration." - WHO*

### Suggested product profile characteristics for CTC prequalified hepatitis B vaccines[1]

| Product Profile Characteristic | Minimally Acceptable Target | Optimal Target |
|---|---|---|
| **Time and temperature for CTC use** | To be determined. | 28 days at 40°C |
| **Doses per container and container type** | Single-dose containers – especially for outreach to homes, though use by lesser-trained health workers may not be possible.<br>Multi-dose containers – especially for birthing facilities without cold chain where vaccine wastage is expected to be low within the CTC duration timeframe. | Single-dose containers* – for all scenarios except where lesser trained health workers are meant to deliver the Hep B-BD.<br>Single dose compact Prefilled Autodisable Devices – for use by lesser trained health workers and where shown to be cost-effective. |
| **Temperature indicator** | Vaccine vial monitor 30 (VVM30) or above with separate peak temperature threshold indicators (PTTIs) accompanying the vaccine during CTC use | VVM with integrated threshold indicator (VVM-TI) |

1. IPAC Meeting 2018: http://www.vhpb.org/files/html/Meetings_and_publications/Presentations/HAN67.pdf

# WHO continues to work to progress towards CTC certification

## Supply chain, infrastructure & logistics

### Position

Hepatitis B Position Paper recommends out of cold chain (OCC) use in settings where administration of a Hep B-BD is restricted by access to cold storage in order to improve coverage

### Availability

No hepatitis B vaccines are currently WHO prequalified for use in a CTC. However, at least two manufacturers are seeking licensure for their hepatitis B vaccines to be used in a CTC.

### Demand

If a CTC-licensed Hep B-BD vaccine was available, WHO estimate that between 6% and 14% of the doses procured in 2018 could have been used in a CTC by the countries in the WHO African, South-East Asia and Western Pacific regions. This crude market share estimate assumes that countries permit the use of the vaccine in a CTC.

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# Risks and mitigation

# Risks of inaction (Gavi investment not approved)

| Strategic concern | Risk |
|---|---|
| **Financial** | • Countries do not introduce despite relatively low vaccine procurement support |
| **Market** | • cPADs e.g. Uniject formulation will remain unavailable |
| **Programmatic** | • Countries continue to deprioritise introduction of Hep B-BD due to Gavi's signal |
| **Reputational** | • Gavi support misaligned with WHO recommendations and global priorities |

# Risk and mitigation plan if Gavi investment approved

| Strategic concern | Risk | Mitigation plan |
|---|---|---|
| **Financial** | • Domestic financing of vaccines may not be sustainable in the long term | • Discuss the financial implications of introducing hep B-BD within broader vaccine portfolio |
| | • Potential that some countries are unable to procure through UNICEF due to domestic preferred supplier agreements and no Gavi co-financing | • Further explore the extent of procurement issue and work with countries to develop solutions |
| **Programmatic** | • Coverage is low if vaccine only delivered in-facility | • cPADs e.g. Uniject and CTC learning agendas would identify long-term solutions for increasing out of facility coverage |
| | • Support for platform establishment and strengthening is insufficient to cover all activities countries require to develop new immunisation timepoint, therefore discouraging countries from introducing | • Bottom-up costing of first several introductions to understand the true cost of introduction to inform future policy reviews<br>• Encourage countries to identify domestic resources to support introduction activities not supported by Gavi |
| | • Countries that have introduced, but achieve very low levels of coverage, do not improve | • Structure support as needed using existing funding tools for health system strengthening |

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# Investment recommendation

# Recommended investment scenario

| | | | |
|---|---|---|---|
| **Traditional vaccine support** *(for vials)* | No Gavi support for hepatitis B birth dose | **Provide support to establish platform as catalytic support for introduction of hepatitis B administered at birth, beginning in 2021** | |
| **cPADs** | No Gavi support for cPADs | **Consider cPADs as part of learning agenda** | Gavi support for cPADs introduction |

**Recommendation**

1. In line with current co-financing policy, Gavi would not fund procurement of hepatitis B vaccine as the price is below the minimum country co-financing level. cPADs are only supported through the learning agenda.

# Illustrative hepatitis B birth dose components of a VIS learning agenda

| Objective | Key questions | Indicative cost |
|---|---|---|
| Feasibility of out-of-facility birth outreach | • Use of traditional vials vs Uniject/cPADs<br>• Out of cold chain use of products | $2-3 million for multi-site study |
| Burden of disease | • Rate of mother-to-child transmission<br>• Seroprevalence | Ongoing studies as part of pentavalent programme |

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

# Hepatitis B: key experts

## Experts consulted

- Yvan Hutin (WHO)
- Tracey Goodman (WHO)
- Karen Hennessy (WHO)
- Lawrence Rodewald (WHO)
- Shalini Desai (WHO)
- Minal Patel (WHO)
- Julien Kabore (WHO)
- Ana-Lea Kahn (WHO)
- Rachel Bauquerez (WHO)
- Yanfeng Lim (CHAI)
- Julia Roper (CHAI)
- Ying Wang (CHAI)
- Andrew Story (CHAI)
- Rania Tohme (CDC)
- John Ward (Task Force for Global Health)
- Yusuke Shimakawa (Institut Pasteur)
- Chris Morgan (Burnet Institute)
- Timothy Hallett[1] (Imperial College)



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.

# Hepatitis B: sources

## Sources

- Centre for Disease Analysis burden data
- Goldstein et al., 2005. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. International journal of epidemiology 34(6):1329-1339
- Global Burden of Disease, Institute for Health Metrics and Evaluation (IHME), 2016
- Global Health Sector Strategy on Viral Hepatitis 2016-2020
- Nayagam, S. et al., 2016. Requirements for global elimination of Hepatitis B: a modelling study. Lancet Infect Dis 16(12): 1399–1408
- UNICEF Vaccine Price Data
- WHO Hepatitis B Position Paper, 2017
- WHO Prequalified Vaccines List
- Coverage estimates of Uniject from CHAI
- Uniject manufacturer insights from CHAI



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# Appendix

# Glossary of Terms

| | |
|---|---|
| **Vaccination schedule** | The number of doses and timing of their administration |
| **Age group** | Age at which vaccination will be administered |
| **Country scope** | Number of Gavi-supported countries included in forecast for vaccine introductions[1] |
| **Target population** | Specific population targeted to receive the vaccine |
| **Delivery strategy** | Implementation approach or programme in which vaccination will be incorporated |
| **Introduction dates** | Forecasted introduction year of vaccine in a country |
| **Vaccine uptake** | Time to ramp up to maximum coverage in target population |
| **Coverage** | Coverage assumption or analogue and yearly increase |
| **Products** | Date of WHO pre-qualification, number of doses per vial and other product-specific characteristics |
| **Logistics** | Wastage assumption[2] based on vial size and presentation, and buffer stock factored into demand |
| **Efficacy / effectiveness** | Best available information on vaccine efficacy / effectiveness |
| **Duration of protection** | Best available information of loss of protection from time of vaccination |
| **Burden of disease** | Burden of disease dataset(s) that is/are being used for modelling health impact |
| **Currency** | All monetary values are presented in US$ |

1. Not all countries in scope may be forecasted to introduce within the timeframe and not all countries in the forecast may benefit from Gavi financing based on the Eligibility and Transition Policy
2. Vaccine wastage assumptions from WHO



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# Phase II scorecard: Hepatitis B *(June 2018)*

## Modelled strategy: Routine immunisation with 1 dose for all in facility births

| VIS criteria | Indicator | Results | Evaluation[1] |
|---|---|---|---|
| Health impact | Total impact averted | ~225K-2,690K future deaths, ~980K-3,200K future cases averted, 2020 – 2035 | |
| | Impact averted per 100K | 85-1,020 deaths, 370-1,210 cases averted, 2020 – 2035, per 100K vaccinated population | |
| Value for money | Procurement cost | ~$ 40-440 procurement cost per death, ~$ 30-100 procurement cost per case averted | |
| Equity & social protection impact | Impact on vulnerable groups | Relatively even distribution of disease burden across groups[2] | |
| | Benefits for women and girls | No special benefits of vaccination for women and girls | |
| Economic impact | Direct medical cost averted | ~0.4% of average consumption per capita averted in out-of-pocket medical costs[3] | |
| | Indirect cost averted | ~$ 32-700 productivity loss averted, 2020 – 2035, per vaccinated person | |
| Global health security impact | Epidemic potential | Not IHR notifiable; little evidence of evolution | |
| | Impact on AMR | Low impact of vaccination on AMR (1.6/10 points in expert consultation) | |
| Vaccine cost | Total procurement cost | ~$ 99 Million total procurement cost to Gavi and countries, 2020-2035 | |
| Relevant second. criteria | Market challenges / Catalytic investment / Broader health system impact | Limited market challenges to address, but high potential to catalyse additional investments and strengthen health systems across birth delivery platform and linkages with MNCH services | |

**Additional considerations**

- 38 Gavi eligible countries currently not delivering Hep B-BD
- Only 2 Gavi-eligible countries have independently introduced Hep B-BD since 2013 despite WHO recommendation
- A key driver of uncertainty in impact modelling is estimated coverage rates for vaccination within 24 hours of birth
- Contribution to reducing burden of non-communicable diseases (e.g., liver cancer, cirrhosis) in low-resource settings where treatment may not be accessible

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. 2. When considering Hep B-BD only, although some indication that there might be higher burden among lower socioeconomic groups. 3. Low medical cost partially driven by lack of access to expensive treatments for liver cirrhosis or cancer.



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# Phase II secondary criteria and financial implications: Hepatitis B *(June 2018)*

## Modelled strategy: Routine immunisation with 1 dose for all in facility births

| VIS criteria | Indicator | Results | Evaluation[1] |
|---|---|---|---|
| Other impact | U5 deaths averted, total | ~30-10,000 future U5 deaths averted, 2020 – 2035 | |
| | U5 deaths averted, per 100K | ~0-4 U5 deaths averted, 2020-2035, per 100K vaccinated population | |
| | DALYs averted (cost per DALY) | ~12-254 Million DALYs averted, 2020 – 2035, ~$ 0-8 procurement cost per DALY | |
| | DALYs averted, per 100K | ~4K-96K DALYs averted, 2020-204, per 100K vaccinated population | |
| Gavi comp. advantage | Vaccine market challenges | Low potential to influence the market (e.g., Gavi experienced suppliers, predictable demand) | |
| | Catalytic investment | High potential to catalyse investments in country financing of vaccine & promotion of facility-births | |
| Implementation feasibility | Ease of supply chain integration | Packed volume of 3-17cc; 24-48 months shelf life at 2-8°C; VVM = 30 | |
| | Need for HCW behaviour change | Strong need for HCW change required: Training for implementation of new platform and to ensure administration within 24 hours after birth | |
| | Feasibility of vaccination time point | Existing access point, but new vaccination time-point | |
| | Acceptability in target population | Ranked highest (1/9) in country stakeholder survey, but likely need for education of target pop. | |
| | Long-term financial implications | Falls within the category of price per course <$ 2 | |
| Alt. interventions | Alternative interventions | No cure, treatment options for chronic infections available, but not sufficiently scalable | |
| Broader health system impact[2] | Broader health system impact | Opportunity to improve PNC, maternal health, and promotion of routine childhood immunizations; promotion of in-facility births | |
| Operational cost[3] | Incremental costs per vac. person | Low incremental cost of ~$ 0.30 per vaccinated person | |
| Implementation costs | Additional costs for introduction | Medium: HCW training, need to establish surveillance systems | |

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** | • 1 dose | • WHO Position Paper |
| **Age group/Target population** | • Within 24hrs of birth[1]<br>• All in- and out of-facility births | • WHO Position Paper |

Note: WHO recommendation is that neonates receive Hep B-BD within 24 hours of birth but vaccination within first 7 days of life can prevent peri-natal infection. Modelling accounts for any benefit up to the first penta dose.

# Demand forecasting assumptions

| Element | Assumptions | | Rationale / Source |
|---|---|---|---|
| **Country scope** | 36 countries without Hepatitis B BD (Gavi-supported in year of introduction based on current policy) | | Hepatitis B burden is global, no specific geographic distribution. WHO-UNICEF reported coverage is source for which countries have introduced. |
| **Target population** | All live births | | WHO Position Paper |
| **Delivery strategy** | Routine in health facilities and outreach to out of facility births | | Potential strategies for introduction |
| **Introduction dates** | First introduction: 2020<br>Country Introductions to be phased by:<br>• Penta introductions<br>• Other new vaccine introductions (e.g., not before PCV, Rota, HPV)<br>• County interest/commitments (insights from CHAI) | | Vaccine currently licensed and PQ, introduction timeline dependent on country appetite and operational considerations |
| **Vaccine uptake** | Standard Gavi assumption of 2 to 4 years to max uptake, depending on country size | | Standard assumption applied to Gavi forecasts of current portfolio |
| **Coverage** | **In facility** | Percent of births in a health facility discounted by 7.69% (average difference between Hepatitis B BD coverage and % facility births for Gavi countries with Hepatitis B BD already introduced)<br>3% increase/year up to 70%, 1% annual increase up to BCG coverage | Nearest analogue given administration at birth in facilities (WUENIC 2017)<br>WHO endorsed coverage assumptions. |
| | **Out of facility** | 60% of out of facility births<br>1% annual increase | |
| **Products** | PQ Date: Already PQ'd, Schedule: 1 dose, Presentation: 1-dose vial | | |
| **Logistics** | Wastage factor: 1.05, Buffer: 25% | | WHO assumption for 1-dose vial |

# Impact modelling assumptions

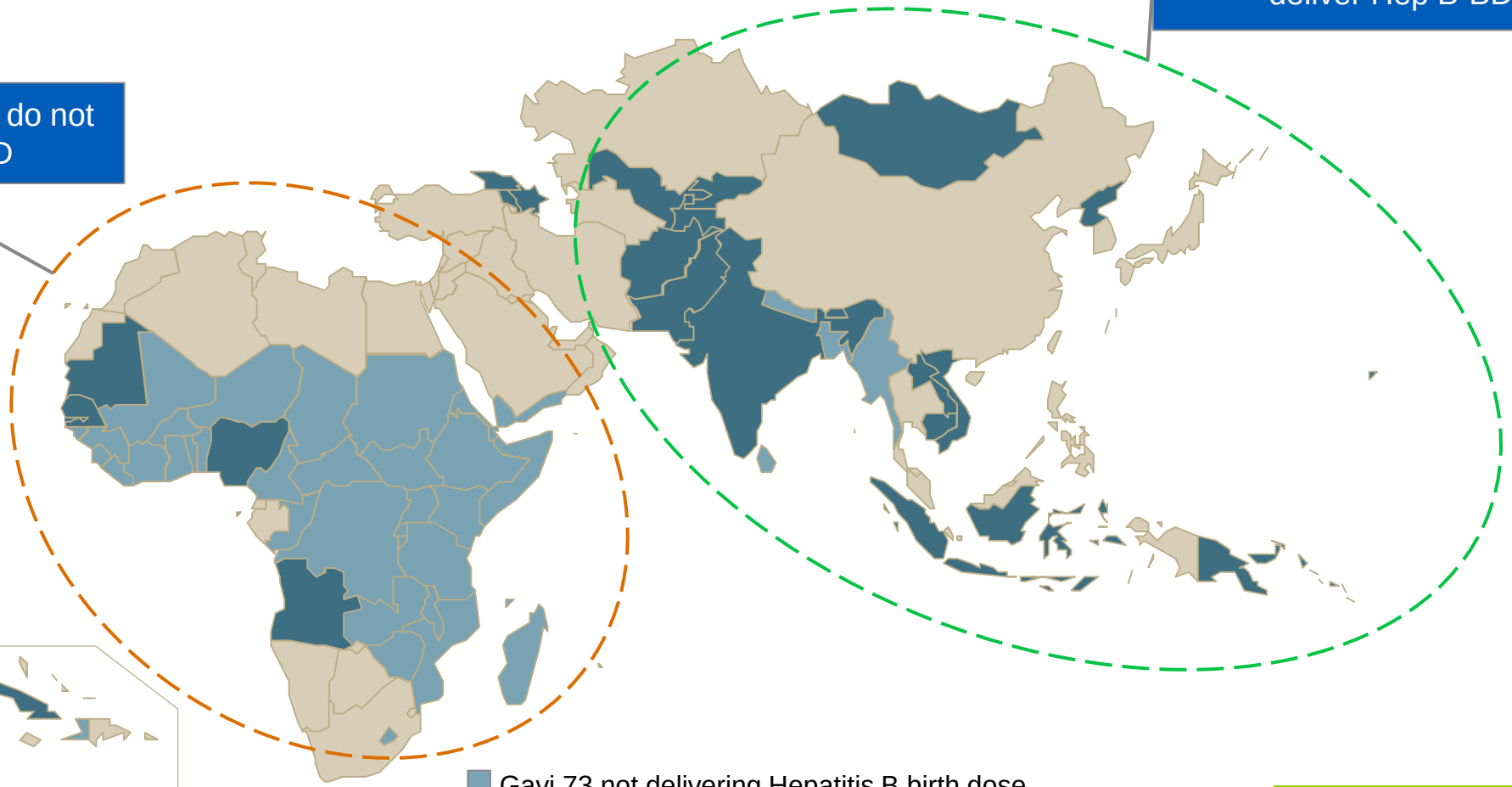
***Assumptions apply to all three vaccination strategies***

| Element | Assumptions | Rationale / Source |
|---|---|---|
| **Efficacy** | Efficacy of preventing vertical transmission depends on the prevalence of s (HbsAg) and e (HbeAg) antigen positivity in mothers, which varies by region with high uncertainty, thus risk of transmission data is variable between models depending on input parameters and model structure | Transmission assumptions differ between models to capture uncertainty |
| **Duration of protection** | n/a | Impact of Hep B-BD is inherently the duration between its administration and 1st dose Penta |
| **Burden of disease** | Disease-specific models: Centre for Disease Analysis (CDA) data from Polaris Observatory, and from systematic reviews | CDA: best projected data available<br>Ott/ Goldstein papers: established Hep B-BD reviews |

# Most of the 38 Gavi-eligible countries not delivering hepatitis B birth dose are in Africa

Most Asian countries already deliver Hep B-BD

Most African countries do not deliver Hep B-BD



Moldova & Ukraine not represented on map and have introduced Hep B-BD

Bolivia, Guyana not represented on map and have not introduced Hep B-BD

Gavi 73 not delivering Hepatitis B birth dose

Gavi 73 delivering Hepatitis B birth dose

Never Gavi eligible



Source: WHO/UNICEF Joint Reporting Form as of November 2017

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# Alongside global targets, each WHO region has specific targets regarding hepatitis vaccination

| Source | Policy summary and considerations |
|---|---|
| **Global Health Sector Strategy on Viral Hepatitis 2016-21** | • Goal is to eliminate viral hepatitis as a major public health threat by 2030<br>• Focused on using available interventions including, vaccines, Hep B-BD specifically, injection, blood and surgical safety, harm reduction for injecting drug users and treatment<br>• Pertinent goals include reducing HBV infection in children to less than 1% prevalence by 2020 and 0.1% by 2030 and 90% Hep B-BD coverage by 2030 |
| **SDG Indicator** | • **Target:** By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases<br>• **Indicator:** Hepatitis B incidence per 100,000 population |
| **Western Pacific 2016-2020** | • Achieve prevalence of HBsAg in 5-year-olds of less than 0.1% & in countries that have achieved less than 1% prevalence in children under 5 years, mother-to-child transmission is reduced to less than 2%<br>• Achieve birth-dose and three-dose hepatitis B vaccination coverage of at least 95% |
| **South-East Asia 2016-2021** | • All Member States that have policy have reached 90% coverage with Hep B-BD and 95% coverage with Hep B3 and 95% of newborns in Member States are covered with the Hep B-BD within 24 hours<br>• Goal of <1% HBsAg among children aged 5 years by 2020 |
| **EMRO 2017–2021** | • Hepatitis B birth-dose vaccination coverage of at least 50% is achieved & 3-dose hepatitis B vaccination coverage of at least 90%<br>• Reducing Prevalence of chronic hepatitis B virus infection to <1% among children less than 5 years of age by 2020 |
| **Africa 2016-2020** | • 30% reduction of new cases of chronic viral hepatitis B and C infections<br>• 10% reduction of viral hepatitis B and C related deaths.<br>• Hepatitis B virus vaccine coverage among infants at 90% region-wide<br>• At least 25 countries have introduced a Hep B-BD of hepatitis B vaccine |
| **PAHO 2016-2019** | • 25 countries maintain high HBV coverage (95% or above) as part of the routine childhood vaccination schedule (below 1 year of age)<br>• 25 countries that have included immunization of newborns against HBV within the first 24 hours in their vaccination programs<br>• Goal to eliminate MTCT by 2020 & <0.1% HBsAg in 4-6 yo. by 2020 |
| **Europe 2016-21** | • 90% reduction in the number of new chronic hepatitis B and C infections and a 65% reduction in the number of deaths by 2030, with milestones for 2020 set as 30% and 10% reductions respectively<br>• 95% coverage with three doses of HBV vaccine in countries that implement universal childhood vaccination<br>• 90% coverage with interventions to prevent mother-to-child transmission of HBV<br>• <0.5% HBsAg prevalence in vaccinated cohorts by 2020 |