06a - Annex C: Respiratory Syncytial Virus 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

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Executive summary

Respiratory Syncytial Virus Executive Summary (1/2)

Respiratory Syncytial Virus (RSV)-associated acute lower respiratory infections (ALRI) are estimated to cause ~33M cases annually and 3.2M related hospitalizations in children under 5 years old resulting in ~77K deaths per year

- 90% of burden occur in children under 5, with mortality primarily concentrated in neonates and children under 6 months
- RSV places large burden on health systems due to high rates of hospitalization

Uncertainty exists around RSV immunisation product development and country demand but Gavi has opportunity to proactively shape emerging market and ensure equitable access to new products when commercially available

- No licensed RSV vaccines currently exist – lead candidate (maternal vaccine) could become prequalified (PQ) by ~2020-2021
- As of August 2018, 45 vaccines (for different target populations) and 4 monoclonal antibodies (mAbs) were in development, of which 4 are in Phase 2 or later of clinical trials, with a view to supplying to high-income markets
- Gavi commitment would signal to manufacturers there is a global market for RSV immunisation product(s), encouraging manufacturers to proactively install appropriate capacity to supply LMIC markets and increase long term product and supplier diversity

As currently modelled, RSV maternal vaccine shows higher value for money at currently estimated prices compared to the RSV mAb:

- A maternal vaccine could avert ~26 – 206K deaths and ~1.8 – 10.4M cases between 2021-2035 at ~$3 – 22K per death averted
- RSV infant mAb strategy could avert ~47 – 192K deaths and ~2.9 – 12.2M cases between 2021-2035 at ~$10 – 49K per death averted
- Uncertainty regarding efficacy and duration of protection as products are still in late-stage development
- Disease burden data likely significantly underestimated in community settings in low-income countries and projected impact of RSV immunisation products could increase with improved data

Respiratory Syncytial Virus Executive Summary (2/2)

RSV immunisation is an opportunity to catalyse the integration of Expanded Programme on Immunization (EPI) and Maternal, Neonatal and Child Health (MNCH) service delivery and strengthen platforms to provide health services specifically targeted to women and infants

- Integrating EPI and MNCH services has potential to increase the quality and demand for antenatal/prenatal care, improve maternal and infant health outcomes (e.g. institutional deliveries) and optimise effective maternal immunisation delivery approaches for additional maternal vaccines that become available in the future
- Effectively preventing RSV disease can reduce ALRI burden among neonates and infants and support reduced antimicrobial resistance by decreasing the inappropriate use of antibiotics
- Potential for economic impact by reducing the burden and economic strain on healthcare systems due to RSV disease burden and increased systems efficiencies gained from more integrated health service provision

RECOMMENDATION

- **Provide support for respiratory syncytial virus products contingent on WHO SAGE recommendation and a licensed, prequalified product that meets the financial assumptions of this case**
- **Provide support beginning in 2019 for pre-introduction activities for respiratory syncytial virus products including evidence and demand generation**

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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

No vaccine within timeframe of evaluation, therefore RSV immunisation products were not considered in VIS 2013

Peer-reviewed meta-analysis published in 2017 providing new global RSV burden estimates which include data from low and middle income countries

- Some improvement in burden estimates for treatment-seeking patients in hospitals but burden of non-treatment seeking patients in communities requires further investigation
- WHO Surveillance Pilot provided new data on burden in select low income countries (2 Gavi-supported countries)

Progress made in vaccine development

- 45 maternal, paediatric, elderly vaccine and mAb candidates are in development, 19 of which are in clinical testing
- Lead maternal vaccine candidate is in Phase 3
  - Preliminary analysis of vaccine efficacy against RSV lower respiratory tract infections events from 0-90 days among the 1307 subjects showed some initial evidence of efficacy[1]

Improved alignment between EPI and MNCH stakeholders regarding feasibility and value of additional maternal immunisation programmes

- Partner-led gap analysis identified and prioritised key areas to be addressed for successful implementation of maternal vaccines

1. DSMB statistician conducted analysis of RSV LRTI outcome events which determined the lower bound of a 90% confidence interval of vaccine efficacy was above 0. Based on this result, using the total number of RSV LRTI events, Novavax estimated the range of vaccine efficacy values, between 45-100%, that were possible for this outcome to occur. The estimated range of vaccine efficacy assumes perfect randomisation and all values within the estimated range of vaccine efficacy are equally likely to occur. The final vaccine efficacy estimate produced from the Phase 3 trial based on full enrolment could be within or below the range estimated in the preliminary analysis made publically available.

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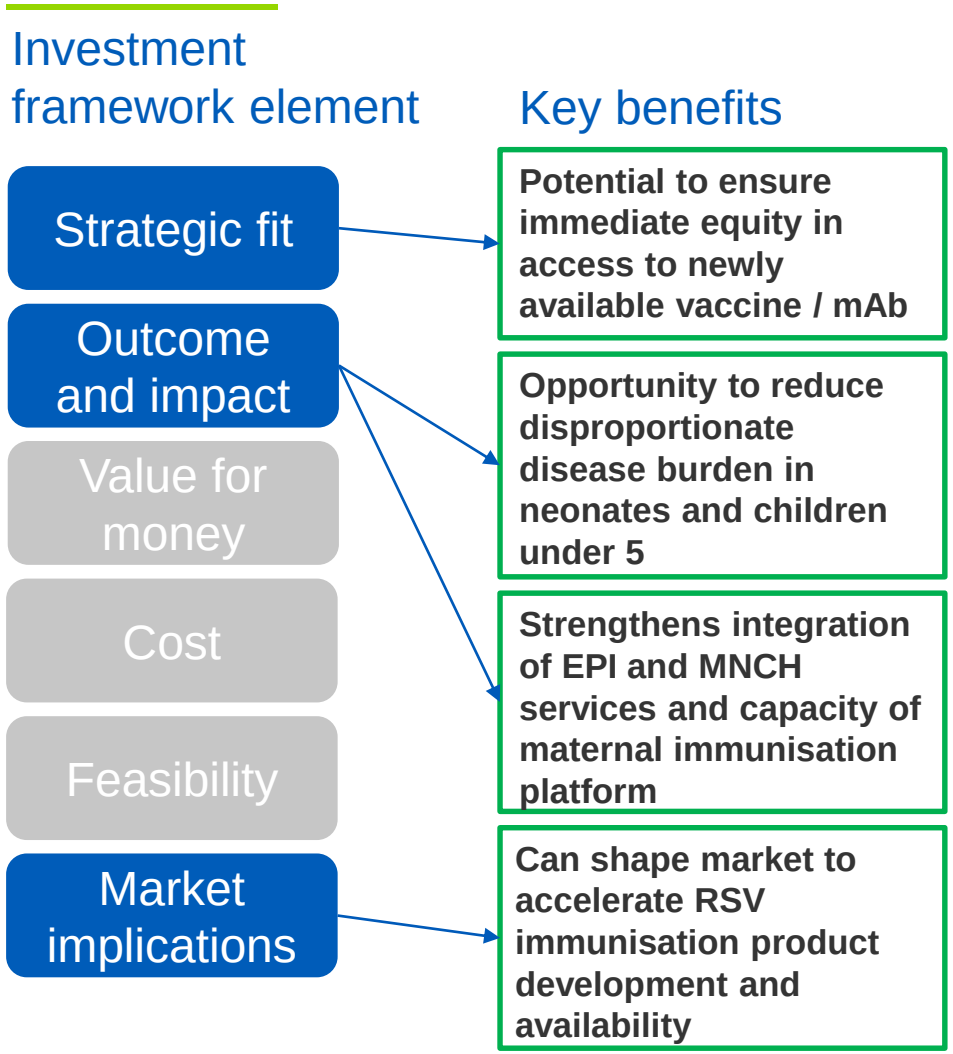
Key vaccine benefits



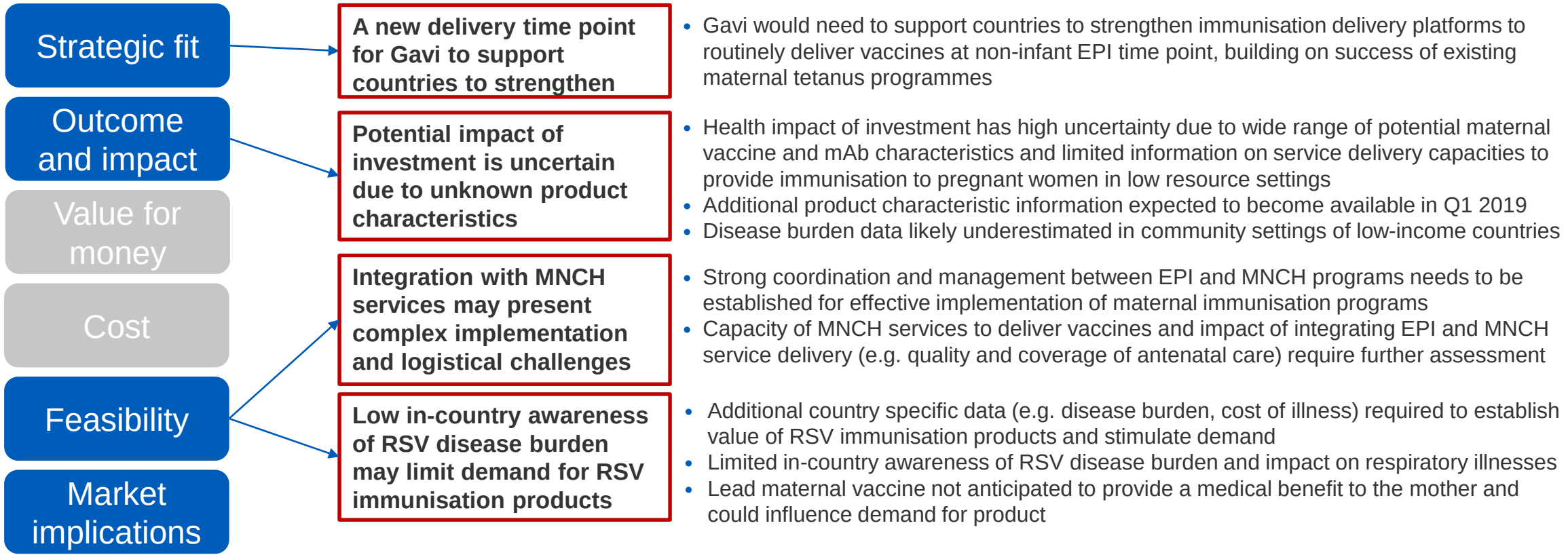
Comments

- Gavi support would enable equal access to products for simultaneous introductions in both high and low income markets once commercially available
- Aligned with Gavi's original mandate to ensure equitable access to immunisation products

- RSV-associated ALRIs estimated to cause ~33M cases annually and 3.2M related hospitalisations in children under 5, with majority of severe disease in low-income countries
- Potential to improve uptake of childhood immunisation through engagement with pregnant women late in pregnancy
- Maternal vaccine could avert ~26,000 – 206,000 deaths 2021-2035
- Opportunity to continue integrating EPI and MNCH service delivery platforms (building on success of maternal tetanus) to execute life course approach to immunisation
- High potential for additional health systems benefits such as increased demand and investment in quality antenatal care services and institutional births, increased systems efficiencies (e.g. shared supply chain) and platform for future maternal vaccines

- Gavi support could:
  - Accelerate robust product development pipeline with indication of a global market for maternal and paediatric vaccines and mAbs
  - Improve long-term market health via diverse set of manufacturers and products able to meet country-specific needs

Key vaccine challenges



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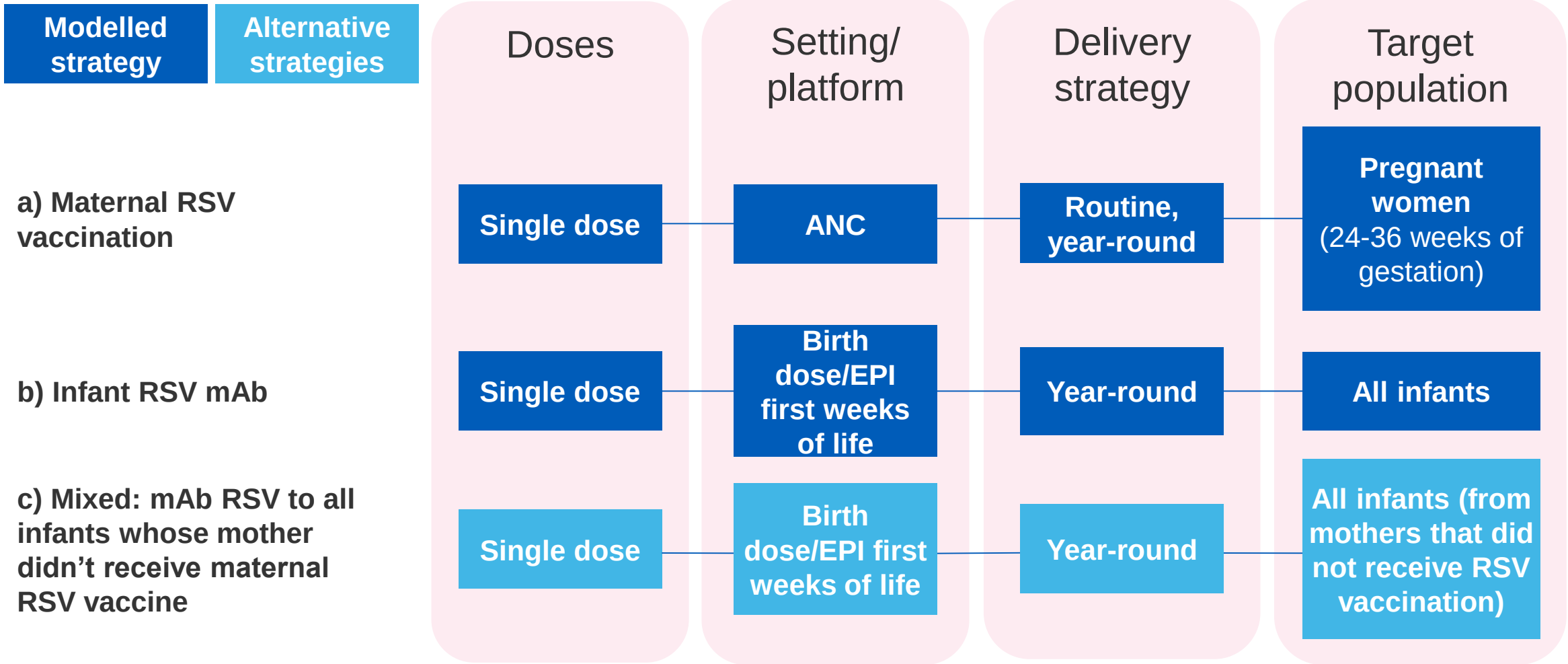
Policy approach

RSV Vaccination strategy: 3 strategies



45 RSV immunisation products currently in the pipeline

Target indication: (E) Elderly (M) Maternal (P) Paediatric

	Preclinical	Phase 1	Phase 2	Phase 3	Market approved
Live-attenuated / chimeric	1 PIVI-3/RSV 1 Delta-G RSV 3 RSV	1 BCG/RSV (P) 1 RSV ΔNS2 Δ1313 (P) 1 RSV ΔNS2 Δ1313/1314L (P) 1 RSV LID ΔM2-2 1030s (P) 1 RSV D46/NS2/N/ΔM2-2 (P) 1 SeV/RSV (P)			
Whole-inactivated	1 RSV				
Particle based	7 VLP 1 Peptide microparticle	1 RSV F Nanoparticle (P)	1 RSV F Nanoparticle (E)	1 RSV F Nanoparticle (M)	
Subunit	3 RSV F Protein 3 RSV G Protein	4 RSV F Protein (E) (M) 1 DPX-RSV-SH Protein (E)			
Nucleic acid	1 RNA 1 DNA				
Recombinant vectors		1 Adenovirus (E)	1 Adenovirus (P) (E) 1 Adenovirus (P) 1 MVA (E)		
Combination/ immuno-prophylaxis	1 DNA prime, particle boost 1 Anti-N mAb 2 Anti-F mAb		1 Anti-F mAb (P)		1 Synagis (P)

Source: PATH, November 2017

One mAb market approved, 4 vaccines and mAb in phase 2 or 3 indicated for maternal / paediatric use

	Phase 2	Phase 3	Market approved
Particle based		1 RSV F Nanoparticle (Novavax) (M)	
Gene-based vectors	1 Adenovirus (GSK) (P) 1 Adenovirus (Janssen) (P)		
Combination/ immuno-prophylaxis	1 Anti-F mAb (MedImmune, Sanofi) (P)		1 Synagis (Medimmune) (P)

Maternal vaccine candidate used as basis for VIS assessment

mAb candidate used as basis for VIS assessment

High-cost product not currently relevant for Gavi-supported countries

Target indication: (M) Maternal (P) Paediatric

Note: Only includes paediatric and maternal immunisation products. Additional phase 2 candidates indicated for elderly populations include Bavarian Nordic's gene-based vector MVA candidate and Novavax's particle based RSV F nanoparticle candidate
Source: PATH, July 2018

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Current status of the lead maternal vaccine and mAb pipeline candidates

	Product element	Maternal vaccine	mAb
Product information	*Manufacturer*	Novavax, Inc.	MedImmune, LLC/ Sanofi Pasteur SA
	Product candidate	RSV F nanoparticle vaccine adjuvanted with aluminum phosphate	Recombinant human neutralizing mAb specific for RSV F Site Ø, with extended antibody half-life
	Clinical trial phase	Phase 3 trial in pregnant women	Phase 2b trial in preterm infants (Phase 3 trial anticipated to commence in 2019)
	Primary trial endpoint	Incidence of RSV LRTI with hypoxemia or very fast breathing (10 breaths above current WHO cutoffs for age) in infants	Prevention of respiratory disease caused by RSV in infants
	Administration	Single dose (0.5 mL IM injection) in the third trimester of pregnancy	Single dose, IM injection administered to infants at birth or prior to their first RSV season
Product development timelines	*Availability of trial results*	Final efficacy analysis in Q1 2019	Efficacy analysis and trial data readout in Q1 2019
	Estimated licensure date	2020	2022
	Estimated WHO PQ date	2021	2024

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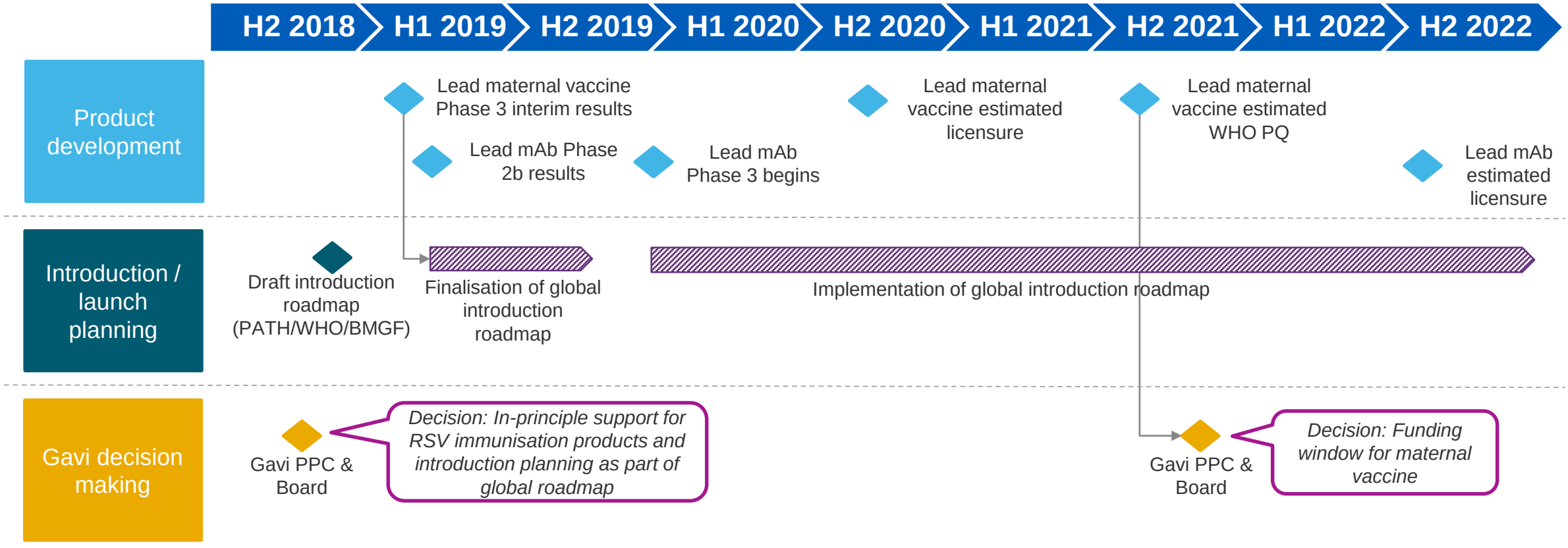
Product development timelines should inform nature of Gavi policy decisions over time



Gavi decision making and support for RSV can be stage-gated based on product development timing

By end of 2018 limited additional information to inform VIS decision

Critical product characteristics for Phase 3 maternal vaccine available after VIS 2018 decision making

PATH / WHO / BMGF LMIC RSV introduction planning and coordination assessment in early stages; roles for key partners not established until early 2019

Gavi support for RSV defined over time as product development advances (potential pathway shown, other scenarios may unfold)

1. In-principle VIS decision in 2018 for support for introduction planning and future RSV immunisation products

2. Gavi Board reviews opening funding window for RSV immunisation on basis of maternal vaccine receiving WHO PQ / SAGE recommendation (~2021-2022)

3. Once infant mAb receives WHO PQ / SAGE recommendation (~2022-2024), Gavi offers to countries *if* product shows similar cost-effectiveness. If not similar cost-effectiveness, Board would review for potential support in addition to maternal vaccine.

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Demand, health impact, cost and value for money

RSV key assumptions

xx: included in model uncertainty range
xx: not included

Models	Univ. Antwerp /LSHTM[1]	PATH[1]	IPM (direct impact only)[1]
Vaccination strategies	Single dose RSV vaccine for pregnant women (24-36 weeks)	Single infant birth dose mAb	Mixed (Pregnant women vaccine + Infants mAb)
Uncertainty analysis driving ranges	Efficacy • RSV vaccine (30%[2], 50%, 70%, 90%) • mAb (60%, 70%, 80%, 100%)	Duration of protection • RSV vaccine (3 mo., 4 mo., 5 mo., 6mo.) • mAb (4 mo., 5 mo., 6 mo., 7 mo.)	Coverage ANC coverage[3] DTP3 coverage

1. All models used in evaluation only model direct impact and do not account for any potential herd effects
2. Not included because very unlikely that the vaccine would reach the market with an efficacy of 30%
3. ANC coverage during the vaccination window (24-36 weeks) discounted by number of services received by ANC visitors from DHS

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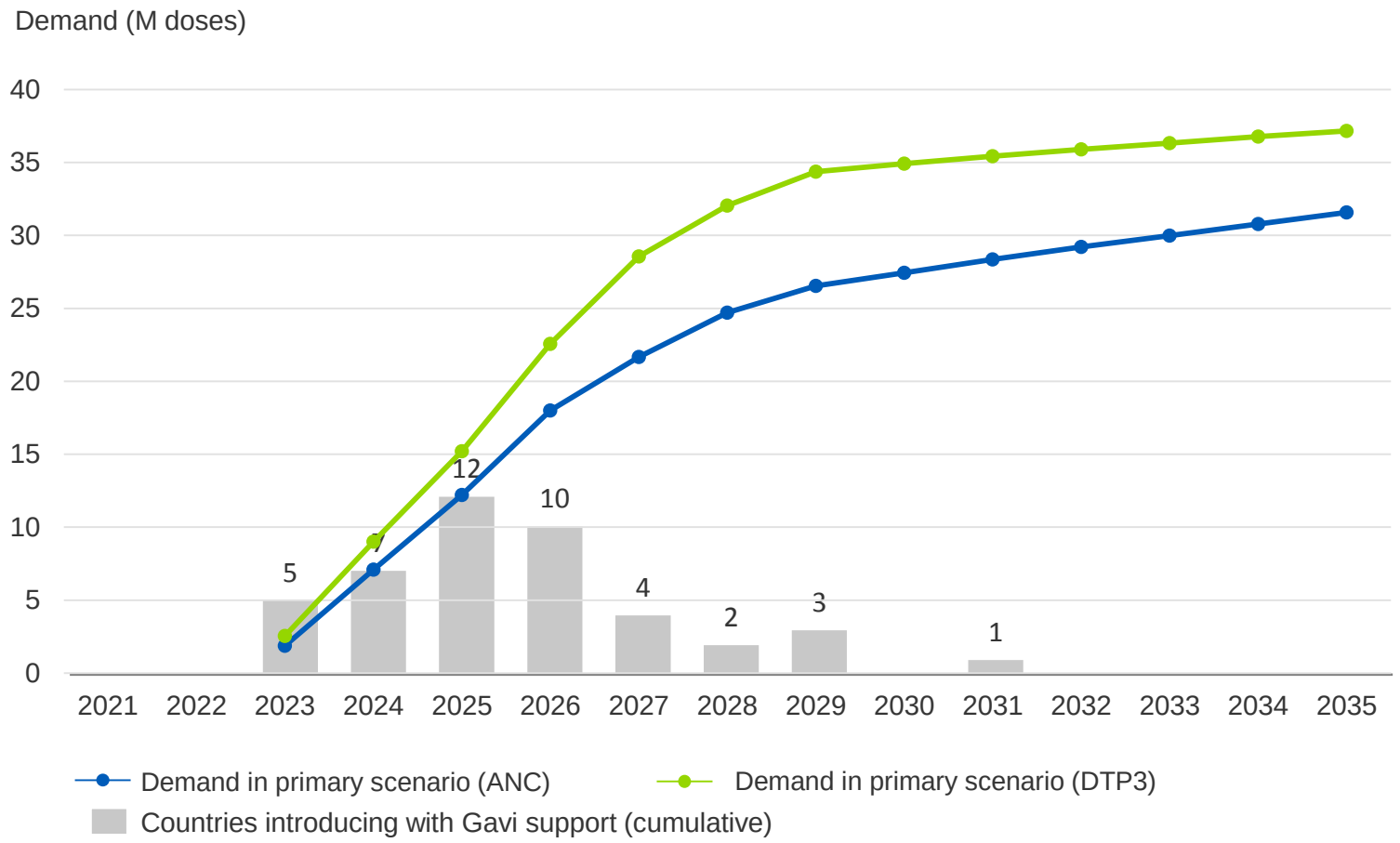
Expected cumulative demand 2021-2035 ~289M doses[1]



Nigeria excluded

Scenario: 1-dose, routine, year-round ANC delivery at 24-36 weeks gestation[2], coverage analogues of ANC and DTP3

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

Primary scenario (ANC coverage) — **~289M**

Alternative scenario (DTP3 coverage) — **~361M**

1. Based on Gavi's current eligibility and transition policy
2. Gavi VIS forecast; single dose, delivered in ANC, routine year-round, all pregnant women at 24-36 weeks); coverage based on ANC or DTP3
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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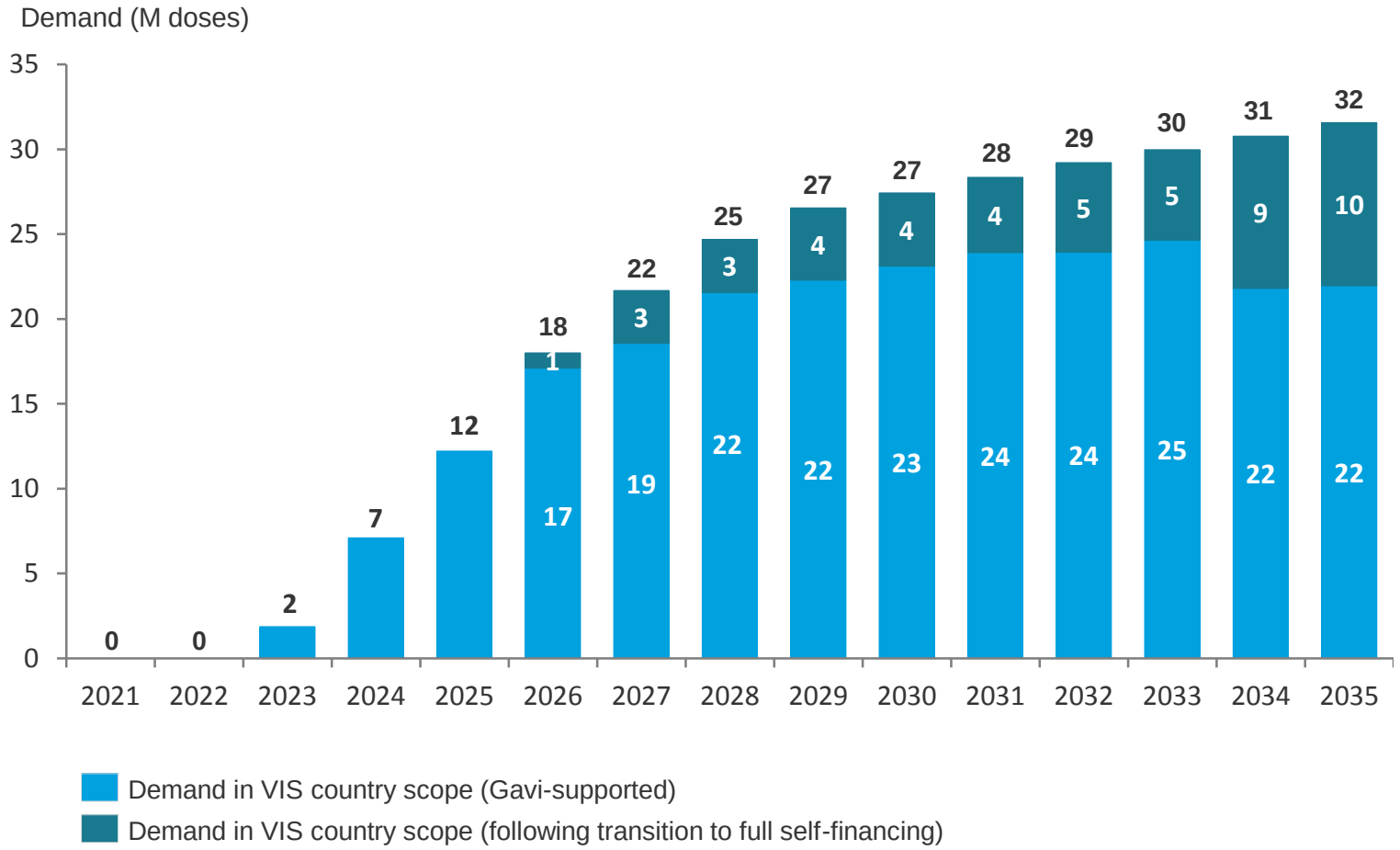
Gavi anticipates supporting up to ~240M doses between 2021-2035[1]

Nigeria excluded

Countries supported by Gavi for introduction

Scenario: 1-dose, routine, year-round ANC delivery at 24-36 weeks gestation[3], ANC coverage analogue



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

Gavi supported demand[2] ~240M

Post transition demand ~50M

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'
3. Gavi VIS forecast; single dose, delivered in ANC, routine year-round, all pregnant women at 24-36 weeks); coverage based on ANC or DTP3, 50% efficacy & 0.33 years duration of protection

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

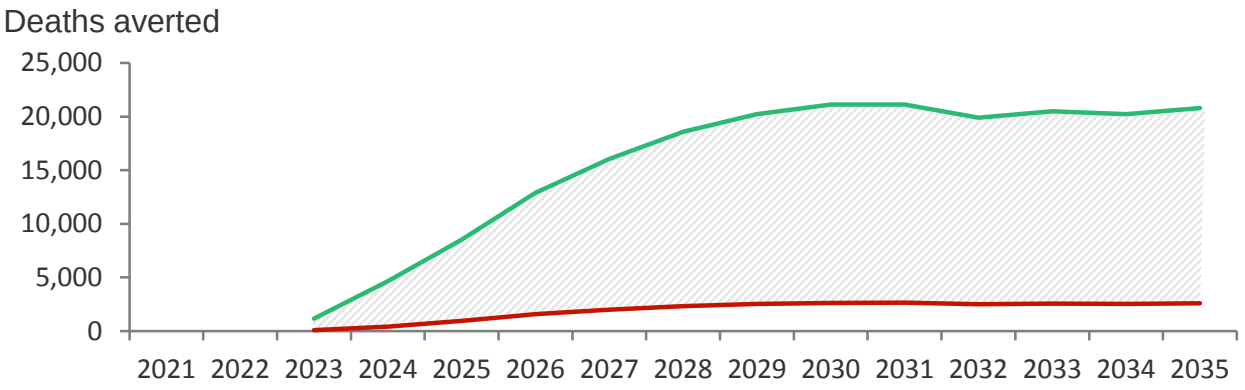
Maternal vaccine could avert ~26K-206K future deaths and ~1.8M-10.4M future cases through 2035

Nigeria excluded

Range of projected impact Maximum / Minimum

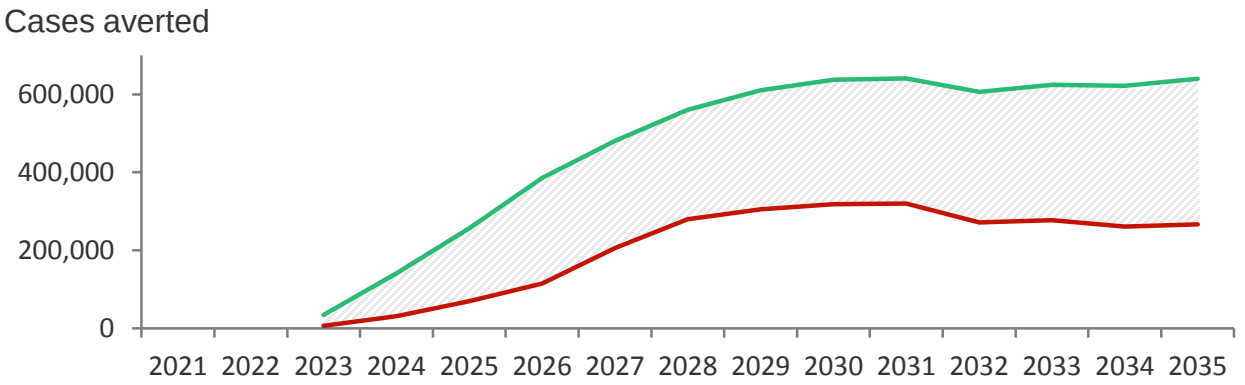
Scenarios: 1-dose, routine, year-round ANC delivery at 24-36 weeks gestation; variable efficacy, duration of protection and coverage[1]

Deaths



	Total deaths averted (2021-2035)	Deaths averted per 100K vaccinated
Max	~206K	~82
Min	~26K	~10

Cases



	Total cases averted (2021-2035)	Cases averted per 100K vaccinated
Max	~10.4M	~4 137
Min	~1.8M	~703

1. IPM (direct impact only), UA, PATH models; single dose, delivered in ANC, routine year-round, all pregnant women at 24-36 weeks); coverage based on ANC or DTP3, vaccine efficacy (50-90%), duration of protection (3-6 months), coverage (low/high)
Range of impact driven by high levels of uncertainty around vaccine efficacy, duration of protection, coverage and disease burden
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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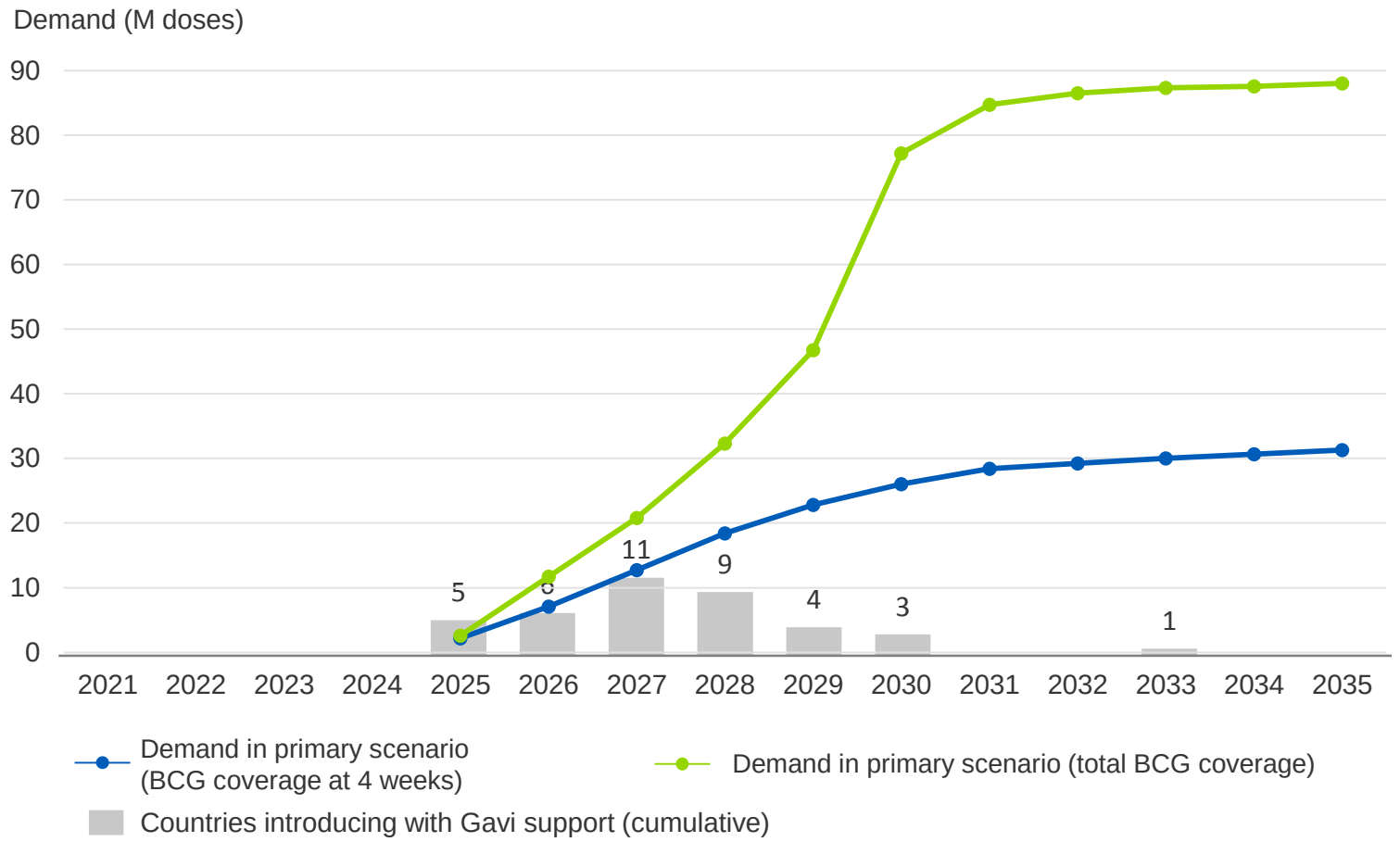
Expected cumulative demand 2021-2035 ~239M doses[1]



Nigeria excluded

Scenario: 1-dose, routine, year-round delivered at birth[2], coverage analogue of BCG at 4 weeks and total BCG

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

Primary scenario (BCG coverage at 4 weeks) — **~239M**

Alternative scenario (total BCG coverage) — **~626M**

1. Based on Gavi's current eligibility and transition policy
2. Gavi VIS forecast; single dose, delivered at birth, routine year-round, converge of BCG at 4 weeks

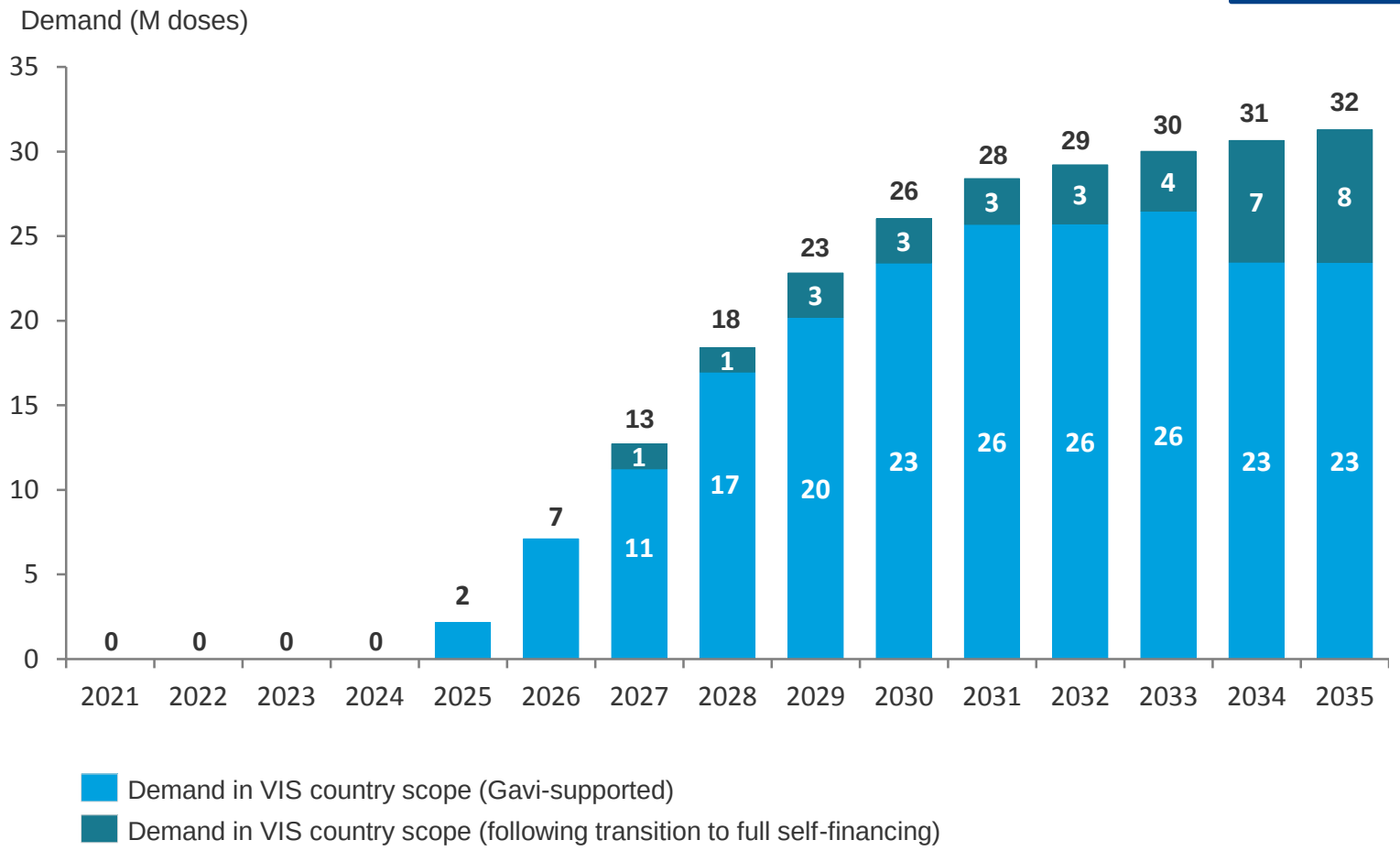
Consideration for Gavi support to Nigeria for VIS candidates would be considered separately through the Nigeria-specific strategy which was approved by the Gavi Board in June 2018

Gavi anticipates supporting up to ~206M doses between 2021-2035[1]

Nigeria excluded

Countries supported by Gavi for introduction

Scenario: 1-dose, routine, year-round delivered at birth[3], coverage analogue of BCG at 4 weeks



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

Gavi supported demand[2] ~206M

Post transition demand ~33M

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'
3. Gavi VIS forecast; single dose, delivered at birth, routine year-round, converge of BCG at 4 weeks

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

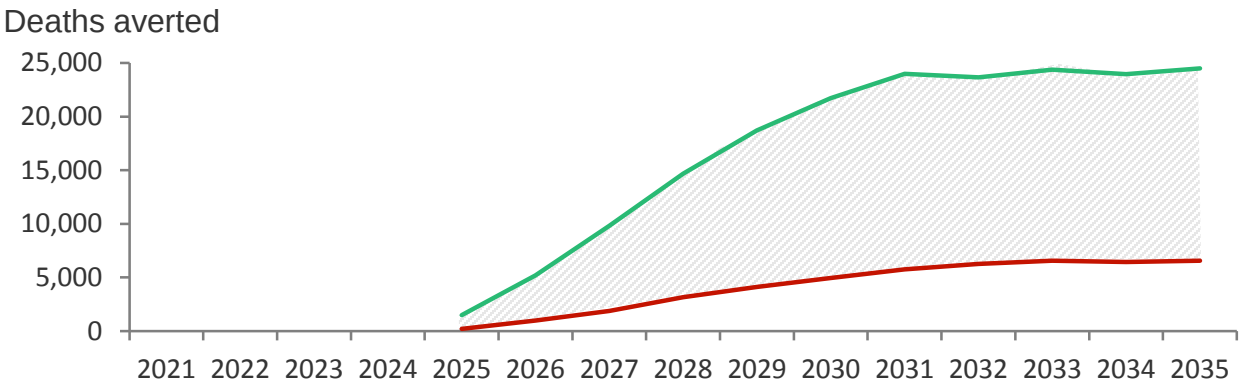
Infant mAb could avert between ~47K-192K future deaths and ~2.8M-12.2M future cases through 2035

Nigeria excluded

Range of projected impact Maximum / Minimum

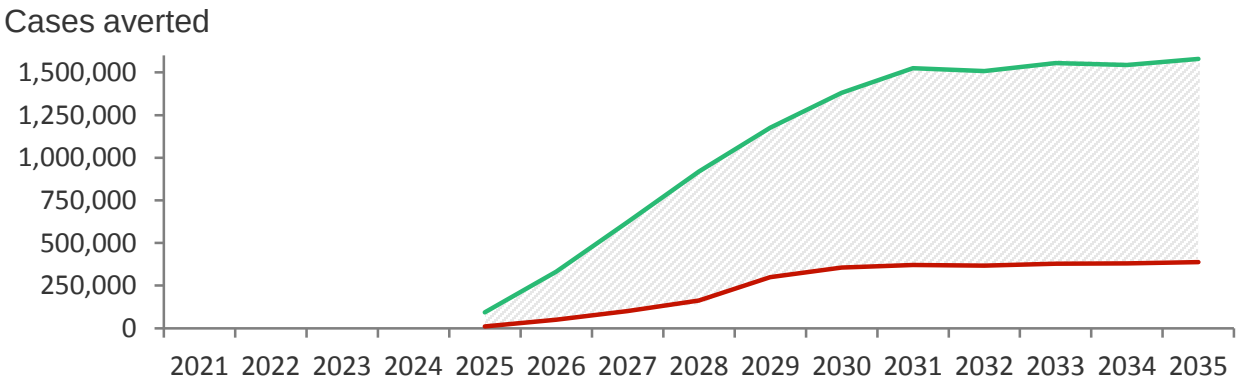
Scenarios: 1-dose, routine, year-round delivered at birth; variable efficacy, duration of protection and coverage[1]

Deaths



	Total deaths averted (2021-2035)	Deaths averted per 100K vaccinated
Max	~192K	~91
Min	~47K	~20

Cases



	Total cases averted (2021-2035)	Cases averted per 100K vaccinated
Max	~12.2M	~5 778
Min	~2.9M	~1 188

1. IPM (direct impact only), UA, PATH models; Gavi VIS forecast; single dose, delivered at birth, routine year-round, converge of BCG at 4 weeks; mAb efficacy (60-100%), duration of protection (4-7months), coverage (BCG at 4 weeks/total BCG)
Range of impact driven by high levels of uncertainty around vaccine efficacy, duration of protection, coverage and disease burden
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 RSV maternal vaccine or infant RSV mAb introductions.

Scenario vaccine: 1-dose, routine, year-round ANC delivery at 24-36 weeks gestation; variable efficacy, duration of protection and coverage[2]

Scenario mAb: 1-dose, routine, year-round delivered at birth; variable efficacy, duration of protection and coverage[3]

		Maternal vaccine scenario	Infant mAb scenario
Impact	Fully vaccinated persons	252M	212M
	Total future deaths averted	26-206K	47-192K
Cost	Gavi procurement costs	$346M	$1,259M
	Gavi operational costs	$25M	$24M
	Total Gavi cost	$371M	$1,283M
	Country procurement costs	$219M	$708M
	Country operational costs	$75M	$73M
	Country recurrent delivery costs	$177M	$152M
	Total Country cost	$472M	$934M
	Total cost	*$843M*	*$2,217M*
Value for money	Cost per death averted[1]	~$2,748-21,999	$10,238-48,758

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 RSV vaccine and mAb 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. IPM (direct impact only), UA, PATH models; single dose, delivered in ANC, routine year-round, all pregnant women at 24-36 weeks); coverage based on ANC or DTP3, vaccine efficacy (50-90%), duration of protection (3-6 months), coverage (low/high)
3. IPM (direct impact only), UA, PATH models; Gavi VIS forecast; single dose, delivered at birth, routine year-round, converge of BCG at 4 weeks; mAb efficacy (60-100%), duration of protection (4-7months), coverage (total BCG/BCG at 4 weeks)

Assessment of uncertainty in demand and impact analyses

	Comments
Demand	• Introduction dates tentative due to uncertainty in product development pipeline • Limitations regarding coverage analogue (discounted ANC coverage for provision of full services) • Uncertainty regarding coverage scale-up assumptions due to requirements to strengthen new timepoint for routine vaccination • Little RSV-specific information on health care utilization
Price	• Large range in demand forecast which drives ranges/uncertainty on cost of investment • Based on expert consultation with estimates on product development and uptake across Gavi-supported countries
Health impact	• Uncertainty in burden data, estimates only based on severe hospital cases which likely underestimates burden in areas with limited access to healthcare due to delayed or no care seeking. Community burden in low-income settings with poor health utilisation not well estimated. Community burden was estimated using a multiplier value and then adjusting for influenza cases. Burden data used in impact modelling also pooled and not taken at country level • Herd-immunity not accounted for, but difficult to estimate effect because of anticipated short duration of vaccine effectiveness • Uncertainty over force of infection in new-borns, two year olds may confer highest risk of transmission. Vaccination may lead to age shift (which would be seen as reducing vaccine impact) but older children may be more resilient to disease, decreasing severity and mortality • Waning immunity not included, but expert consultation suggests efficacy likely to wane, with higher efficacy early on. If this is the case, impact in younger children may be underestimate (as efficacy is higher than estimated) & greater risk in very young infants • High uncertainty in vaccine efficacy of both maternal vaccine and mAb products, resulting in wide range of potential impact • Seasonality not considered • Burden estimates calculated differently for each modelling group, leading to high uncertainty bounds in impact

High uncertainty | Medium uncertainty | Low uncertainty

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Implications for demand, health impact and cost when including Nigeria

	RSV maternal vaccine % increase if Nigeria included	RSV mAb % increase if Nigeria included
Demand	~17%	0%
Deaths averted	~9-12%	0%
Cases averted	~7-8%	0%
Cost	~17%	0%

No difference for mAb as Nigeria already projected to be fully self-financing at time of forecasted introduction

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

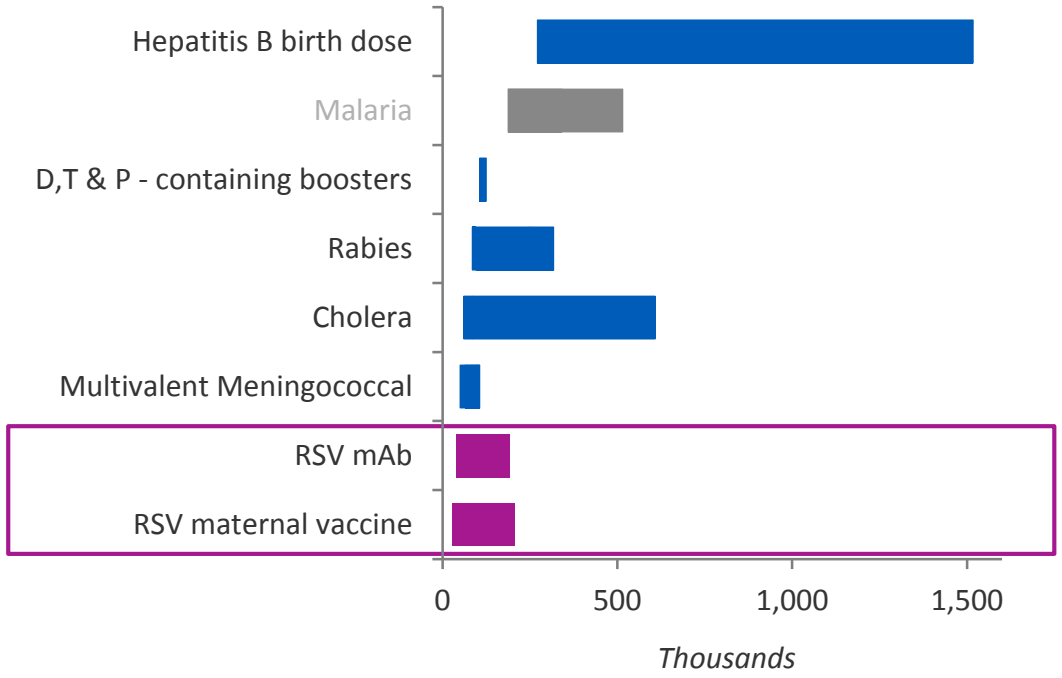
Health impact compared across VIS candidates

Scenario vaccine: 1-dose, routine, year-round ANC delivery at 24-36 weeks gestation; variable efficacy, duration of protection and coverage[1]

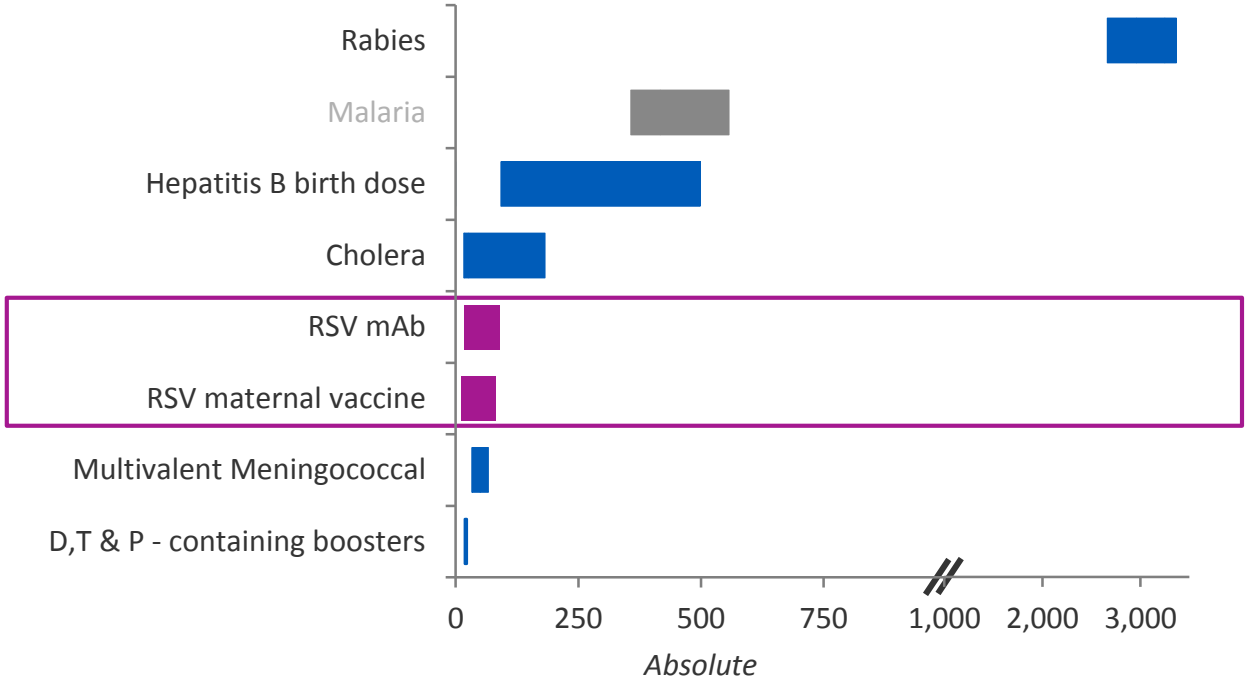
Scenario mAb: 1-dose, routine, year-round delivered at birth; variable efficacy, duration of protection and coverage[2]

Nigeria excluded

Total future deaths averted (K), 2021-2035



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



1. IPM (direct impact only), UA, PATH models; single dose, delivered in ANC, routine year-round, all pregnant women at 24-36 weeks); coverage based on ANC or DTP3, vaccine efficacy (50-90%), duration of protection (3-6 months), coverage (low/high)
2. IPM (direct impact only), UA, PATH models; Gavi VIS forecast; single dose, delivered at birth, routine year-round, converge of BCG at 4 weeks; mAb efficacy (60-100%), duration of protection (4-7months), coverage (total BCG/BCG at 4 weeks)

Range of impact driven by high levels of uncertainty around burden & vaccine efficacy
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

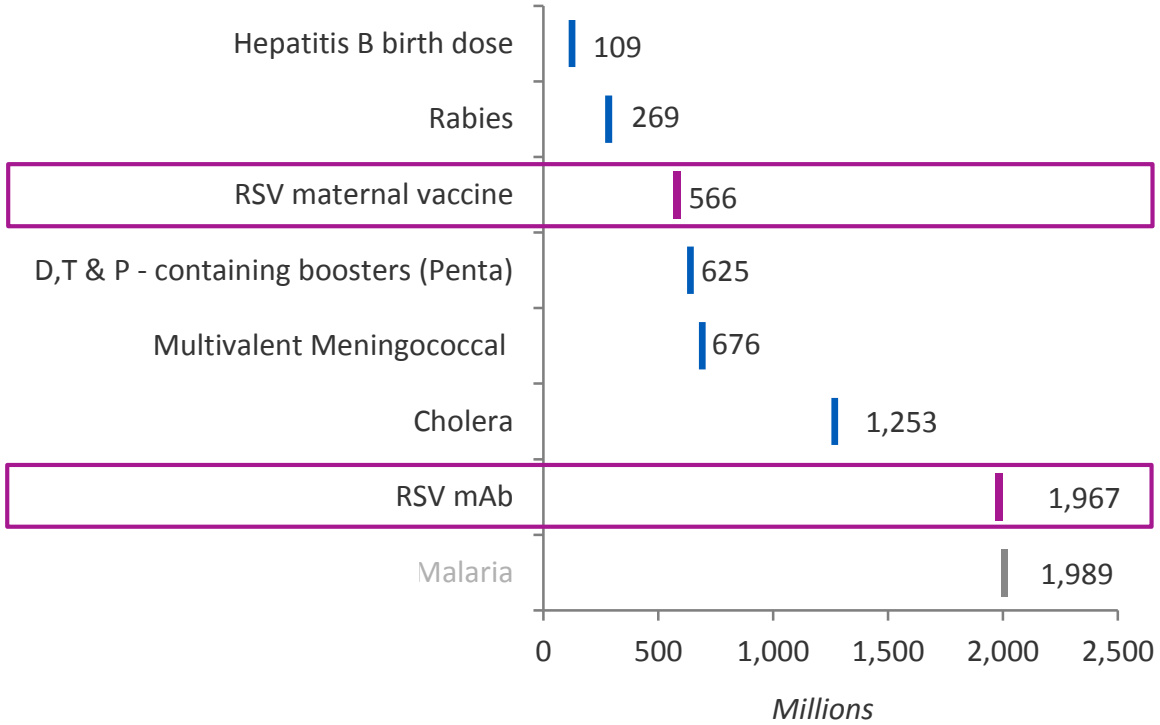
Procurement cost and cost per death averted compared across VIS candidates

Scenario maternal vaccine: 1-dose, routine, year-round ANC delivery at 24-36 weeks gestation; variable efficacy, duration of protection and coverage[1]

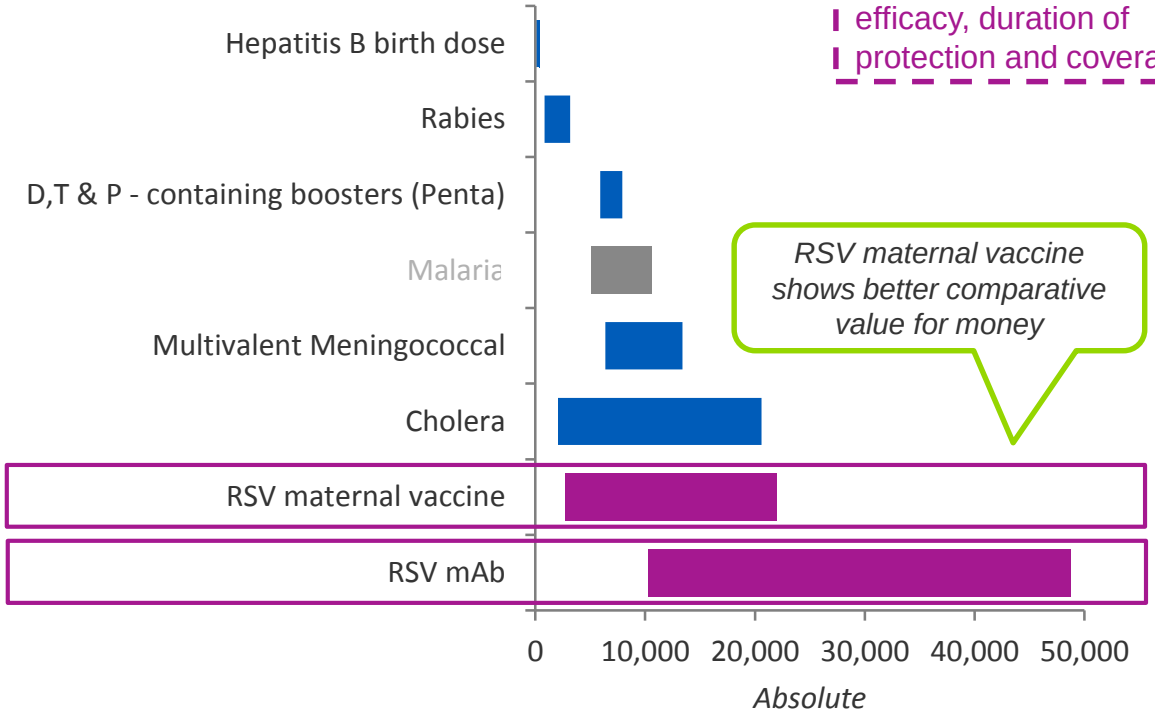
Scenario mAb: 1-dose, routine, year-round delivered at birth; variable efficacy, duration of protection and coverage[2]

Nigeria excluded

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 RSV maternal vaccine or infant RSV mAb introductions.

1. IPM (direct impact only), UA, PATH models; single dose, delivered in ANC, routine year-round, all pregnant women at 24-36 weeks); coverage based on ANC or DTP3, vaccine efficacy (50-90%), duration of protection (3-6 months), coverage (low/high)
2. IPM (direct impact only), UA, PATH models; Gavi VIS forecast; single dose, delivered at birth, routine year-round, converge of BCG at 4 weeks; mAb efficacy (60-100%), duration of protection (4-7months), coverage (total BCG/BCG at 4 weeks)
Range of impact driven by high levels of uncertainty around burden & vaccine efficacy
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

6

Country perspective

Interviews with country stakeholders revealed that RSV priority difficult to assess as burden unknown

Priorities and approach

- Respondents indicated RSV was low priority at national/government-level due to lack of information about disease and disease burden, however:
  - Respiratory illnesses are generally of concern among consulted in-country stakeholders
  - At clinical level, physicians/paediatricians see many suspected RSV-related bronchiolitis cases and would prioritise vaccine if made available
- Some respondents suggested diagnostics would help improve value proposition

Burden of disease and surveillance

- Country-level hospital and community disease burden not well understood by decision makers at national level
- Many countries have surveillance for respiratory infections, but not RSV specifically

Programmatic considerations and challenges

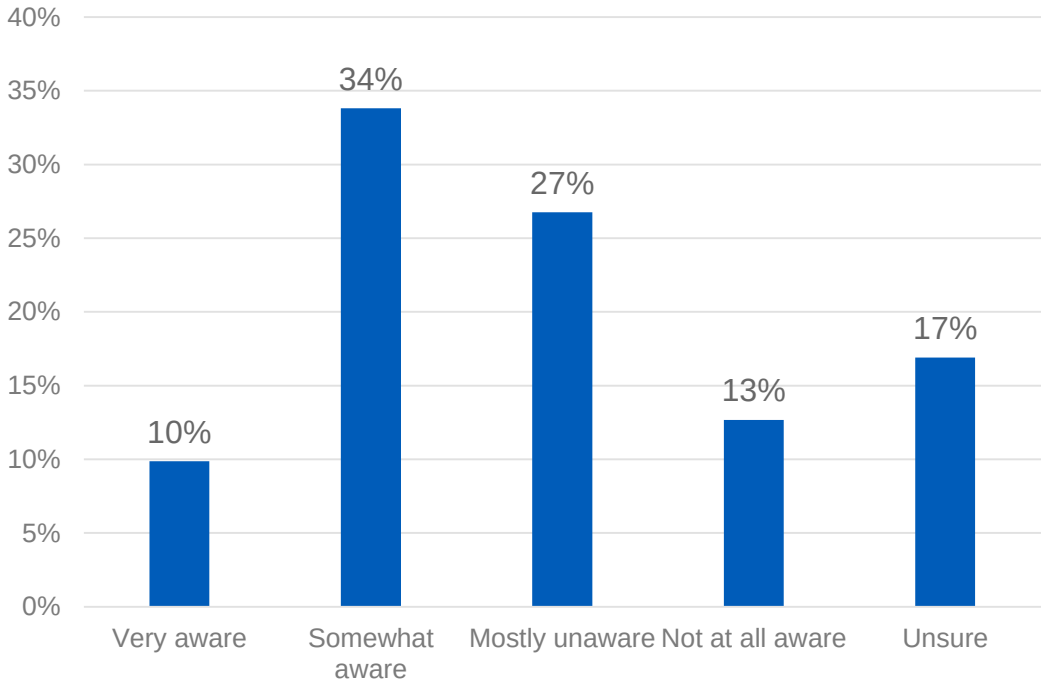
- Maternal immunisation overall not viewed as a challenge, because many countries already have tetanus toxoid (TT) or tetanus-diphtheria (Td) programmes for pregnant women
  - In some countries, TT/Td vaccine given during ‘immunisation day’ in local communities, so more easily accessible (and often free) vs during antenatal check when women travel to hospital or clinic
  - Some countries noted low coverage of maternal TT/Td due to gender barriers (e.g., sex of vaccinator)
- Need for demand generation and social mobilisation to improve knowledge of disease burden
- Some respondents cautioned that TT/Td coverage might not translate to RSV coverage because there is understanding that tetanus is untreatable; similarly other non-treatable infections higher priority (e.g., dengue)

Source: VIS Phase III in-depth country interviews

RSV remains an unfamiliar disease in many countries but acceptability is likely high

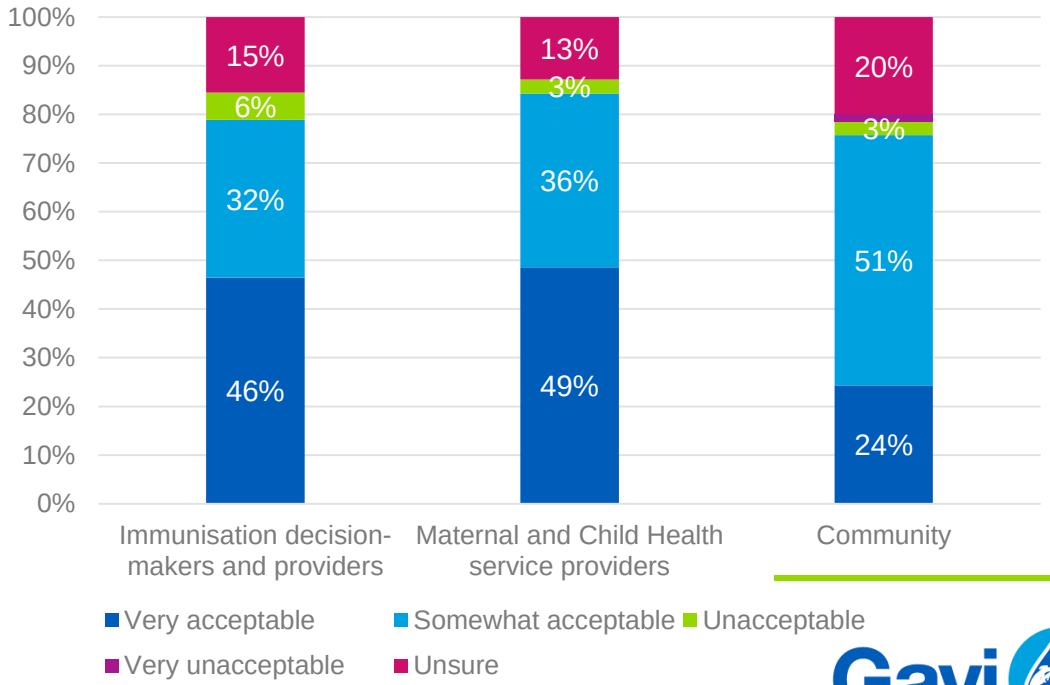
How familiar is the public health community in your country with respiratory illness (pneumonia, bronchiolitis) caused by respiratory syncytial virus (RSV)?

% respondents who say public health community is familiar with RSV



How acceptable is vaccination in pregnancy among the following groups of stakeholders in your country?

% respondents regarding level of acceptability of vaccination during pregnancy

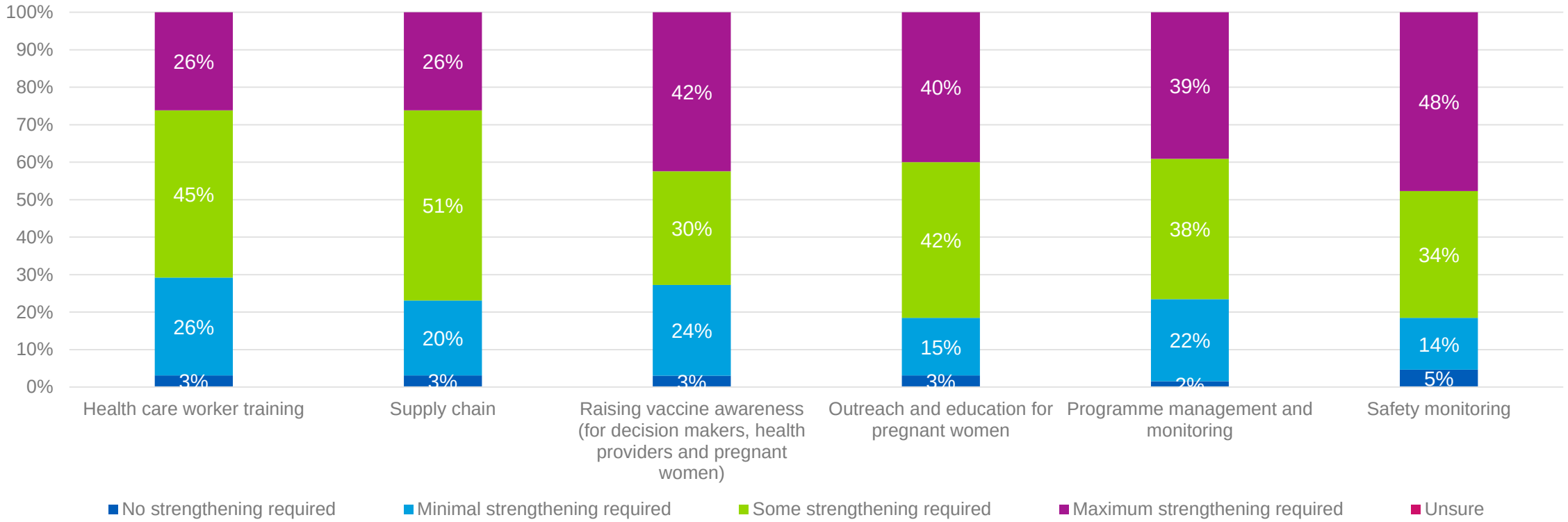


Source: VIS Phase III country survey

According to most respondents, some or a lot of strengthening is required across all activities

What is the extent to which each of the following would need to be strengthened to optimally deliver maternal RSV vaccine via antenatal care in your country?

% respondents regarding level of strengthening required to deliver RSV vaccine

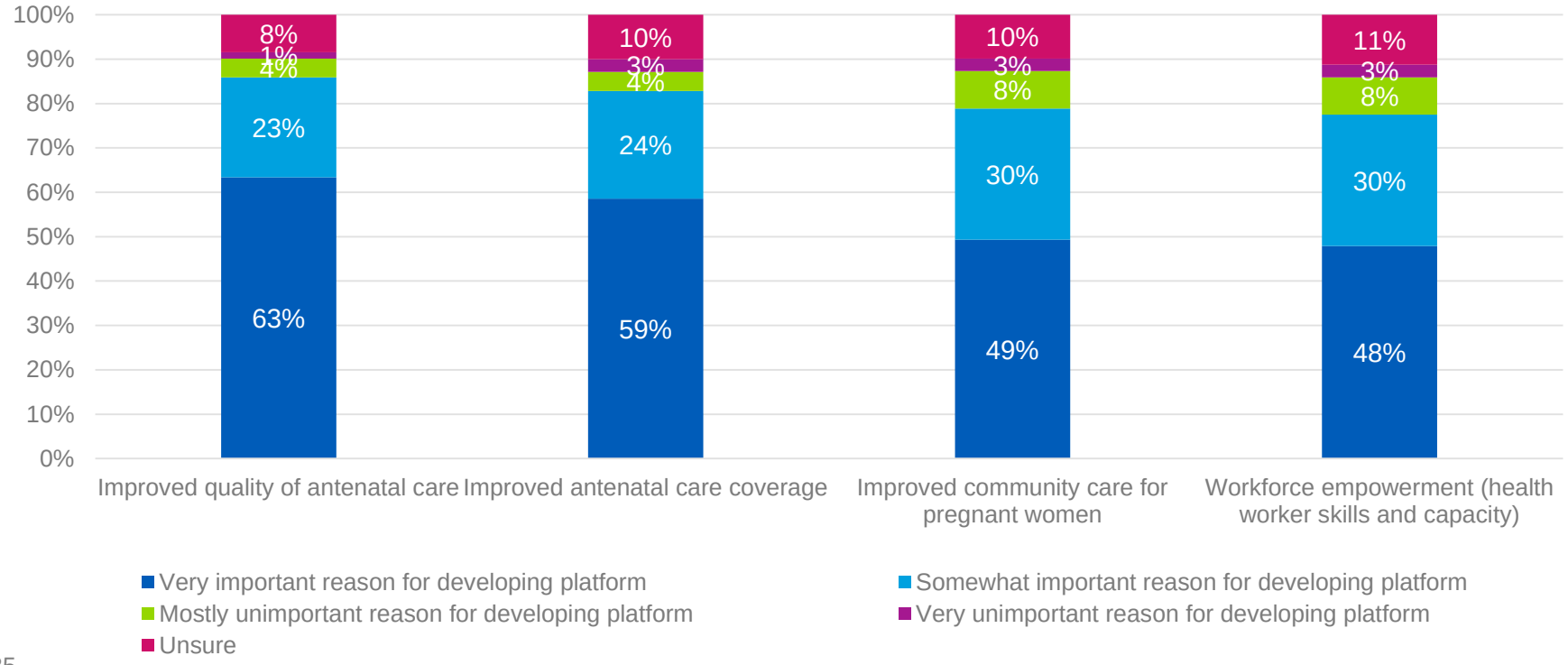


Source: VIS Phase III country survey

All benefits of maternal vaccination are viewed equally amongst respondents

The table below lists several supplemental benefits associated with introducing a vaccine for pregnant women through a maternal immunisation platform incorporated in antenatal care. Please rate the degree to which they could influence a decision to develop a maternal immunisation platform.

% respondents regarding the degree to which each benefit might influence the decision to introduce maternal immunisation



Source: VIS Phase III country survey

7

Implementation requirements

Unique implementation requirements

	Area of focus	Unique implementation requirements	Associated costs
Global level	Policies and processes	• Technical recommendation from WHO on delivery strategy and introduction guidelines • Development of global introduction coordination group to support demand generation and country introduction planning (ADIP-like)	• "ADIP" coordination and execution
	Supply	• Management of available supply with manufacturer(s) to support country introductions; demand projections for Gavi market to support capacity planning	
Country level	Planning, coordination, integration	• Coordination between MNCH and EPI departments to ensure alignment in delivery strategies, division of labour, shared resources, management and execution • Integrations of private health providers and reduced financial barriers for RSV immunisation products where service fees are required (e.g. for ANC visits)	• Policy execution and strategy development • EPI-MNCH coordination
	Supply chain infrastructure and logistics	• Leverage existing EPI cold chain systems to deliver product to health facility • Ensure availability of cold chain where antenatal care and institutional delivery services are provided	• Additional cold chain equipment
	Health workforce	• Additional training required to support product administration, task delegation, data capture and reporting for both EPI and MNCH service providers, including community health workers	• Additional training inclusive of both EPI and MNCH
	Social mobilization, education, communication	• Intensive RSV-focused education and communication strategies for national and sub-national stakeholders to stimulate demand • Information on RSV to drive awareness and advocacy among local champions	• Social mobilisation initiatives for decision makers, clinicians, target population
	Surveillance	• Strengthened surveillance systems to establish disease burden at all levels, background rates on adverse obstetric and neonatal outcomes and AEFIs • Improved pharmacovigilance systems to monitor vaccine safety for pregnancy/birth outcomes	• Enhanced surveillance for both EPI and MNCH

Most challenging

Unique but manageable

Few unique implementation requirements

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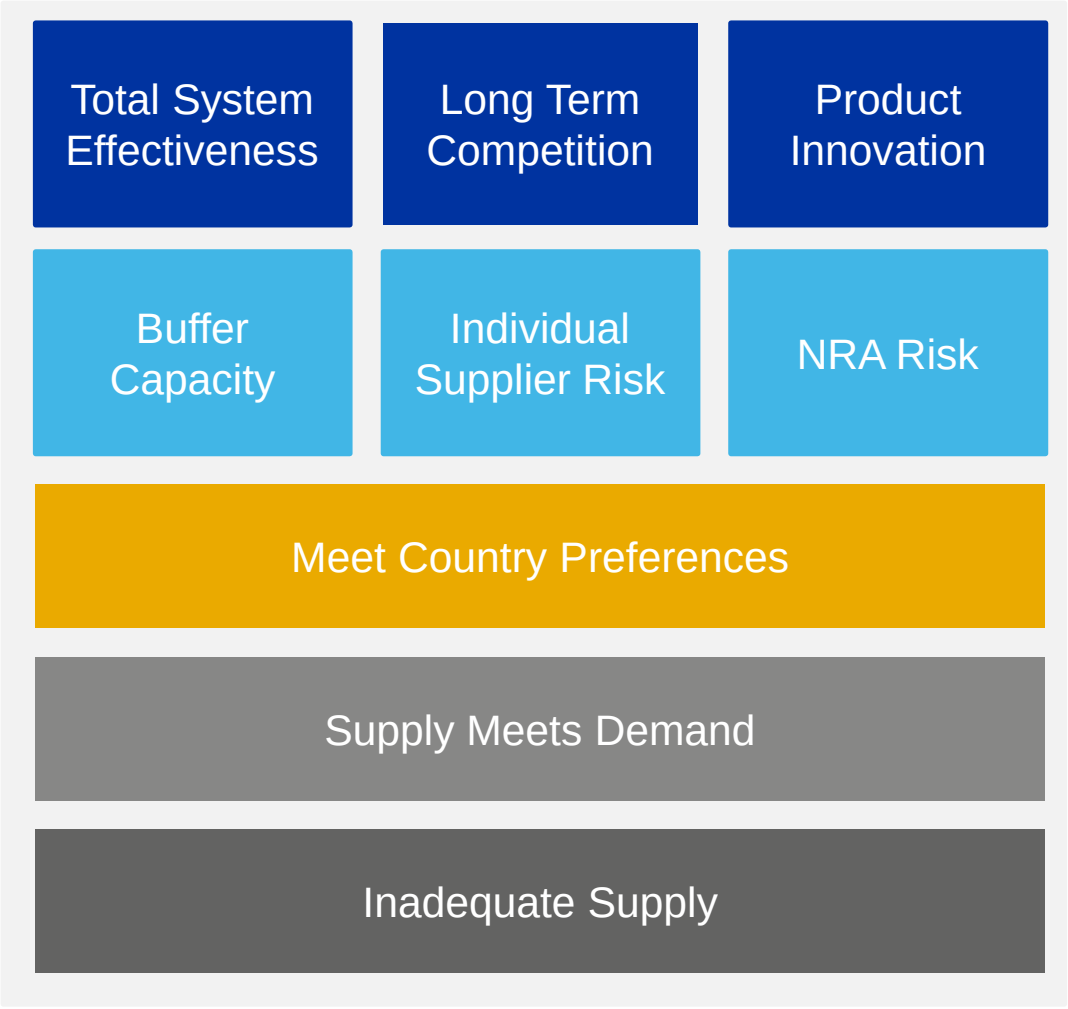
Key gaps identified for mitigation to accelerate demand and introduction of maternal RSV vaccine

Epidemiology	• RSV burden of disease data collected in hospital and non-urban, community settings, stratified by narrow age bands for infants in low and middle income countries
Vaccine and immunisation characteristics	• Evidence of maternal vaccine effect against severe RSV disease in infants to support licensure/marketing approval and inform cost-effectiveness analyses • Data on the effect of maternal comorbidities and premature delivery and factors affecting placental transfer of antibodies that could impact RSV immunogenicity and effectiveness • Vaccine effectiveness, immune and safety data to inform the broadening of vaccination window used in Phase 3 maternal vaccine trial, particularly for regions where assessing gestational age is difficult
Health economics and financing	• Costs associated with providing maternal immunisation through antenatal care, including for different vaccination strategies and those associated with strengthening ANC infrastructure • Funding mechanisms to support integration between EPI and MNCH programmes and enable planning for vaccine introductions
Programmatic considerations	• Data from variable settings on current mechanisms for ANC delivery and their capacity to routinely deliver vaccines • Information on appropriate management models and effective coordination mechanisms between EPI and MNCH programmes • Defined cold chain, logistical and vaccine management requirements and process for maternal RSV vaccines • Data on the impact of integrating RSV immunisation with existing ANC services on ANC quality and coverage
Policy and advocacy	• Understanding the drivers and barriers for RSV maternal immunisation acceptance and uptake in LMIC settings • Evidence based advocacy and communications strategies for global, regional, national and sub-national stakeholders to support policy making, information sharing and demand generation for RSV • Information on RSV disease and maternal immunisation to support stakeholder awareness, engagement and advocacy at regional and country levels
Monitoring and safety surveillance	• Post-marketing studies and routine surveillance to further evaluate RSV vaccine safety and AEFIs • Strengthened immunisation surveillance systems to reliably track and report pregnancy/birth outcomes, vaccine coverage and AEFIs • Background rates on pregnancy outcomes in LMICs to enable maternal RSV vaccine safety data interpretation

Source: PATH/WHO Advancing RSV Maternal Immunisation: A Gap Analysis Report, July 2018

Near-term challenges in emerging RSV market that may impact successful introductions



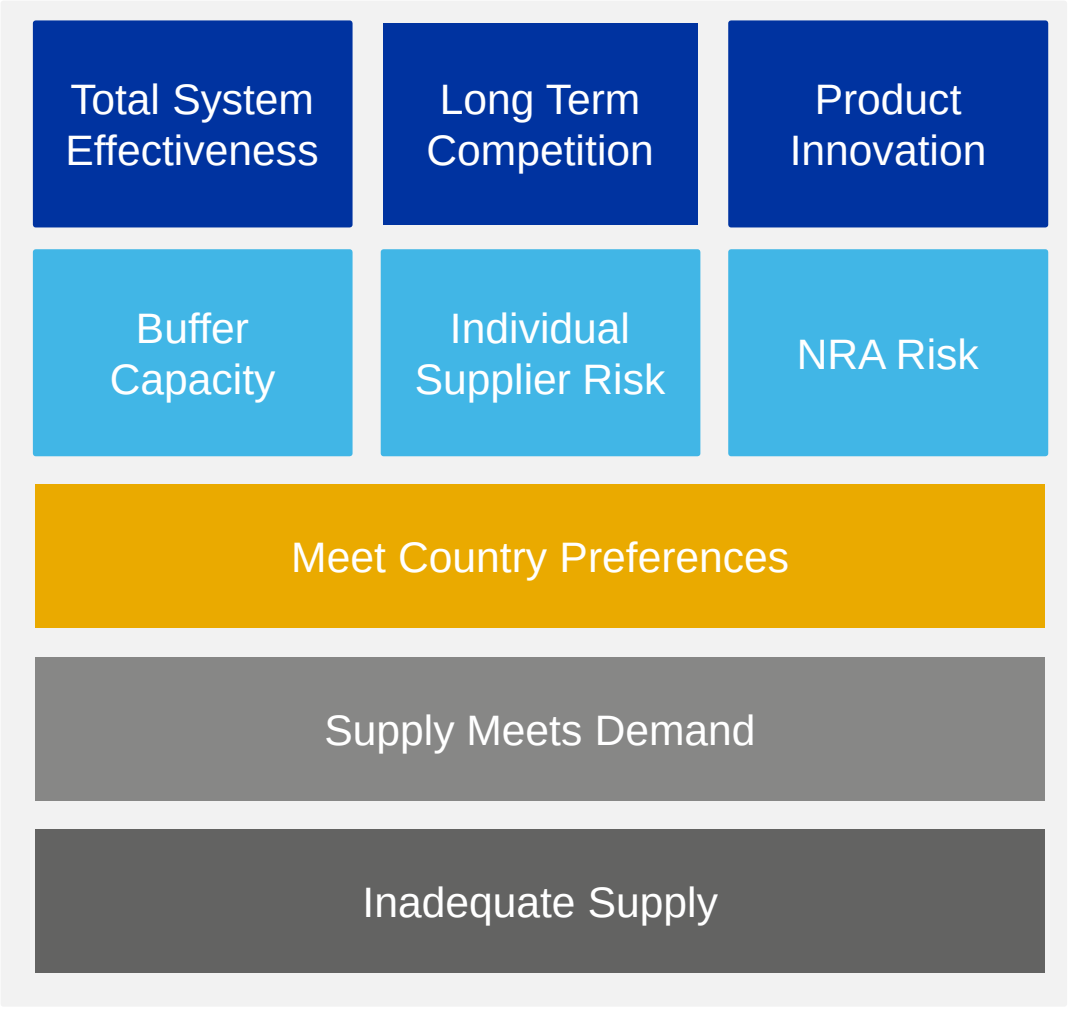
Limited near-term competition as single source of supply of only one vaccine and one mAb product anticipated to achieve licensure in Gavi's next strategic period

Lead maternal vaccine manufacturer has **limited commercialization experience could lead to inadequate global supply as a result of challenges in scaling up production.** However, Access agreement in-place with lead maternal vaccine manufacturer to ensure supply for LMICs

Unclear if global demand can be met through planned capacity of lead maternal vaccine manufacturer; supply plans of lead mAb manufacturer unknown

Additional manufacturers for both maternal vaccine and mAb may be required to ensure capacity for both high income and Gavi markets

Gavi has a long-term role to support increased market competition, product diversity and supply



Additional products anticipated to become available in next 5-10 years being developed by manufacturers with experience supplying Gavi markets

A number of **paediatric vaccines in development** which can complement passive immunisation products (i.e. maternal vaccine and mAb)

Longer term product diversity (maternal and paediatric vaccines, mAb) should be able to meet diverse country preferences when available in future

Emergence of **additional capacity to supply global markets could be by 2027-2030**

However, high degree of uncertainty on product development timings and risk of product development setbacks. **Urgency and prioritisation of RSV immunisation products by manufacturers unclear** compared to competing market opportunities.

8

Risks and mitigation plan

Risks of inaction (Gavi investment not approved)

Strategic concern	Risk
Financial	• RSV burden and hospitalisations continue to strain resource limited healthcare systems
Market	• RSV immunisation products marketed primarily in high-income countries once commercially available, limiting equitable access for Gavi-supported countries • Manufacturers may not adequately develop capacity to supply and product choice to meet needs of low and middle income countries, prioritising high-income markets • Could reduce incentives for accelerated development of pipeline RSV immunisation products

Programmatic	• Missed opportunity to:
	  • Strengthen and prioritise a platform specifically targeted to pregnant women for immunisation services for existing and future vaccines (RSV, influenza, GBS)
	  • Strengthen ANC platform to routinely deliver package of health services to pregnant women
	• Preventable RSV burden continues to cause significant morbidity and undue mortality in children U5 in Gavi-eligible countries where access to health care is limited

Risk and mitigation plan if Gavi investment approved

Strategic concern	Risk	Mitigation plan
Financial	• Financial requirements to facilitate integration between EPI and MNCH may be underestimated	• With help from partners, support countries to develop bottom-up costing to appropriately plan and budget for integrated service delivery
Market	• Delayed or limited availability of RSV maternal vaccine and/or mAb due to product development and production issues (e.g. poor trial data, delayed PQ, slower production scale-up and limited supply)	• In-principle decision contingent on WHO / SAGE recommendation and prequalification • Introductions prioritised based on need and demand, with support from partners • Explore additional market shaping interventions to improve global supply
Programmatic	• Poor coverage of maternal vaccine or mAb due to poor integration between EPI and MNCH programmes • False attribution and rumors (e.g. via social media) of AEFIs leading to resistance among pregnant women	• Provide technical support to countries to develop context specific models for integrated service delivery • Develop and execute targeted social mobilisation strategies to limit vaccine hesitancy

9

Investment recommendation

Recommended investment scenarios: RSV maternal vaccine and mAb

No Gavi commitment to future support for RSV immunisation products

Defer until next VIS when additional data available from clinical trials

In principle support for Respiratory Syncytial Virus (RSV) immunisation products, contingent on the availability of a licensed product suitable for Gavi-supported countries, outcomes of regulatory and technical review processes (including WHO prequalification and SAGE recommendation), and meeting the financial assumptions used as the basis for the RSV investment case set out in Doc 6a Annex C

1. **Provide support for respiratory syncytial virus products contingent on WHO SAGE recommendation and a licensed, prequalified product that meets the financial assumptions of this case**
2. **Provide support beginning in 2019 for pre-introduction activities for respiratory syncytial virus products including evidence and demand generation**

Recommendation

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10

Experts and sources

RSV: key experts

Experts consulted	Topics
Daniel Feikin (WHO) Tracey Goodman (WHO) Emily Wootten (WHO) Philipp Lambach (WHO) Erin Sparrow (WHO)	Epidemiology, burden data, vaccination strategy vaccine & market characteristics, implementation feasibility
Niteen Wairagkar (BMGF) Tasleem Kachra (BMGF) Amanda Beal (BMGF)	Epidemiology, burden data, vaccination strategy, vaccine & market characteristics, implementation feasibility
Clint Pecenka (PATH) Deborah Higgins (PATH) Jessica A. Fleming (PATH) Ranju Baral (PATH) Evan Simpson (PATH)	Burden data, vaccination strategy, modelling, vaccine & market characteristics, implementation feasibility
Kate O'Brien (Johns Hopkins University) Ruth Karron (Johns Hopkins University)	Vaccine characteristics
Linda Eckert (University of Washington)	Vaccine characteristics, implementation feasibility
Harish Nair (University of Edinburgh)	Burden data, modelling
Mark Jit (LSHTM)	Burden data, modelling
Susan McKinney (USAID) Rebecca Levine (USAID) Bernard Gonik (USAID)	Implementation feasibility

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

RSV: sources

Sources

- WHO. Preferred Product Characteristics for Respiratory Syncytial Virus (RSV) Vaccines. 2017.
- RSV vaccine research and development technology roadmap: Priority activities for development, testing, licensure and global use of RSV vaccines, with a specific focus on the medical need for young children in low-and middle-income countries. 2017.
- PATH. Protecting Infants from RSV disease: Evidence and considerations to inform investments. 2018.
- Shi T, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet. 2017;1–13.
- Giersing BK, et al. Meeting report: WHO consultation on Respiratory Syncytial Virus (RSV) vaccine development, Geneva, 25-26 April 2016. Vaccine 2017;(April 2016):25–6.
- WHO Vaccine Trial Tracker (accessed March 2018)

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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

Phase II scorecard RSV *(June 2018)*

Modelled strategy: Routine immunisation with single dose for pregnant mothers (24-36 weeks)

VIS criteria	Indicator	Results	Evaluation[1]
Health impact	Total impact averted	~21-111K deaths averted, ~1.4-5.2 million cases averted, 2020 – 2035	
	Impact averted per 100K	~10-53 deaths, 0.7-2.5K cases averted per 100K vaccinated population 2020 – 2035	
Value for money	Procurement cost	~$ 3,440 – 17,970 procurement cost per death, ~$ 70-280 procurement cost per case averted	
Equity & social protection impact	Impact on vulnerable groups	Relatively even distribution of burden; slightly increased among lower socioeconomic groups	
	Benefits for women and girls	No special benefits of vaccination for women and girls	
Economic impact	Direct medical cost averted	~1.8% of average consumption per capita averted in out-of-pocket medical costs	
	Indirect cost averted	~$ 6-46 productivity loss averted, 2020 – 2035, per vaccinated person	
Global health security impact	Epidemic potential	Not IHR notifiable; antigenic changes -> recurring epidemics; vaccine interrupts H2H transm.	
	Impact on AMR	Medium impact of vaccination on AMR (2.8/10 points in expert consultation)	
Vaccine cost	Total procurement cost	~$ 380-480 million total procurement cost to Gavi and countries, 2020 – 2035	
Relevant second. criteria	Vaccine market challenges	Important market challenges to address, while also providing a signal to manufacturers	

Additional considerations

- Uncertainty around vaccine development and characteristics – lead candidate could become available by ~2022-2023
- Limited country interest (ranked 9/9 in country stakeholder survey) – difficult to distinguish RSV from other acute LRI
- Opportunity to strengthen ANC/PNC care and improve maternal and infant health outcomes
- Potential for impact on RSV-related long-term sequelae (e.g., asthma and wheezing)

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: RSV *(June 2018)*

Modelled strategy: Routine immunisation with single dose for pregnant mothers (24-36 weeks)

VIS criteria	Indicator	Results	Evaluation[1]
Other impact	U5 deaths averted, total	~21-111K future U5 deaths averted, 2020 – 2035	
	U5 deaths averted, per 100K	~10-53 U5 deaths averted, 2020 – 2035, per 100K vaccinated population	
	DALYs averted (cost per DALY)	~1-6 million DALYs averted, 2020 – 2035, ~$ 70-270 procurement cost per DALY averted	
	DALYs averted, per 100K	~700-2,800 DALYs averted, 2020 – 2035, per 100K vaccinated pop.	
Gavi comp. advantage	Vaccine market challenges	High potential to influence the market (e.g., ensure supply availability)	
	Catalytic investment	Limited potential to catalyse additional investments (e.g., strengthen ANC)	
Implementation feasibility	Ease of supply chain integration	Insufficient information on vaccine characteristics	n/a
	Need for HCW behaviour change	Strong need for HCW change: Training of new HCW group required	
	Feasibility of vaccination time point	Existing access point, but new vaccination time-point (possibility to combine with maternal Tetanus toxoid TBD)	
	Acceptability in target population	Ranked last (9/9) in country stakeholder survey, limited understanding of benefits	
	Long-term financial implications	Falls within the category of price per course <$ 2 (but mAb: Price per course >$ 5)	
Alt. interventions	Alternative interventions	Mostly supportive; Palivizumab; Antivirals further out in the pipeline	
Broader health system impact[2]	Broader health system impact	Opportunity to improve delivery platform for ANC, maternal and family planning services; reduce inappropriate antibiotic use; decreased economic strain on healthcare systems	
Operational cost[3]	Incremental costs per vac. person	Medium incremental cost of ~$ 0.70 per vaccinated person	
Implementation costs	Additional costs for introduction	High: Demand generation, tech. assistance, HCW training	

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 maternal RSV vaccination strategy

Element	Strategy to model	Rationale/Source
Vaccination schedule	• 1 dose	• Dosing: manufacturer-recommended schedule
Setting / platform	• As part of the ANC provided services	• However, alternative delivery strategies for some Gavi supported countries might be considered
Delivery strategy	• Routine • Year-round	• Based on principles of maximizing protection to infants (highest-burden group), higher value for money • RSV seasonality not considered, due to limited data from Gavi supported countries. • Giersing BK et al. Vaccine 2017

Target population	• Pregnant women, 24 – 36 weeks	• Expanded vaccination window during pregnancy considering the ongoing Phase 3 clinical trials (which is 28-36 weeks) since:
		  • May offer higher maternal antibody titres transferred to the new-born
		  • May offer more protection to preterm infants
		• Based on the later WHO recommendations: 4 of the proposed contacts (at 26, 30, 34 and 36 weeks) occur during the proposed window.

Demand forecasting assumptions

Element	Assumptions	Rationale / Source
Country scope	Gavi-supported in year of introduction based on current policy	RSV burden is global, no specific geographic distribution
Target population	Pregnant women (live + still births)	Live births: UNPOP 2017. Still birth rates: Lawn et al. Lancet 2016.
Delivery Strategy	Routine (year round), 24-36 weeks of gestation	
Introduction dates	First introduction: 2023 Country Introductions to be determined/phased by: • ANC Coverage • Other introductions (e.g., not introduced before PCV, Rota, HPV in EPI) • Penta historical introduction (early v. late adopters) • Maternal and neonatal tetanus elimination status	WHO PQ estimated for 2021 + 2 years before first introduction to account for introduction in delivery platform (ANC)
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	***Base scenario:*** Modelled ANC coverage during the vaccination window (24-36 weeks) discounted by number of services received by ANC visitors from DHS. ***Alternative scenario (upper bound estimate):*** DTP3 coverage, with no discount. Coverage trajectory: 3% annual increase up to 70%, 1% annual increase up to 95%	ANC coverage is nearest analogue given administration would occur at those visits. DHS data on coverage of other interventions at ANC provides proxy of accessibility to health services and acceptability. Considering that women attend at least one and at least four ANC visits and the timing of the first visit. TT2+ coverage was not utilized since it is recommended to be given at the first ANC contract (prior RSV window) and because it measure coverage at least 2 doses)
Products	PQ date: 2021. Schedule: 1 dose. Presentation: single-dose vial	
Logistics	Wastage factor: 1.05. Buffer: 25%	WHO assumption for single-dose vial

Impact modelling assumptions

Element	Input assumptions	Rationale / source

Infants disease burden	• Incidence of RSV cases
	• Incidence of RSV severe cases
	• Hospital admission rates
	  • Duration of hospital stay: 3 days
	• Mortality:
	  • Hospital case fatality rates (%):
	  • 0-5 months: 2.2; 6-11 months: 2.4; 12-59 months: 2.2
	  • Inflation factor to adjust for community deaths: 2.2
		• Shi et al. Lancet 2017
		• Disability weights: GBD 2010

Long term sequelae	• Estimates did not include impact on long term sequelae (such as association of RSV infection with wheezing and asthma)	• Giersing BK et al. Vaccine 2017.

Vaccine efficacy infants	• Maternal RSV VE infants against severe RSV disease: 50-70%
	  • Minimum: 30%[1] / Optimistic: 90%
	• Infant mAb RSV against severe RSV disease: 70-80%
	  • Minimum: 60% / Optimistic: 100%
		• WHO Preferred product characteristics (PPC).
		• BMGF iTPP parameters.
		• Expert input

Duration of protection	• Maternal RSV vaccine against severe RSV disease: 4-5 months of age
	  • Minimum: 3 months / Optimistic: 6 months
	• Infant mAb RSV against severe RSV disease: 5-6 months
	  • Minimum: 4 months / Optimistic: 7 months
		• WHO Preferred product characteristics (PCC).
		• BMGF iTPP parameters.
		• Griffin P et al. Antimicrob Agents Chemother 2017.

1. Not included in ranges