06a - Annex C: Multivalent Meningococcal Investment Case

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

Gavi
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Agenda

1. Executive summary
2. Key benefits / challenges and strategic rationale
3. Policy approach
4. Demand, health impact, cost and value for money
5. Impact and value for money compared to VIS candidates
6. Country perspective
7. Implementation requirements
8. Risks and mitigation
9. Investment recommendation
10. Experts and sources

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Executive summary

Multivalent meningococcal Executive Summary (1/2)

In 2016, meningococcal disease caused ~560K cases and ~130K deaths worldwide[1] with ~89% of deaths in Gavi countries, focused in sub-Saharan Africa's "meningitis belt" (26 countries)

- Meningococcal disease is caused by multiple serogroups of *Neisseria meningitidis* (Nm), and has historically been dominated by NmA, addressed by MenAfriVac (meningococcal A conjugate vaccine)
- Of the 26 countries in the 'meningitis belt', 21 have completed a mass preventive campaign with MenAfriVac and 3 more are doing so in 2018. Seven have introduced the vaccine in their routine immunisation programmes, 15 are forecasted to do so by 2020, and 4 have not yet defined plans for introduction
- In recent years, there have been some indications of changing serogroup composition with frequent outbreaks of NmC and NmW, and an increase in NmX
- Some experts expect an increased risk of meningococcal meningitis epidemics due to hyper invasive NmC strains in the coming years

Multivalent vaccines can address possible shifts in disease burden and a prequalified (PQ) pentavalent conjugate vaccine is expected to become available in 2021

- Three tetravalent ACWY conjugate vaccines exist on the market at high cost; additional tetravalent vaccines are in the pipeline and could be available at lower cost in the future
- Pentavalent (ACWYX) expected to be lower price than current tetravalent vaccines, driving higher value for money; vaccine is under development and specific vaccine characteristics (e.g., # of doses) are still uncertain
- Manufacturer of pentavalent conjugate vaccine is the same as MenAfriVac, indicating a potential market shift away from monovalent products

1. Source: Global Burden of Disease - IHME

Multivalent meningococcal Executive Summary (2/2)

The current modelled strategy focuses on multivalent conjugate routine vaccination with a campaign at the time of introduction

- Assumes replacement of monovalent MenAfriVac with a multivalent conjugate; currently available tetravalent vaccines were excluded from modelling results due to limited supply availability, high price and challenges of multiple product switches within a few years
- Since the pentavalent product is still in development and the technical recommendations from SAGE are still pending, there are a few uncertainties around the country scope and age range for campaigns, as well as schedule and dosage for routine
- Possible scenarios vary from an uniform delivery strategy (all 26 meningitis belt countries) to a risk-based strategy focusing on high/ mid incidence countries and assuming subnational campaigns in high risk areas; the latter is used for investment case projections.
- SAGE will review evidence to inform recommendations on the multivalent conjugate vaccine, expected discussions for information in 2019 and for decision in 2020. SAGE final recommendations will inform the vaccination strategy and program design.

Potential impact is ~50-106K deaths averted and ~0.5-1M cases averted between 2021-2035 with a risk-based approach

- ~$6,363-13,383/per death averted based on improved pricing via market shaping (assumed to be up to $3/dose initially with low volumes in VIS analysis)
- This risk based vaccination strategy assessed in the investment case represents ~70% lowered cost and significantly improved value for money compared to a uniform delivery strategy in which all meningitis belt countries conduct campaigns
- Health impact and value for money projections capture best estimate of total health impact of multivalent conjugate vaccines, which is still largely driven by protection against NmA; the incremental impact to MenAfriVac is unclear given uncertainty regarding future incidence of non-NmA serogroups

RECOMMENDATION

Expand the existing meningococcal programme to support a targeted approach that includes ACW-containing multivalent meningococcal conjugate vaccines, contingent on WHO SAGE recommendation and a licensed, prequalified product that meets the financial assumptions of this investment case

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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

Not prioritized for shortlist in 2013

- Opportunity to address multiple serogroups causing meningococcal disease
- At the time there was a high procurement cost and burden predominantly of NmA (addressed with MenAfriVac).

Multivalent conjugate vaccine market has evolved

- More tetravalent vaccines and a pentavalent vaccine in the pipeline projected to be at a lower cost than currently available multivalents, including one from same manufacturer as MenAfriVac

Increased burden of C, W, and X serogroups

- Experts expect an increased risk of meningitis epidemics in the upcoming years due to a hyper invasive NmC serogroup in populations with low immunity[1]
- Less than 1% of confirmed cases caused by NmA serogroup in 'meningitis belt' in 2015[2] after MenAfriVac introduction.

Additional considerations

- WHO SAGE working group comprised, with ongoing discussions in 2019 to inform vaccination strategy for multivalent conjugate vaccines

1. Trotter, C. 2017. Stockpile needs for epidemic meningitis response 2018-2022. Report prepared for WHO, 8th December 2017
2. Trotter, C. et al. 2017. Impact of MenAfriVac in nine countries of the African meningitis belt, 2010-15: An analysis of surveillance data. The Lancet Infectious Diseases. 17:867-72

Key vaccine benefits

Investment framework element	Key benefits	Comments
Strategic fit	**Expands on existing MenA* programme to respond to country needs**	• Leveraging gains from MenAfriVac and enhance protection against NmA with a multivalent campaign • Expands on existing MenA programme to proactively address additional burden • Reduced dependence on stockpile, lowering costs of emergency response • Opportunity to strengthen 2nd year of life (2YL) platform and deliver additional interventions at the time of a campaign
Outcome and impact	**Proactively addresses potential increased burden of NmC, NmW and NmX**	• Direct impact from preventing outbreaks, reducing cases and deaths • Indirect benefits by minimizing disruptions to primary health care caused by disease outbreaks • Protective herd effect when high levels of coverage with multivalent conjugate are attained
Value for money		
Cost		
Feasibility	**Low barrier of implementation due to existing MenA programme**	• Assumes replacement of existing MenAfriVac in country and routine administration alongside measles containing vaccines • Increased demand with countries already interested in introducing/switching to multivalent products, as well as increased vaccine confidence by preventing more cases with a multivalent product
Market implications	**Shape the market for multivalent conjugate vaccines**	• Pentavalent product in the pipeline at a more affordable price from a manufacturer with proven capacity • In principle commitment as part of VIS 2018 would provide signal to help positively shape the future multivalent market

* Using MenAfriVac vaccine against *Neisseria meningitidis* group A

Key vaccine challenges

Investment framework element	Key challenges	Comments
Strategic fit		
Outcome and impact	**Incremental impact of multivalent over MenA is unclear**	• Added value over MenAfriVac unclear given uncertainty regarding future burden of non-NmA serogroups and whether recent trend in NmC outbreaks will continue or whether incidence of other serogroups will increase
Value for money	**Significant incremental cost of multivalent vs MenA conjugate vaccine, driving lower overall value for money**	• Higher cost per dose than current MenAfriVac (e.g., 4-5x even with future lower priced vaccine), which would imply higher co-financing and increased investment for countries once they self-finance • Additional cost to Gavi with cash grants to support the switch/introduction (Vaccine Introduction Grants, Product Switch Grants and/or Operational Cost Grants) • A targeted, risk-based strategy would improve the value for money, but still lower than MenAfriVac
Cost		
Feasibility		
Market implications	**Need to manage price and supply availability of multivalent products in the market**	• In near term, need to ensure pricing of upcoming pentavalent is affordable and enables countries to switch from MenA • Supply availability of both monovalent and multivalent products required as countries switch, allowing for timely scale up

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Policy approach

Defeating meningitis by 2030 – A global action plan

A roadmap is being developed – led by WHO – to defeat bacterial meningitis by 2030. Recently, technical partners[1] were involved in the first phase assessment of this action plan, and additional partners will be further involved as part of the Strategy Support Group (including Gavi Secretariat).

Strategic goals include reducing cases and deaths from vaccine preventable meningitis and eliminating meningitis epidemics. In order to achieve these goals, the introduction and uptake of multivalent meningitis vaccine is considered.

Key timeline:

- Q4 2018 – First meeting of the Technical Task Force, tasked to develop a baseline situation analysis and define priority research areas
- Q1 2019 – Initial SAGE consultation on meningococcal vaccines, as well as Stakeholders' consultation.
- Q3 2019 – Roadmap submitted to WHO regional committees
- Q2 2020 – Action plan submitted to the World Health Assembly (WHA)

1 WHO, MRF, CDC, MSF, LSHTM, UNICEF, PATH and BMGF

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Considerations prior to final programme design

Current modelling and proposed investment case reflect uncertainties to be informed by the following:

- **Technical recommendations from SAGE on multivalent vaccine** (working group first meeting in 2019). Open issues for consideration:
  - Scope of countries (within the ‘meningitis belt’)
  - Age group for campaigns
  - Dosage (informed by new product characteristics)
  - Vaccination strategy (campaigns/routine)

- **Pentavalent vaccine** (currently in development and expected to be available in 2021)

Current areas of uncertainty in programme design

Current uncertainties	Key drivers
Country scope for campaigns	• Impact • Cost effectiveness • Burden of disease
Target age group for campaigns	• Burden of disease • Carriage data • Equity
Choice of 1 vs 2 dose routine	• Efficacy of multivalent products (immunogenicity and persistence data of upcoming pentavalent vaccine) • Duration of protection • Target age

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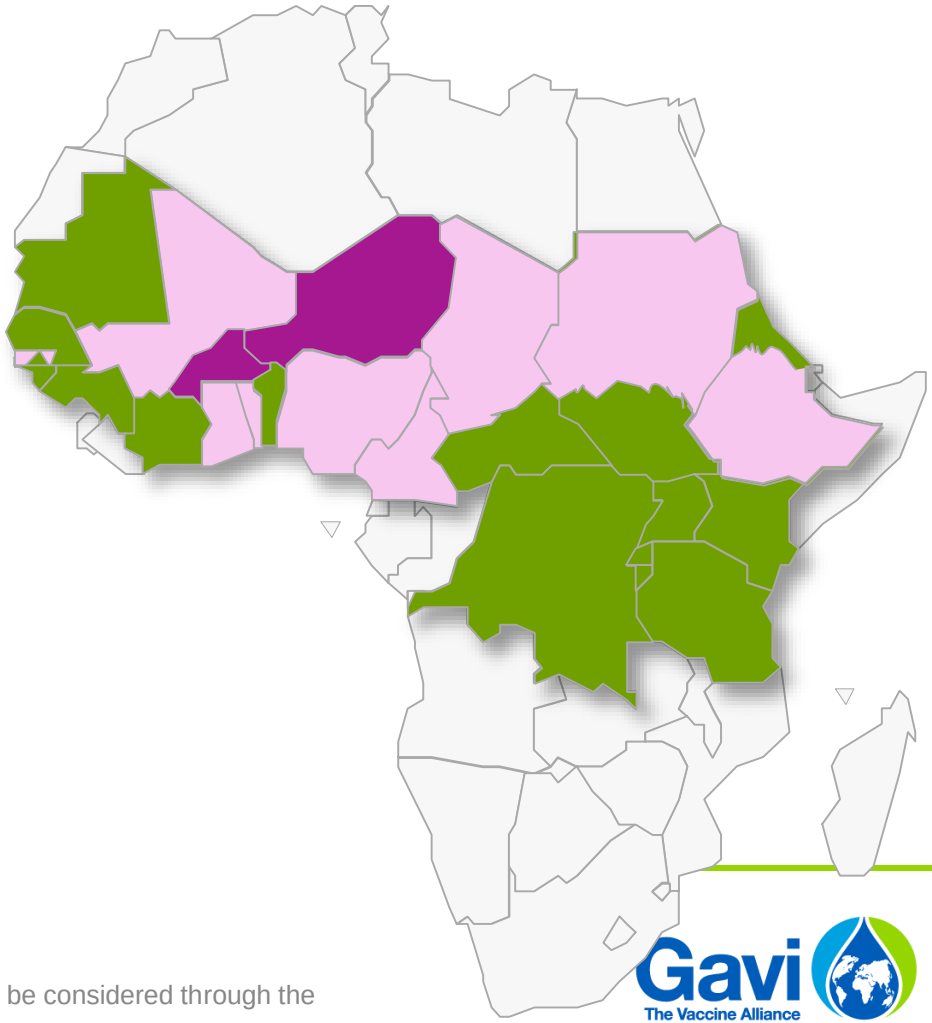
Potential country risk classification

- A risk-based delivery strategy would present a more cost-effective scenario by focusing on higher risk countries to introduce in routine and higher risk areas to additionally implement campaigns
- The current classification is based on the incidence of meningoccal meningitis using suspected cases, taking into account surveillance data and MenAfriVac introduction
- Pending additional data and technical recommendations from SAGE, classification of countries and higher risk areas might vary



High Incidence Countries (N=2):
Burkina Faso and Niger

Medium Incidence Countries (N=9):
Mali, Nigeria*, Chad, Sudan, Ethiopia, Cameroon, Gambia, Ghana, Togo

Low Incidence Countries (N=15):
Senegal, Mauritania, Cote d'Ivoire, Benin, CAR, Eritrea, South Sudan, Guinea, Guinea-Bissau, DRC, Burundi, Kenya, Rwanda, Uganda, Tanzania

* Nigeria not included in impact as cost estimates; investment decisions on VIS candidates for Nigeria would be considered through the Nigeria-specific strategy
Source: Karachaliou, Andromachi & Caroline Trotter. Incidence of meningitis for country-specific NmA models.

Meningococcal vaccination scenarios

Two broad strategies possible, uniform vs. risk-based. Within each, different scenarios considered based on dosing for routine, age group for campaigns and national/subnational scope. Not exhaustive, other scenarios possible.

	Scenario	Routine		Campaign	
		1 dose 15-18m	2 doses 9/15-18m	1 dose 1-29 yo	1 dose 5-14 yo
Uniform delivery strategy	1	✓		✓	
	2	✓			✓
	3		✓	✓	
	4		✓		✓
Risk-based strategy (not exhaustive)	5	✓		✓	
		✓			
	6	✓			✓
		✓			
	7		✓	✓	
			✓		
	8		✓		✓
			✓		
	9	✓			✓(subnational)

All meningitis belt countries (N=26)

High/Medium Incidence countries (N=11)

Low Incidence countries (N=15)

Scenario 9 used as base for the analysis (scenario 2 as comparator)

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Demand, health impact, cost and value for money

Meningococcal key assumptions

xx: included in model uncertainty range
xx: not included

Models	Cambridge	IPM (direct impact only)		
Vaccination strategies	Routine 1 dose at 15-18mo Campaign 1-29yo	Routine 2 doses at 9mo and 15-18mo Campaign 1-29yo	Routine 1 dose at 15-18mo Campaign 5-14yo	Routine 2 doses at 9mo and 15-18mo Campaign 5-14 yo
Uncertainty analysis driving ranges	None			
Other key assumptions	Effectiveness: 85%[1]	Duration of protection: 8 years[2]	Coverage: MCV1 and MCV2[3]	Strategies applied to 1) all 26 'belt' countries and 2) a subset differentiated by risk

1. Based on evidence from immunogenicity data and widespread use of other meningococcal-protein conjugate vaccines(TT-conjugate). 2. For strategies with 2 doses, IPM assuming duration of protection of 8 years in total while Cambridge assuming coverage in between 2 doses + 8 years afterwards so ~9 years in total.
3. MCV1 and MCV2 analogue coverage based on 2017 WUENIC

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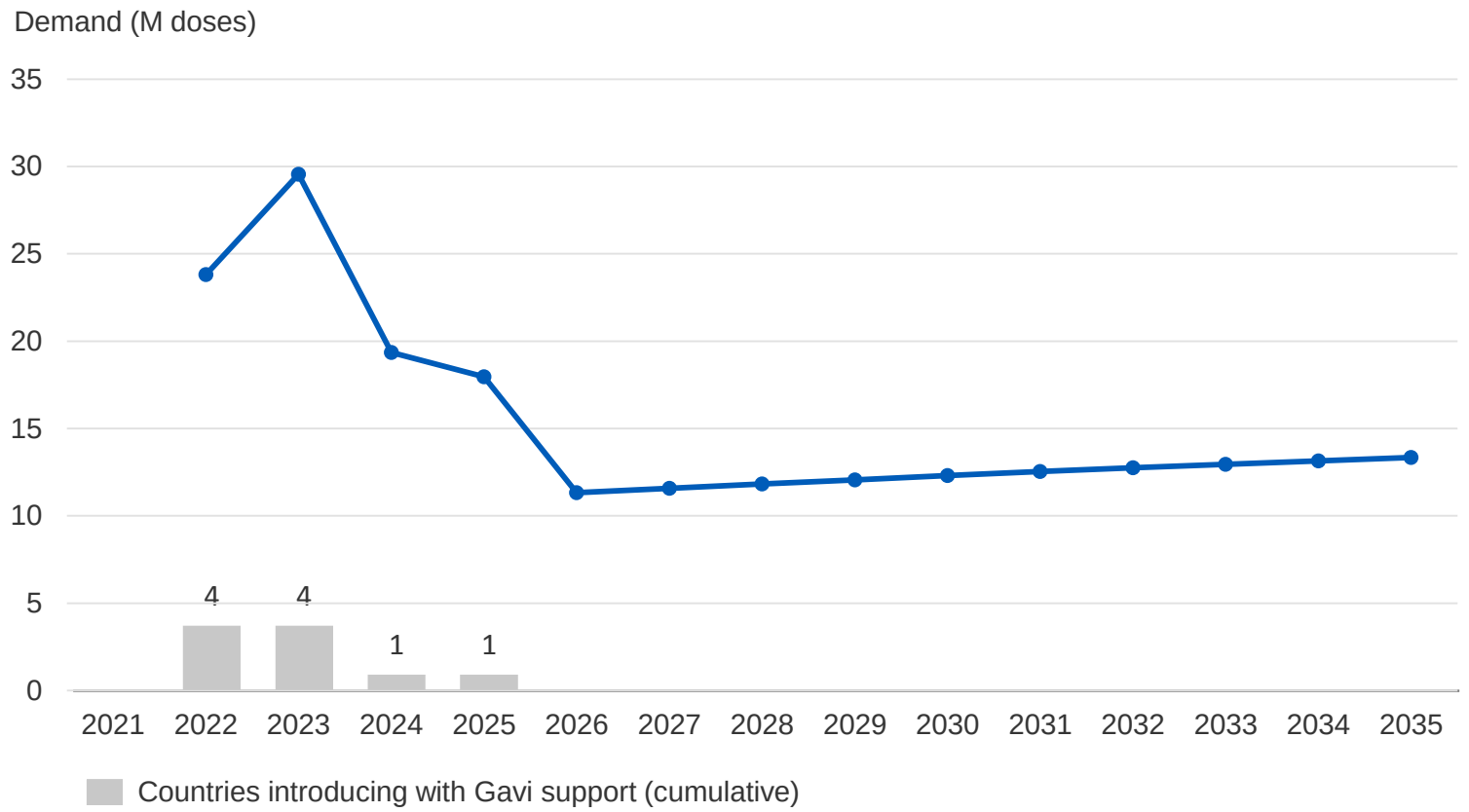
Expected cumulative demand 2021-2035 ~215M doses[1]



Nigeria excluded

Risk-based strategy: national routine 1-dose at 15-18 mo. and national and sub-national campaign 5-14 yo.[2] in high/medium risk countries only

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

Risk-based strategy (campaigns for med-high risk countries) **~215M**

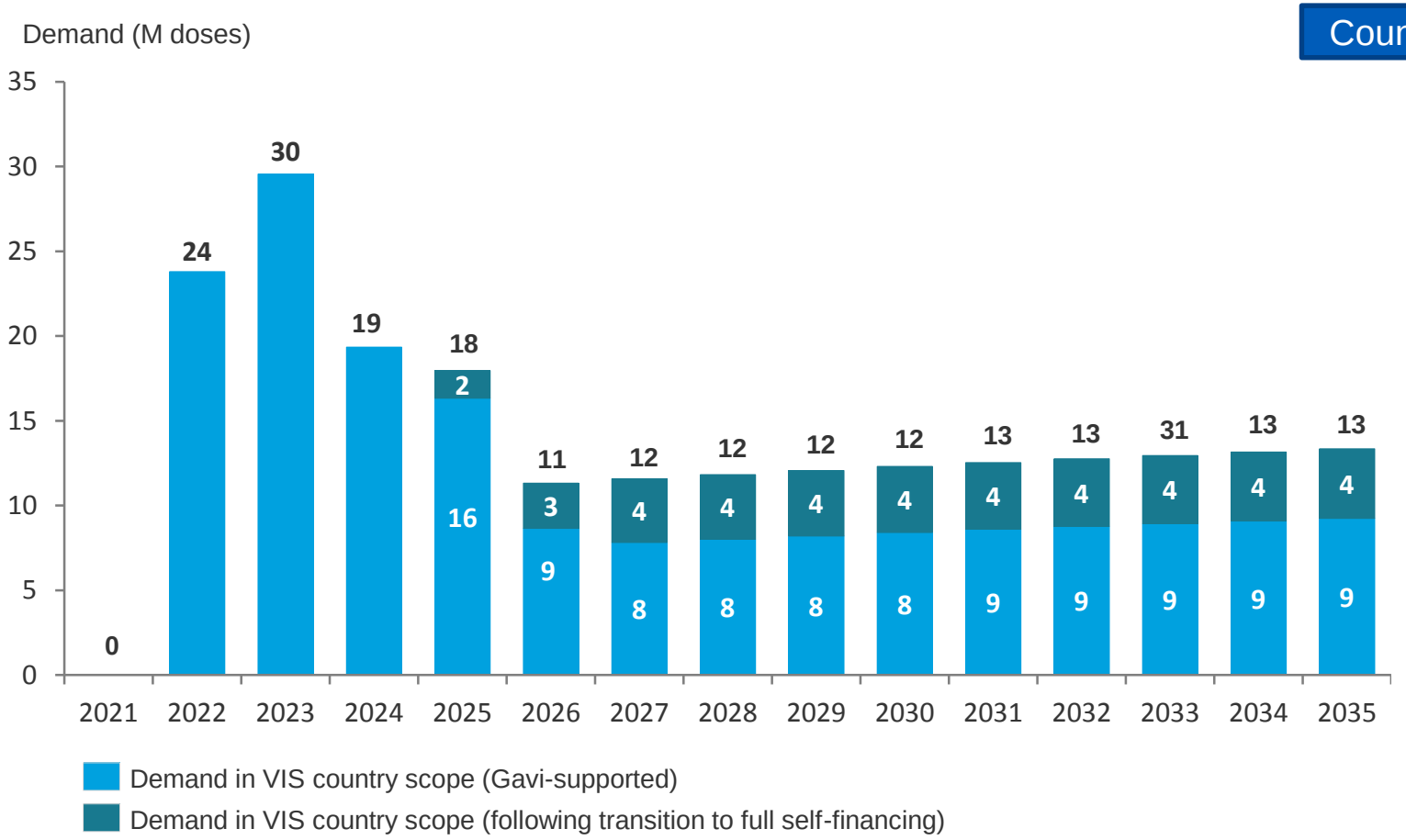
1. Based on Gavi's current eligibility and transition policy
2. Gavi VIS forecast; risk-based scenario, routine 1 dose at 15-18mo and campaign 5-14 years and MCV2 coverage
Consideration for Gavi support to Nigeria for VIS candidates would be considered separately through the Nigeria-specific strategy which was approved by the Gavi Board in June 2018

Gavi anticipates supporting up to ~175M doses from 2021-2035 under a risk-based approach[1]

Nigeria excluded

Countries supported by Gavi for introduction

Risk-based strategy: national routine 1-dose at 15-18 mo. and national and sub-national campaign 5-14 yo.[2] in high/medium risk countries only



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

Gavi supported[2] ~175M

Post transition demand ~40M

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. Demand estimated assuming Risk-based scenario, routine 1 dose at 15-18mo and campaign 5-14 years and MCV2 coverage

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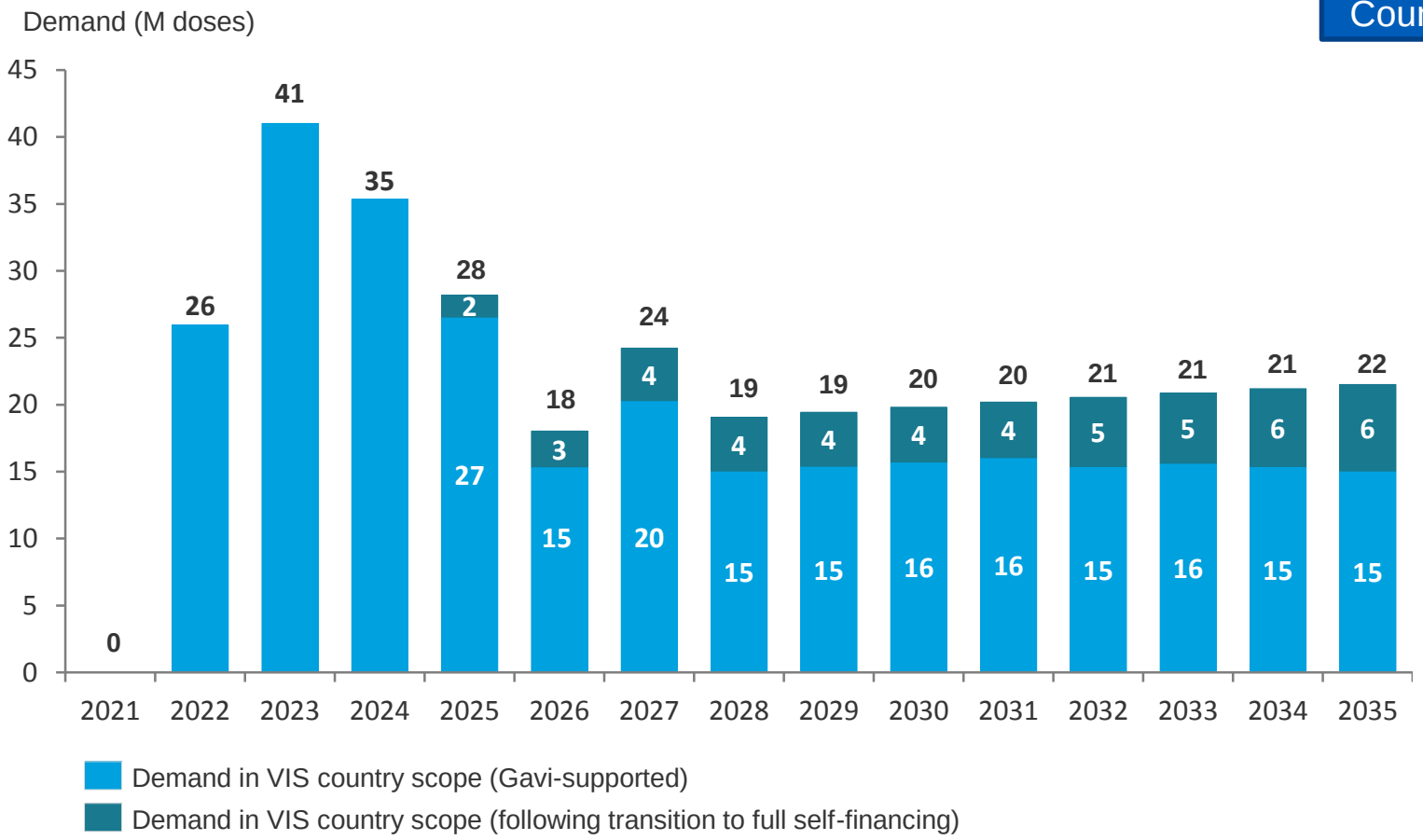
Demand in Gavi-supported countries ~288M doses from 2021-2035 for a uniform delivery approach[1]

Nigeria excluded

Countries supported by Gavi for introduction

Uniform delivery strategy: national routine 1-dose at 15-18 mo., national campaign 1-29 yo.[2] in all meningitis belt countries



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

Gavi supported[2] **~288M**

Post transition demand **~47M**

1. Based on Gavi's current eligibility and transition policy
2. Gavi SDS; uniform delivery scenario, routine 1 dose at 15-18mo, campaign 1-29 yo; all 26 countries; only pentavalent and MCV2 coverage
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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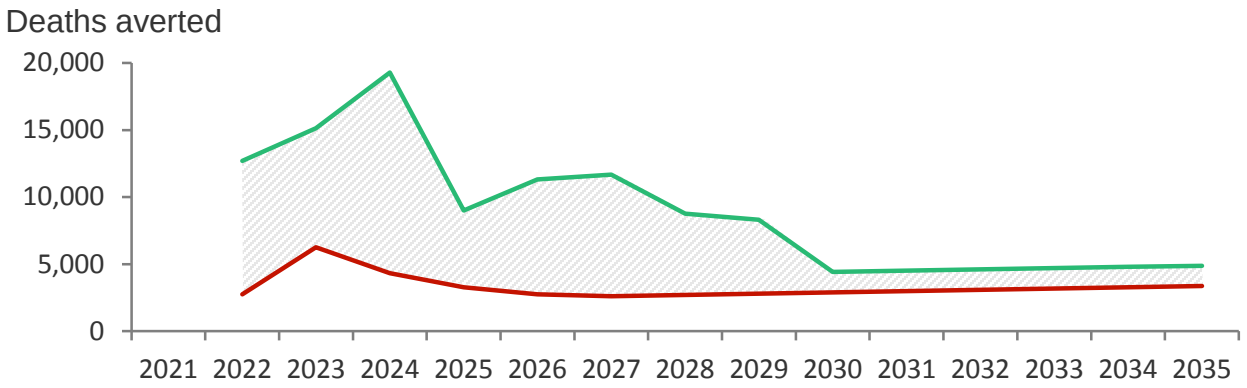
Vaccination could avert between ~50K-106K future deaths and ~0.5M-1M future cases through 2035

Nigeria excluded

Range of projected impact: Maximum / Minimum

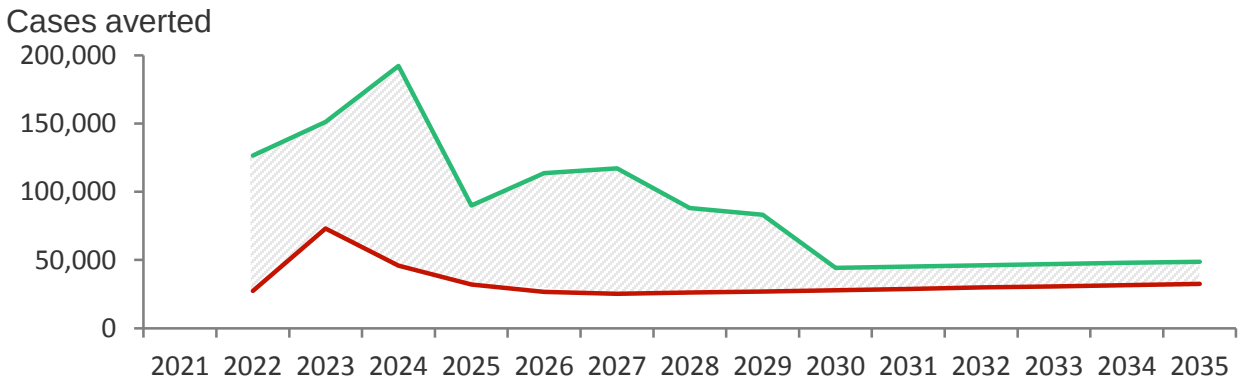
Risk-based strategy: national routine 1-dose at 15-18 mo. and national and sub-national campaign 5-14 yo.[2] in high/medium risk countries only

Deaths[1]



	Total deaths averted (2021-2035)	Deaths averted per 100K vaccinated
Max	~106K	~67
Min	~50K	~33

Cases[1]



	Total cases averted (2021-2035)	Cases averted per 100K vaccinated
Max	~1M	~669
Min	~0.5M	~325

1. Full impact of multivalent vaccine, not just incremental to MenA
2. Cambridge & IPM model; multiple scenarios due to unknown product characteristics and recommended vaccination strategy: 1-dose or 2-dose schedule, introduction into routine for high and medium-risk countries with campaign at time of introduction for either 5-14 yo. or 1-29 yo.
Range of impact driven by uncertainty in future non-A serogroup 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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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 multivalent meningococcal introductions.

Impact scenarios: routine 1 or 2 dose at 9 and/or 15-18 mo., campaign 5-14 yo. (risk based) or routine 1 or 2 dose at 9 and/or 15-18 mo., campaign 1-29 yo. (uniform delivery) [3,4]

		Risk-based	Uniform delivery	Meningitis A (current portfolio)[1]
Impact	Fully vaccinated persons	~196M	~461M	~228M
	Total future deaths averted	~50-106K	~70-242K	~262K
Cost [4]	Gavi procurement costs	$463M	$1,708M	$153M
	Gavi operational costs	$108M	$522M	$4M
	Total Gavi cost	$571M	$2,230M	$157M
	Country procurement costs	$213M	$546M	$70M
	Country operational costs	$24M	$242M	Not estimated in VIS
	Country recurrent delivery costs	$88M	$176M	Not estimated in VIS
	Total Country cost	$325M	$965M	Not estimated in VIS
	Total cost	*$895M*	*$3,195M*	Not estimated in VIS
Value for money	Cost per death averted[2]	~$6,363-13,383	~$9,305-32,117	~$859

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 multivalent meningococcal vaccine introductions
1. Impact and cost projections only through 2030; 2. Calculated using procurement cost only
3. Cambridge & IPM model; multiple scenarios due to unknown product characteristics and recommended vaccination strategy: 1-dose or 2-dose schedule, introduction into routine for high and medium-risk countries with campaign at time of introduction for either 5-14 yo. or 1-29 yo.
4 Cost presented in risk based scenario reflects a 1 dose 15-18 m schedule and campaign at introduction for 5-14 yo. in only high and medium-risk countries; costs presented in uniform delivery scenario reflects a 1 dose 15-18 m schedule and campaign at introduction for 1-29 yo. in all meningitis belt countries
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

- Country product switch and uptake is uncertain, although expected. Some countries[1] are already showing clear interest in the upcoming pentavalent vaccine
- Uncertainty regarding coverage scale-up assumptions for countries where product replacement would occur, may underestimate demand if countries introduce at higher coverage levels

Price

- New manufacturer expected to have PQ vaccine in 2021. Pricing of pentavalent vaccine assumed to be initially up to $3/dose at low volumes, declining with increased volumes; impact on pricing of competitors is unclear
- Additional new entrants expected post 2021; COGS/pricing unknown

Health impact

- Comparison with past studies, used to validate results and increase reliability
- Cambridge model captures both direct and indirect (meningococcal carriage), increases reliability of estimates
- NmA currently estimated as main serogroup (80% of disease), potential for serogroup replacement not captured due to high levels of uncertainty. May underestimate future burden
- Duration of protection and efficacy assumed based on values of existing tetravalent vaccines; pentavalent values are uncertain
- Waning immunity accounted for in Cambridge model, but not IPM, leading to likely over-estimate of impact
- CWYX grouped together, but may have different transmission cycles and disease potential
- Countries grouped into high, medium and low to capture variation in levels of risk across the 26 countries
- Impact not incremental to Gavi's current MenA programme

High uncertainty | Medium uncertainty | Low uncertainty

1. Burundi, Kenya, Rwanda and Tanzania have not introduced MenA in their routine and are waiting for a multivalent product, while Nigeria is planning to introduce MenA in 2019 and switch as soon as the multivalent product is available.

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Implications for demand, health impact and cost when including Nigeria

	% increase if Nigeria included[1]
Demand	56%
Deaths averted	23-59%
Cases averted	25-59%
Cost	62%

1. Assumed risk-based strategy: 1 dose 15-18 m schedule and campaign at introduction for 5-14 yo. in only high and medium-risk countries 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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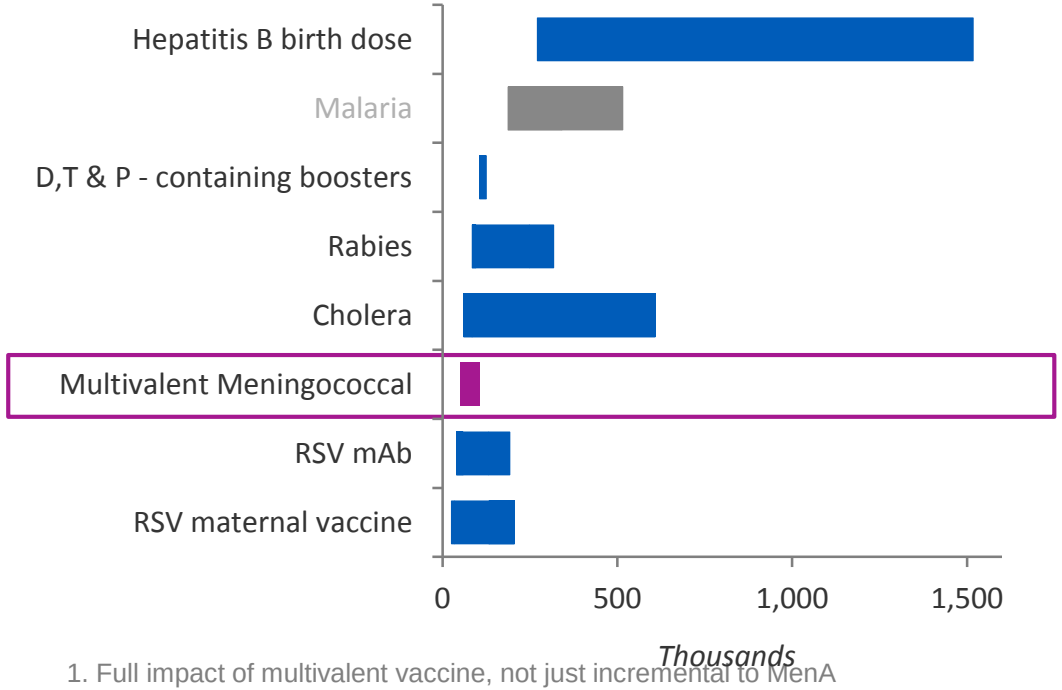
Impact and value for money compared to VIS candidates

Health impact compared across VIS candidates

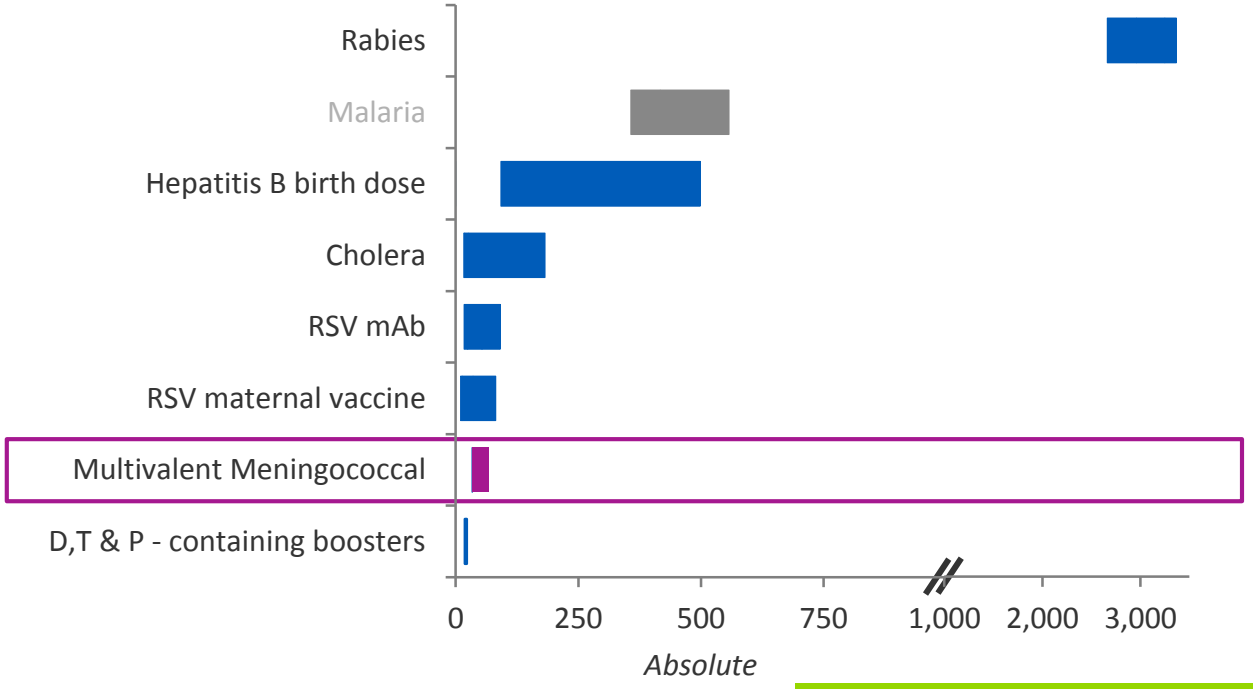
Nigeria excluded

Risk-based strategy: national routine 1-dose at 15-18 mo. and national and sub-national campaign 5-14 yo.[2] in high/medium risk countries only

Total future deaths averted (K), 2021-2035



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



1. Full impact of multivalent vaccine, not just incremental to MenA
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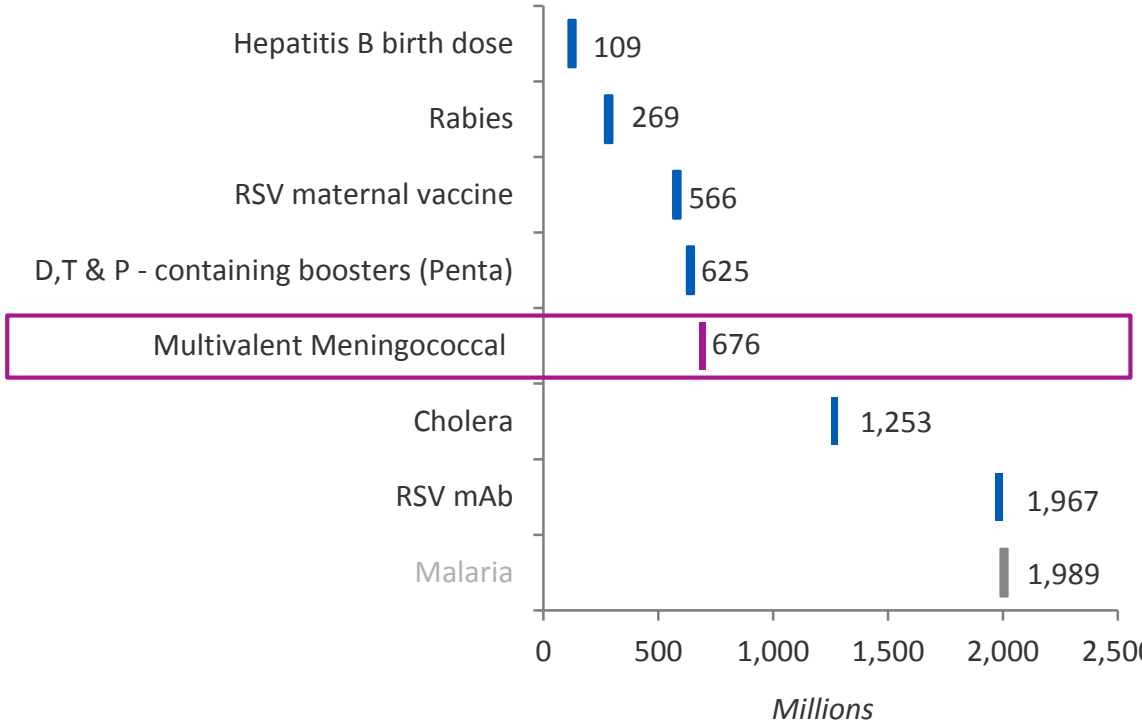
Range of projected impact

Procurement cost and cost per death averted compared across VIS candidates

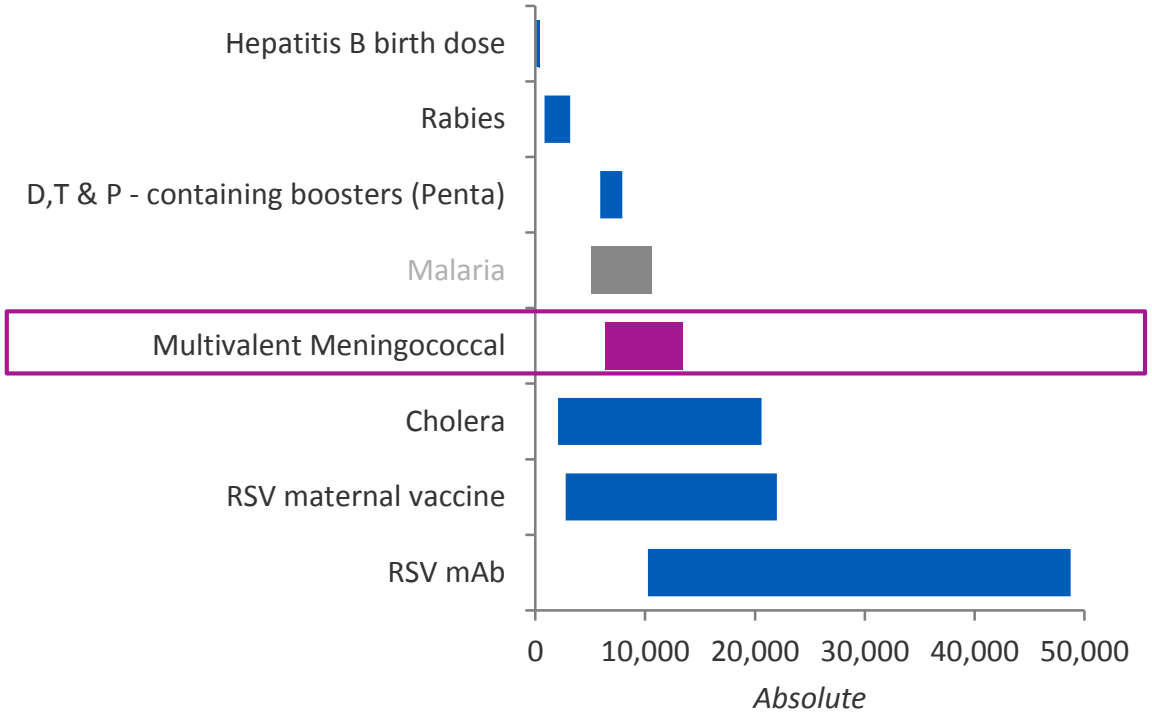
Nigeria excluded

Risk-based strategy: national routine 1-dose at 15-18 mo. and national and sub-national campaign 5-14 yo.[2] in high/medium risk countries only

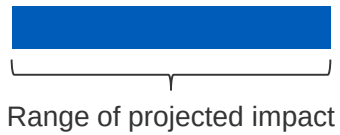
Total procurement cost to Gavi & countries (M$), 2021-2035



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



Cost projections are unconstrained. Values do not account for anticipated introduction of current portfolio and other VIS candidate vaccines that may reduce the number of planned multivalent meningococcal introductions.



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Country perspective

Interviews with country stakeholders revealed that introduction dependent on additional cost vs. MenA

Priorities and approach

- Some countries still yet to introduce Meningococcal A (MenA) vaccine
- Where meningococcal disease occurs, respondents felt a vaccine would be a priority
- Multivalent vaccine preferred though not necessarily due to known disease burden of other serogroups beyond A
- Question whether approach would be to replace current MenA vaccine with multivalent

Burden of disease and surveillance

- Most common serogroups are A and C; W, X, Y unknown burden
- Not always a national problem; meningococcal disease occurs regionally/ subnationally

Programmatic implementation

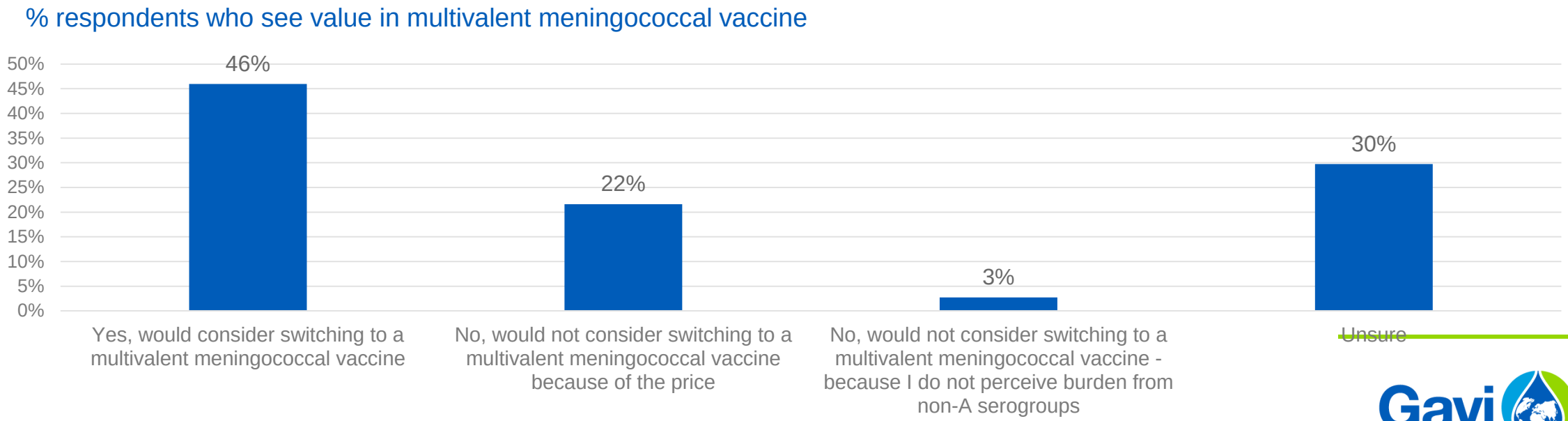
- Cost viewed as biggest barrier, based on pricing of current multivalent vaccines compared to current MenA vaccine
- Could consider subnational approach but would be programmatically challenging and concerned about serogroup emergence and shift
- Campaigns at time of introduction viewed as appropriate initial step, followed by routine immunisation, for successful introduction
- Current experience has been that serogroups occur heterogeneously across areas with meningococcal disease burden (eg, some areas have NmA, others have other serogroups)
- Respondents felt additional training would be required

Source: VIS Phase III in-depth country interviews

Many respondents see value in multivalent vaccines, others unsure about price

40/75 respondents indicated that meningococcal disease burden is important in their country, representing 27 countries[1] - *only these respondents' answers included in analysis*

Based on your country context and given the cost differential, do you think there is value in a multivalent meningococcal conjugate vaccine compared to meningococcal conjugate A vaccine? (Men A ten-dose costs $0.52 per dose for routine and $0.69 per dose for campaign and we expect multivalent meningococcal ACWY or ACWXY to cost ~$1.00-5.00 per dose)



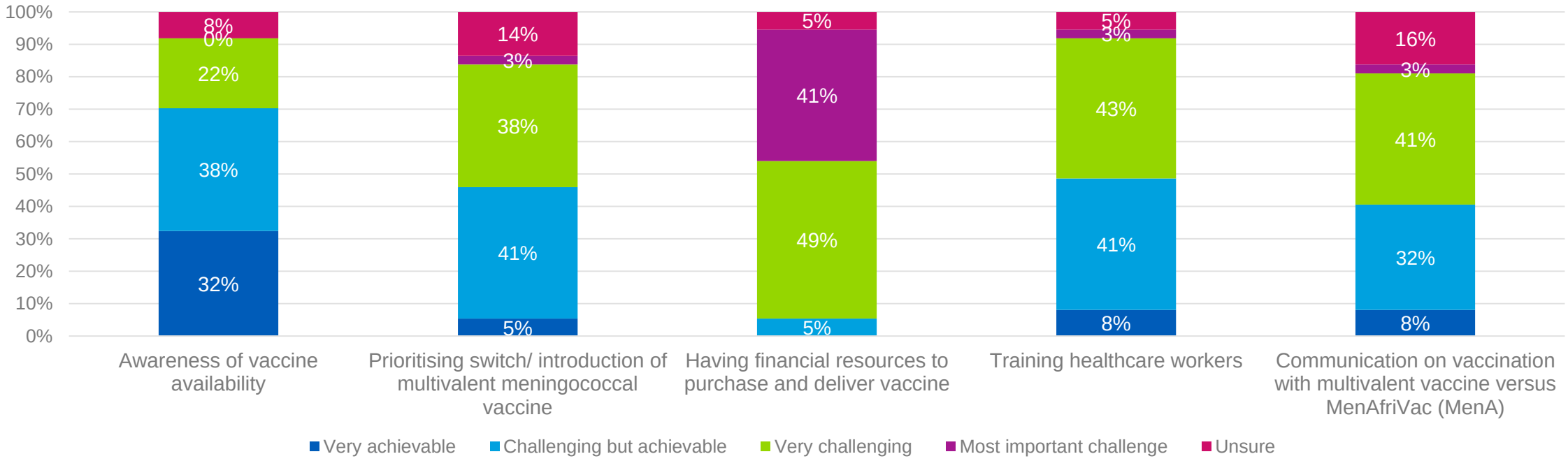
1. Represents all respondents which indicated the meningococcal disease was locally relevant, including respondents in non-Meningitis Belt countries
Source: VIS Phase III country survey

Respondents consider finding financial resources to fund vaccine to be the most challenging activity

40/75 respondents indicated that meningococcal disease burden is important in their country, representing 27 countries[1] - *only these respondents' answers included in analysis*

The table below lists several activities associated with introducing or switching to a multivalent meningococcal vaccine. Please rate the degree to which each activity would be challenging.

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



1. Represents all respondents which indicated the meningococcal disease was locally relevant, including respondents in non-Meningitis Belt countries
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	• Technical recommendation from WHO on delivery strategy and switch/introduction guidelines. • Integration and coordination with existing surveillance networks and the 'Defeating Meningitis by 2030' Global Strategy	
	Supply	• Management of supply availability with new product in the market, and pricing of existing multivalent products	
Country level	Planning, coordination, integration	• Integration with existing MCV/MCV1 delivery • CTC possible with pentavalent (as with MenAfriVac)	
	Supply chain infrastructure and logistics	• For countries switching from monovalent to multivalent, close management of products in country	
	Health workforce	• Handling a new product and minimize safety issues when switching. Opportunity to strengthen training on multidose vial policy and increasing 2YL coverage	• Additional training for health workers
	Social mobilization, education, communication	• Communication on differences between MenAfriVac and multivalent vaccine	• Social mobilization and advocacy for multivalent vaccination
	Surveillance	• Strengthening surveillance to inform decisions of introduction and update risk assessments (when applicable) • Ongoing surveillance to establish rates of disease	• Strengthening disease surveillance • Conducting studies on carriage and/or sero surveys

Most challenging

Unique but manageable

Few unique implementation requirements

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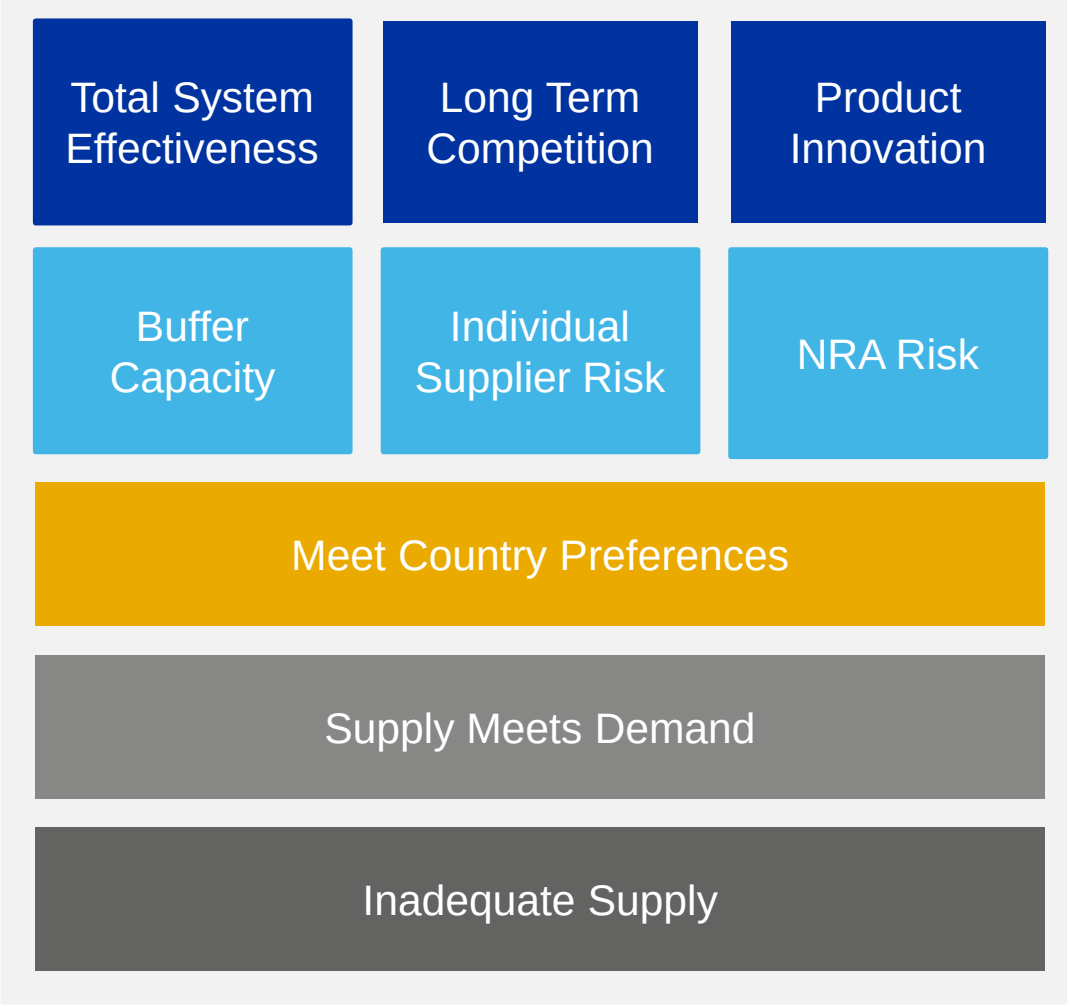
Current supply available at non-sustainable prices and sole-supplier market may develop for Gavi



Limited near-term supply at non-sustainable prices. Several manufacturers have pipeline vaccines with expected reduced prices, however, their business priorities and development progress are uncertain. A sole-supplier market may develop.

Lead pipeline supplier has significant experience in product development and high-volume production for Gavi countries.

Other pipeline manufacturers have limited experience that could lead to unsuccessful development or inadequate supply.

Limited supply from current manufacturers for the outbreak response stockpile. Unclear the level to which supply can be increased for routine/campaigns, but it is expected that it will not be able to meet the Gavi demand forecast. Lead pipeline pentavalent supplier anticipated to be able to meet demand in the future.

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Risks and mitigation

Risks of inaction (Gavi investment not approved)

Strategic concern	Risk
Financial	• No change in forecasted investment for meningitis program, potentially only routine support after 2020 • Increased investment in stockpile, as well as increased direct and indirect cost to countries that need to respond to outbreaks (including treatment and care)
Market	• Multivalent conjugate vaccines remain at high cost and limited supply • Pentavalent vaccine in development marketed to mid-high income countries instead and stockpile • Decreased incentives for additional manufacturers to develop new multivalent conjugate vaccines • Potential shortage of required products for the stockpile, calling for limited allocation, endangering an efficient outbreak response
Programmatic	• Continued cases and deaths caused by non-A serogroups, would potentially decrease interest in ongoing MenA programmes. • Continued outbreaks disrupt the health systems and have a negative economic impact[1]. • Countries that have yet to introduce MenA in their routine potentially further delay introduction, and countries with MenA in RI are not able to switch to multivalent on their own.
Reputational	• Missed opportunity to address non-A burden with lower cost multivalent conjugate vaccine. Partners and manufacturers considering Gavi as having the comparative advantage to make a multivalent conjugate vaccine available to lower income countries and drive uptake

1. Study on the economic impact of meningococcal meningitis in Togo and Nigeria is being finalized, with preliminary results expected in October 2018

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Risk and mitigation plan if Gavi investment approved

Strategic concern	Risk	Mitigation plan
Financial	• Upcoming pentavalent product might have a final price higher than currently assumed • Recommended strategies might imply a higher investment outside the range presented (e.g. booster dose)	• Re-assess with updated assumptions and present for Board review if financial assumptions fall outside current investment case
Market	• Risk that pentavalent product does not align with current assumptions (i.e. PQ at a later date, slower scale up of production or not enough supply to cover demand)	• Introduction of multivalent conjugate would need to be prioritised based on risk and demand, with support from partners
Programmatic	• Recommended strategy falls outside the scope considered in the investment case	• Ongoing engagement with WHO and SAGE Working Group to address pending questions informing the programme development and ensure a risk-based approach that brings value for money

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Investment recommendation

Recommended investment scenario

No change from current programme (no support for multivalent conjugates in routine immunisation)

Expand the existing meningococcal programme to support a targeted approach that includes ACW-containing multivalent meningococcal conjugate vaccines, contingent on WHO SAGE recommendation and a licensed, prequalified product that meets the financial assumptions of this investment case

Recommendation

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Illustrative multivalent meningococcal vaccine components of a VIS learning agenda

Objective	Key questions	Indicative cost
Burden of disease	• Carriage in different age groups; peak of carriage • Contact pattern • Strain/serogroup replacement	$1-2 million for multisite study
Optimal schedule, vaccination strategy	• Vaccine duration of protection • Risk assessment to identify countries requiring campaigns at time of introduction	$1-2 million for multisite study

Note: Impact is measured through the Vaccine Impact Modelling Consortium and Secretariat accountability measures; surveillance funded separately as part of programme roll-out

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10

Experts and sources

Experts consulted

Experts
Marie-Pierre Preziosi (WHO)* Olivier Ronveaux (WHO)* Antoine Durupt (WHO)* Katya Fernandez (WHO)
Myriam Henkens (MSF)*
Leanne Fox (CDC) Ryan Novak (CDC) Nancy Messonnier (CDC)
Imran Mirza (UNICEF PD)
Shannon Larsen (BMGF)* Tina Lorenson (BMGF)
Caroline Trotter (Cambridge) Claire Broome (Emory University)*

* Provided assumptions for Strategic Demand Scenarios and modelling
Note: Materials represent the view of the Gavi Secretariat based on expert input. Individual experts might not agree with all presented information

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Sources consulted

- WHO Position paper on Meningococcal vaccines (2011) http://www.who.int/wer/2011/wer8647.pdf
- Meningococcal A conjugate vaccine: updated guidance (February 2015) http://www.who.int/entity/wer/2015/wer9008.pdf?ua=1
- Trotter, Caroline (8 December 2017) Stockpile needs for epidemic meningitis response 2018-2022.
- Meningococcal meningitis fact sheet (Jan 2018). WHO. http://www.who.int/mediacentre/factsheets/fs141/en/
- Map of serogroup distribution (Feb 2018). WHO. http://www.who.int/emergencies/diseases/meningitis/serogroup-distribution-2018.pdf?ua=1
- Antimicrobial resistance: global report on surveillance 2014 (WHO) http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf?ua=1
- Trotter, Caroline & Lingani, Clément & Fernandez, Katya & Cooper, Laura & Bita, André & Tevi-Benissan, Carol & Ronveaux, Olivier & Préziosi, Marie-Pierre & Stuart, James. (2017). Impact of MenAfriVac in nine countries of the African meningitis belt, 2010-15: An analysis of surveillance data. The Lancet Infectious Diseases. 17. 10.1016/S1473-3099(17)30301-8.
- Global Burden of Disease, Institute for Health Metrics and Evaluation (IHME), 2016
- Karachaliou, Andromachi & Caroline Trotter. Incidence of meningitis for country-specific NmA models.

Vaccine-specific

- Clinicaltrials.gov
- Vaccine package insert for MenAfriVac, Menactra and Nimerix (https://extranet.who.int/Gavi/PQ_Web/)

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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: Multivalent Meningoccal *(June 2018)*

Modelled scenario: Routine (1-2 doses) and mass preventive campaigns (5-14 or 1-29 yo)

VIS criteria	Indicator	Results	Evaluation[1]
Health impact	Total impact averted[2]	~64-170K future deaths, ~0.7-1.7 million cases averted, 2020 – 2035	
	Impact averted per 100K[2]	~23-59 deaths, ~230- 600 cases averted, 2020 – 2035, per 100K vaccinated population	
Value for money	Procurement cost[2]	~$ 7,100-26,600 procurement cost per death, $ 590-1,010 procurement cost per case averted	
Equity & social protection impact	Impact on vulnerable groups	Burden concentrated among urban slum residents and rural populations	
	Benefits for women and girls	No special benefits of vaccination for women and girls	
Economic impact	Direct medical cost averted	~2.0% of average consumption per capita averted in out-of-pocket medical costs	
	Indirect cost averted[2]	~$ 20-34 productivity loss averted, 2020 – 2035, per vaccinated person	
Global health security impact	Epidemic potential	IHR notifiable; serotype switching and changing epidemiology; vaccine interrupts H2H transm.	
	Impact on AMR	High impact of vaccination on AMR (4.3/10 points in expert consultation)	
Vaccine cost	Total procurement cost	~$ 1,0-1.9 billion total procurement cost to Gavi and countries, 2020 – 2035	
Relevant second. criteria	Vaccine market challenges	High potential for Gavi to support the switch to conjugates	

Additional considerations

- Some experts suspect an increased risk of meningitis epidemics due to hyper invasive NmC strains in the coming years expected
- MenAfriVac supply potentially to be replaced by multivalent over time as MenAfriVac manufacturer now developing pentavalent vaccine

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. All impact based on full impact of multivalent vaccine, not just incremental to MenA

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Phase II secondary criteria and financial implications: Multivalent Meningoccal *(June 2018)*

Modelled scenario: Routine (1-2 doses) and mass preventive campaigns (5-14 or 1-29 yo)

VIS criteria	Indicator	Results	Evaluation[1]
Other impact	U5 deaths averted, total[1]	~25-36K future U5 deaths averted, 2020 – 2035	
	U5 deaths averted, per 100K[1]	~ 7-14 U5 deaths averted, 2020 – 2035, per 100K vaccinated population	
	DALYs averted (cost per DALY) [1]	~7.0-11.8 million DALYs, 2020 – 2035 (~$ 100-240 procurement cost per DALY averted)	
	DALYs averted, per 100K[1]	~2 - 4K DALYs averted, 2020 – 2035, per 100K vaccinated population	
Gavi comp. advantage	Vaccine market challenges	High potential to influence the market (e.g., foster competition, support demand forecasting)	
	Catalytic investment	Medium potential to catalyse additional investments	
Implementation feasibility	Ease of supply chain integration	Packed volume of 10-94cc; 24-36 months shelf life at 2-8°C; VVM = 30	
	Need for HCW behaviour change	Some need for HCW behaviour change: Campaign with outreach requiring some training	
	Feasibility of vaccination time point	Existing vaccination time-points (aligns with measles schedule), additional campaigns	
	Acceptability in target population	Ranked 4/9 in country stakeholder survey, likely no significant demand promotion needed	
	Long-term financial implications	Falls within the category of price per course $ 2-5	
Alt. interventions	Alternative interventions	Prevention: Antibiotic prophylaxis; Treatment: Antibiotics	
Broader health system impact[2]	Broader health system impact	Opportunity to improve child health (nutrition interventions, deworming, treat diarrheal disease)	
Operational cost[3]	Incremental costs per vac. person	High incremental cost of ~$ 1.0 per vaccinated person	
Implementation costs	Additional costs for introduction	Medium: Tech. assistance, micro-planning for campaigns, data-related costs	

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
Note: All impact based on full impact of multivalent vaccine, not just incremental to MenA

Rationale for vaccination strategy

Element	Age group/Target Population	Rationale
Routine	• 1 dose • 15-18 month old	• Based on evidence from data relative to other polysaccharide-protein conjugate products and immunologic principles, immune responses are expected to be higher and more sustained with a single dose administered in the second vs. in the first year of life • Age group for routine in line with WHO Position Paper recommendation to align to MCV vaccination
	• 2 dose • 9 & 15-18 month old	• Number of doses for routine vaccination are pending additional evidence from products in pipeline. • Age group for routine in line with WHO Position Paper recommendation to align to MCV vaccination.
Campaign	• 1-29 years old	• Aligned with current vaccination strategy for MenAfriVac
	• 5-14 years old	• Carriage data indicates that carriage prevalence is highest in this age group. It is expected that mass vaccination of this age group will result in decreased transmission and confer enhanced herd protection
Uniform delivery strategy	• 26 countries	• Countries in the African meningitis belt are considered to have the highest annual incidence of meningococcal disease in the world.
Risk-based strategy	• 11 countries with medium/high incidence • 15 countries with low incidence	• The current classification is based on the incidence of meningitis within ‘belt’ countries, taking into account surveillance data and MenAfriVac introduction.

Demand forecasting assumptions

Element	Assumptions	Rationale
Country scope	26 endemic Gavi countries - Uniform delivery: all 26 countries - Risk-based: 11high/mid incidence and 15 low incidence	Aligned to Gavi 73 countries with endemic meningitis Risk-based: Based on incidence of meningitis within 'belt' countries, taking into account surveillance data and MenAfriVac introduction.
Target population	Campaign - 1-29 years old - 5-14 years old Routine - 1 dose at 15-18 yo - 2 doses at 9 months and 15-18 yo	• Campaign 1-29 yo: Aligned with current MenAfriVac schedule • Campaign 5-14 yo: Based on carriage data • 1 dose routine: Based on evidence showing higher immune response at second year of life • 2 dose routine: Pending additional evidence from products in pipeline and aligned with MCV schedule as recommended in WHO Positon Paper.
Delivery Strategy	Routine in health facilities plus campaign	WHO position paper
Introduction dates	First introduction: 2022	Based on estimated product availability timelines for multivalent conjugate products under development
Vaccine uptake	3-6 yrs max uptake, depending on platform readiness	Expert input and consultations
Coverage	Demand (1 dose): MCV2, FVP Demand (2 doses): MCV1 and MCV2, FVP	Nearest coverage analogue based on target population and existing immunization time-point
Products	Multiple PQ products, from 1 or 5-dose vial	Based on current manufacturer labels and product characteristics
Logistics	Wastage Factor: 1.05 (1-dose routine & campaign), 1.43 (5-dose routine) and 1.11 (5-dose campaign) Buffer stocks = 25%	WHO assumption for 1 and 5 dose lyophilised vial in routine and campaign settings Standard assumption for routine vaccination

Impact modelling assumptions

Element	Assumptions	Rationale
Effectiveness	85%	Manufacturer labels for tetravalent products
Duration of protection	8 years	Manufacturer labels for tetravalent products
Burden of disease	Disease burden estimate developed in consultation with WHO. Countries were categorised into high, medium and low incidence groups	WHO consultation and expert consultations recommended selected approach