Annex C: Diphtheria, Tetanus and Pertussis - Containing Boosters Investment Case

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

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Agenda

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

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Executive summary

Diphtheria, Tetanus and Pertussis - Containing Boosters - Executive Summary (1/2)

Diphtheria, Tetanus and Pertussis cause an estimated 110,000 deaths and ~8.7M DALYs per year globally

- 65% of deaths due to Pertussis, 34% due to Tetanus, and 1% due to Diphtheria
- Immunity from primary pentavalent series wanes to non-protective levels after ~3-5 years against the three diseases (assuming 3 doses of primary series), thus requiring further boosting
- Greatest burden is in Asia and Sub-Saharan Africa and most deaths occur in children aged 1-4, however cases are increasing in older age groups due to good coverage with primary series, but waning immunity of vaccination
- Diphtheria outbreaks have been occurring in Gavi-supported countries in areas of low vaccine coverage, e.g., Cox's Bazar (Bangladesh), Yemen, Indonesia with >4000 reported cases in 2017
- Tetanus cases are increasingly reported in Sub-Saharan African countries due to recent voluntary medical male circumcision as an HIV-prevention tool, e.g. Kenya, Mali, Nigeria

Vaccination with the boosters has the potential to avert ~106,000 deaths (~82% in children under age 5), at ~$2,074-$5,912 per death averted from 2021-2035

- Very little data available on addressable burden but experts suspect it is underestimated in Gavi-supported countries
- The three immunisation time points reinforce a move towards a life-course approach to vaccination in Gavi-supported countries, strengthen existing vaccination time points (2nd year of life, child visits, and adolescent HPV) and establish new healthcare touch points at existing access points (e.g., school entry)
- While more challenging to implement, these touchpoints also serve as an opportunity to provide missed doses to achieve a fully immunised child

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Diphtheria, Tetanus and Pertussis - Containing Boosters Executive Summary (2/2)

Diphtheria, tetanus and pertussis-containing booster (D,T&P) strategy would constitute an extension of Gavi's existing support for pentavalent vaccine, in line with updated WHO recommendations

- Gavi strategy would support routine boosters in ages 12-23 months (diphtheria, tetanus and whole cell-pertussis [DTwP] or pentavalent), 4-7 years (Tetanus & diphtheria [Td] – containing) and 9-15 years (Td – containing) per WHO recommendation (2017)
- 59 Gavi countries do not have all or some boosters in programmes, but in-country stakeholders have highly prioritised in consultations
- Strategy would address the problem of waning protection after primary series vaccination and aid in sustaining global goal of elimination of maternal to neonatal tetanus (MNTE)
- Introduction of boosters would bring Gavi-supported countries in line with global recommendations, closing the equity gap in vaccine implementation; however the investment would be atypical in that Gavi has not historically invested in low cost vaccines

D,T&P-containing boosters show high value for money, and Gavi could consider non-traditional investments that address platform establishment or strengthening rather than vaccine financing due to low cost of DTwP and Td

- DTwP and Td would be self-procured by countries as they fall below the co-financing threshold, and support would focus on funding for platform establishment and strengthening to catalyse introduction of the boosters
- If countries chose to use pentavalent vaccine as the 2nd year of life booster, this would represent an expanded Gavi investment in the pentavalent programme, which still represents high value for money
- By potentially using pentavalent vaccine as the first booster, possibility to improve Hepatitis B/Hib coverage from primary series, while simplifying supply chain versus adding DTwP

RECOMMENDATION

Provide support to establish platforms as catalytic support for the introduction of each diphtheria, tetanus & pertussis-containing (D,T&P) booster dose, beginning in 2021[1]

1. In line with current co-financing policy, Gavi would not fund procurement of diphtheria, tetanus and pertussis (DTP) vaccine or tetanus-diphtheria (Td) vaccine as the price is below the minimum country co-financing level within the current co-financing policy, but would provide support for pentavalent vaccines for those countries who choose it as the first booster. Potential Gavi support for use of whole-cell pertussis-containing hexavalent vaccine is being considered within the paper on IPV support post-2020 (Doc 6b)

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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

One booster dose for children 1-6 years – as was recommended by WHO in 2013 – was not put forward for investment

- Insufficient data on addressable pertussis burden and duration of protection of booster vaccination
- Likely low impact on deaths averted compared to other VIS candidates, as majority of pertussis deaths occur in first year of life, before the booster is administered

Several changes to context since VIS 2013

- Updated WHO recommendation due to improved data on immunological basis of protection
- 3 booster doses recommended at 12-23 months (DTwP or pentavalent), 4-7 years (Td or DT) and 9-15 years (Td) years of age to address waning immunity
- Recent diphtheria outbreaks in areas of low primary series coverage, e.g., Cox's Bazar, Yemen, Indonesia, Venezuela
- Recent post-voluntary medical male circumcision (VMMC) tetanus in Sub-Saharan African countries e.g. Kenya, South Africa, Mali, Nigeria
- Continued underestimation of burden due to poor surveillance
- Continued difficulty in modelling the impact of boosters due to limited information on the duration of protection/waning immunity for each individual booster

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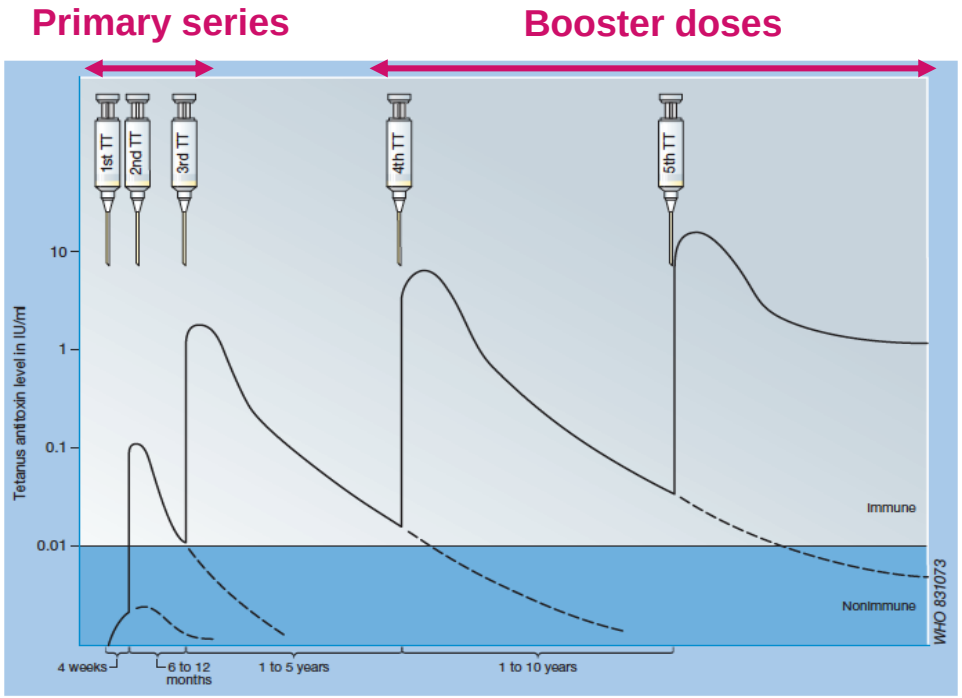
Evidence of waning immunity for tetanus

- There is no natural immunity to tetanus, populations in developing countries with a high level of exposure to tetanus spores usually lack tetanus neutralizing antitoxins
- As the immunity from the primary series wanes after ~3-5 years, boosters are required to ensure high antitoxin levels, which manifests as increased number of deaths in older age groups
- WHO Position Paper GRADE table on boosters vs. primary series shows that six doses of TTCV by adolescence are expected to protect for at least 20-30 years and throughout the reproductive age



Schematic of the antibody response to tetanus toxoid (TT)
Source: The immunological basis for immunization series, Module 3: Tetanus, Update 2017

Evidence of waning immunity for diphtheria & pertussis

Diphtheria

- Recent diphtheria outbreaks where the majority of cases have been in older 5-14 age groups, implying waning immunity
- WHO Position Paper GRADE table duration of protection conferred by diphtheria vaccination concludes a high degree of confidence that 3 primary doses and 3 booster doses until adulthood confer high levels of seroprotection, at least up to age 39 and likely longer

Pertussis

- Neither infection nor vaccination confers long-lasting immunity to subsequent infection or disease
- Levels of antibody and neutralizing antitoxins decline considerably during the first year after completion of a primary series & serological studies provide strong evidence for the booster effect of the fourth dose of vaccine administered at the end of the second year of life

Key vaccine benefits

Investment framework element	Key benefits	Comments
Strategic fit	**Extends protection from primary series already offered**	• Represents expanded investment to Gavi's existing support for the pentavalent vaccine • Leverages existing platforms at 12-23 months (MCV2) and 9-15 yrs. (HPV)
Outcome and impact	**Improves equity in immune protection and provides opportunity for platform establishment and strengthening**	• Addresses inequity in male tetanus vaccination and difference in immune protection between Gavi and non-Gavi-supported countries – most of the burden of tetanus and diphtheria is in Gavi-supported countries • Provides opportunity for catch-up vaccination of missed primary series doses • Strategy would address the problem of waning protection after primary series vaccination and aid in maintaining global goal of elimination of maternal and neonatal tetanus (MNTE)
Value for money	**High value for money compared to other VIS candidates given low cost of vaccines**	• Vaccination with boosters has the potential to avert ~106,000 deaths (~82% in U5s), at ~$2,074-$5,912 per death averted from 2021-2035 • Both Td & DTwP currently cost <$0.20 per dose, which drives high value for money
Cost		
Feasibility	**High country interest**	• Highest overall priority among VIS candidates based on country stakeholder consultations
Market implications		

Key vaccine challenges

Investment framework element	Key challenges	Comments
Strategic fit	**Atypical vaccine for Gavi support**	• Low cost vaccines have not historically been where Gavi invests
Outcome and impact		
Value for money		
Cost	**One time and recurrent operational costs to countries high compared with other VIS vaccines given 3 separate boosters**	• Compared to other VIS candidates, introduction costs and recurrent delivery costs to countries are high at ~$178M and ~$452M between 2021-2035, respectively, due to three vaccine timepoints and need for new platforms
Feasibility	**Requires countries to establish up to three new vaccination time points**	• May require the establishment of up to three new vaccination time-points, if vaccines in 2nd year of life and/or HPV are not currently delivered; however many countries deliver MCV2 or Meningitis A at the time point of 1st booster and some deliver HPV at the time point of the 3rd booster • Introduction would likely require specialised technical assistance to support sustainable development of new vaccination platforms and mitigate risk that insufficient upfront investment into systems results in poor coverage
Market implications		

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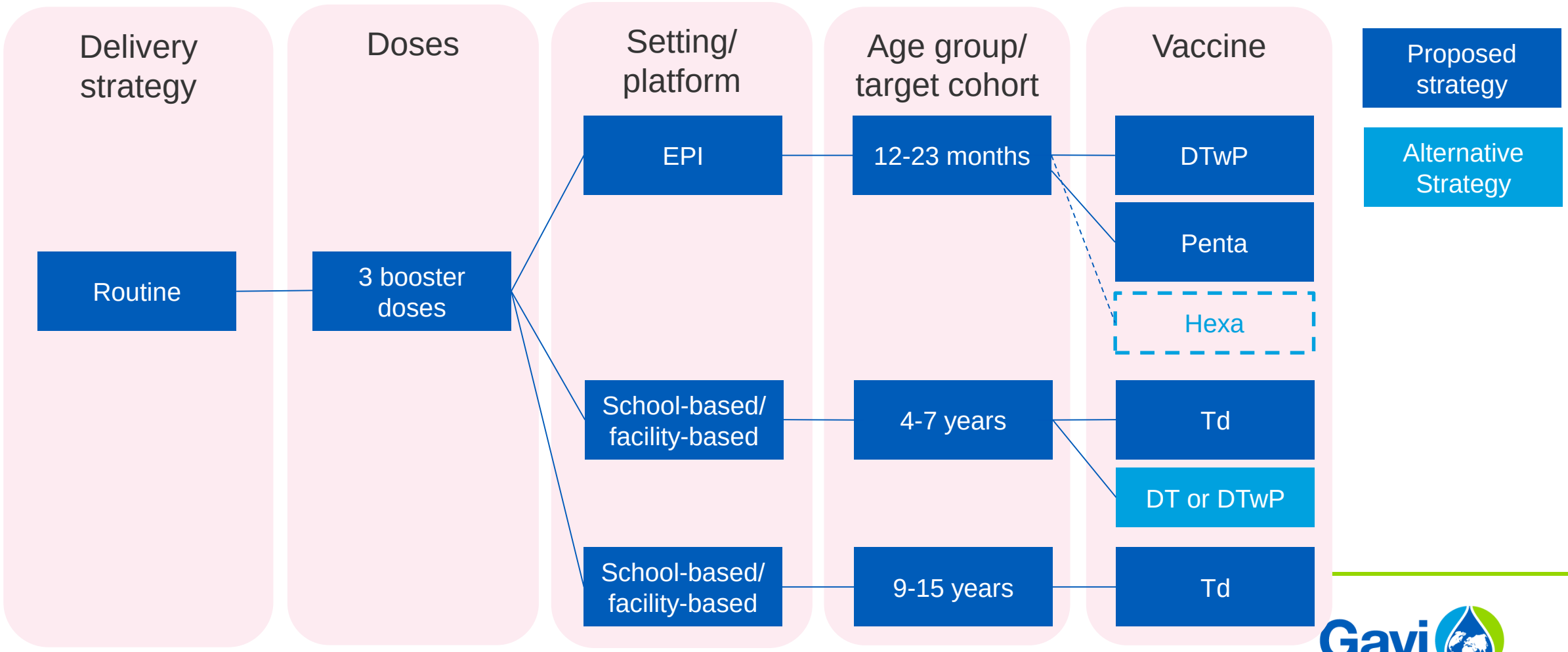
Policy approach

Proposed vaccination strategy



Proposed strategy is based on WHO recommendations
Hexa: evaluated as part of the IPV strategy

Recommendation to support country choice of either DTwP or pentavalent for the first booster

Options:

- Support DTwP only for 1st booster
- Support pentavalent only for 1st booster
- **Support country choice between DTwP & Pentavalent for 1st booster**

Benefits

- Allows countries to evaluate trade-offs between programmatic benefits of pentavalent – which is already used in-country – and the lower cost of DTwP, and make a choice based on local context
- Pentavalent offers the opportunity to provide catch-up on missed doses and provide Hib & Hepatitis B protection

Risks to be mitigated

- Slightly greater uncertainty in producing demand forecasts for manufacturers, which would be exacerbated if hexavalent was also offered
- Supporting a 4th dose of pentavalent would increase the cost to Gavi and transitioning countries vs. country self-procurement of DTwP
- Countries would need to consider financial sustainability of 4th dose of pentavalent

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Gavi vaccine support for boosters based on co-financing policy

Gavi support based on current co-financing policy

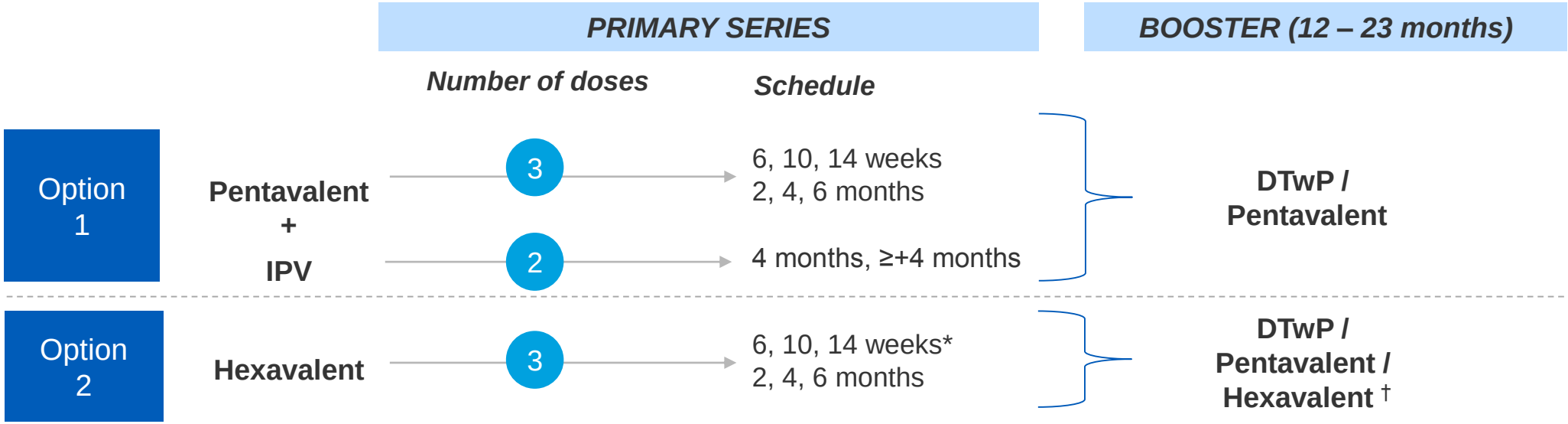
- **No Gavi support for DTwP or Td given the price is below the minimum country co-financing level for low income countries ($0.20)**
- **Gavi would provide support for pentavalent vaccine if chosen as 1st booster**

Considerations

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

Whole-cell hexavalent vaccine is under consideration as part of Gavi support for IPV post-2020

Future Gavi support for hexavalent vaccine would need to be under certain market considerations to minimise risks to IPV and pentavalent supply. The use of hexavalent as an immunisation option for a D,T & P-containing booster during the second year of life will be considered once there is more information regarding the immunogenicity of the vaccine and sufficient supply to initiate introduction in Gavi-supported countries, by ~2022.



* Based on the latest WHO recommendations, if IPV is given at 6,10 and 14 weeks, a 4th dose is needed at ≥+6 months.

† Based on the polio seroconversion rate and the need for a booster of IPV following a primary series of Hexavalent at 6, 10, 14 weeks to be confirmed by clinical trials.

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Platform strengthening support is required for introducing D, T & P-containing boosters

Approach for platform establishment and strengthening support

- Lack of strong/established immunisation timepoints poses a **barrier to introduction of D,T&P-containing boosters**
- To enable high coverage of these vaccines, **supplementary Gavi support** provided to countries would aim to strengthen or establish the necessary immunisation **timepoints** within the broader, **integrated service delivery platforms**
- This supplementary funding would **complement a country's broader package of health systems strengthening support** and aim to improve delivery of all antigens
- The types of activities that could be executed with the platform strengthening support could include:
  - Identifying key issues driving low immunisation coverage in existing immunisation timepoints
  - Expansion of existing EPI data systems to new immunisation timepoints (e.g. targeting a wider age range) for data recording, reporting and analysis
  - Additional training to ensure effective task sharing among HCWs and across sectors (e.g. health & education)
  - Social mobilisation activities targeting new age groups
  - Identification of the appropriate setting for administering vaccine (e.g. outside health facilities) and establishing this delivery point
  - Effective integration between health care sectors
- This would be the **sole support Gavi offers to countries for boosters 2 & 3** due to low cost of vaccines

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

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Demand, health impact, cost and value for money

Key assumptions

xx: included in model uncertainty range
xx: not included

Models

IPM (direct impact only)

Vaccination strategies

EPI/1 yo (DTwP/penta)
School entry /5 yo (Td)
Adolescent /10 yo (Td)

Uncertainty analysis driving ranges

Primary series vaccination	FVPs as baseline (excl. PVPs)	FVPs as baseline (excl. PVPs)	FVPs and PVPs as baseline	FVPs and PVPs as baseline
Booster series vaccination	FVPs only (excl. PVPs)	Partial completion of boosters (PVPs) and FVPs	FVPs only (excl. PVPs)	Partial completion of booster (PVPs) and FVPs

Other key assumptions

Efficacy (1st/2nd/3rd booster):
Diph: 95.5%/95.5%/98.4%
Tet: 99%/99%/99%
Pert: 96%

Duration of protection (1st/2nd/3rd booster):
Diph: 10y/10y/29y
Tet: 3 to 5y/20y/20y
Pert: 10y

Coverage:
MCV2 analogue

Note: FVP – fully vaccinated persons; PVP – partially vaccinated persons
Assumptions regarding historical booster introductions which informed country scope in demand forecast were made based on data available in December 2017

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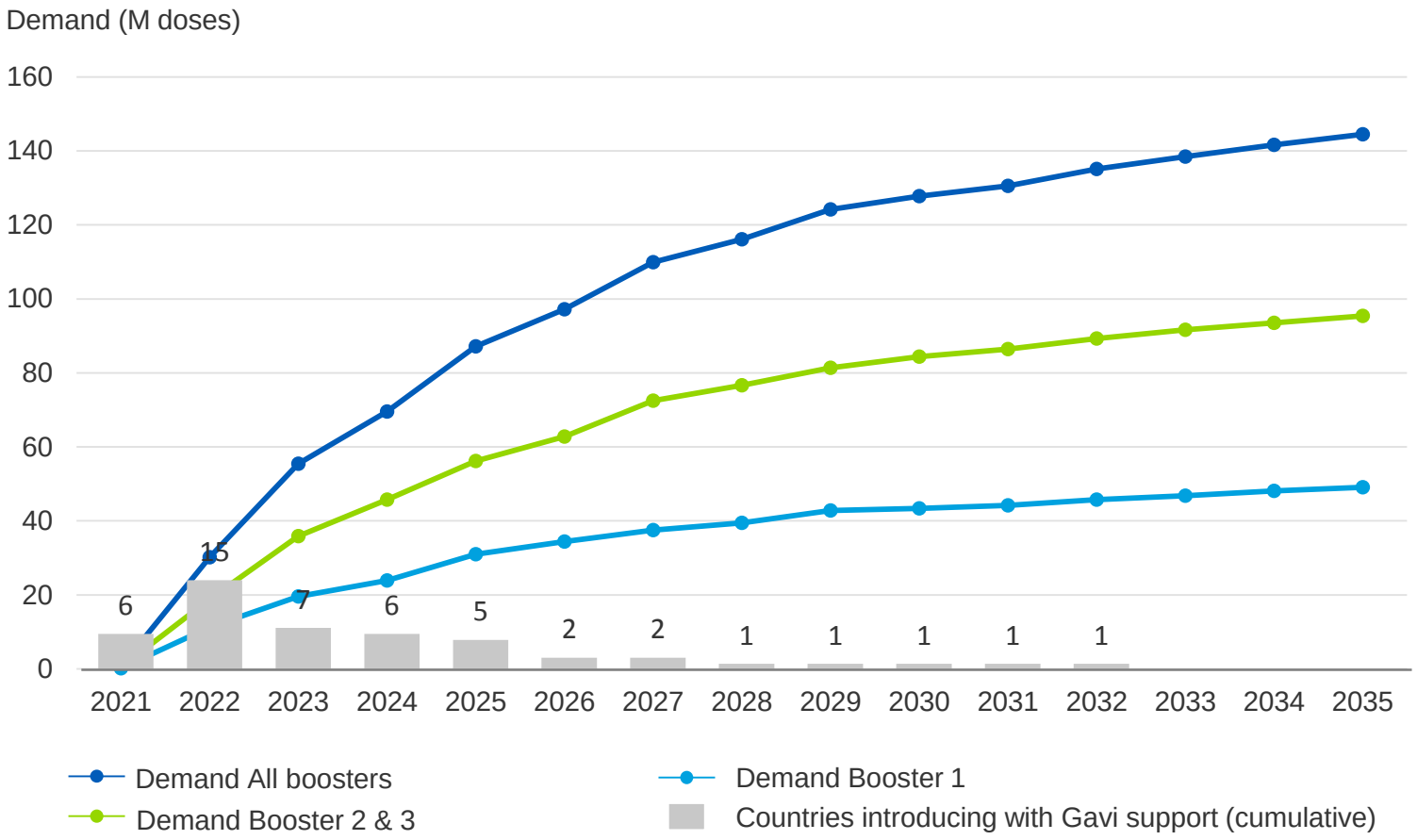
Expected cumulative demand 2021-2035 ~1.5B doses[1]



Nigeria excluded

Scenario: Full target population – partially and fully vaccinated with boosters[2]

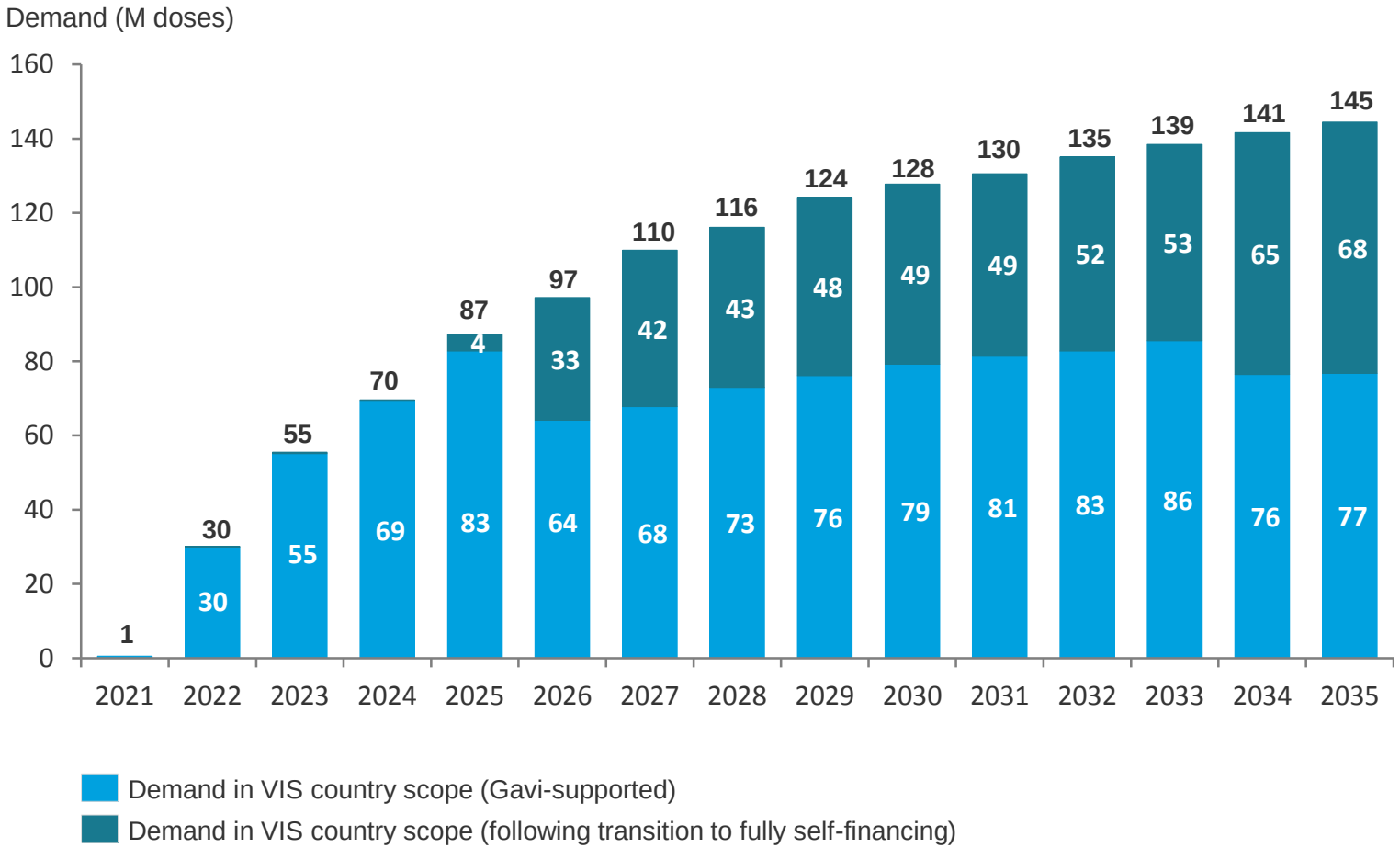
Total cumulative demand from countries that introduce with Gavi support (2021-2035)

Booster 1 demand	**~517M**
Booster 2 & 3 demand	**~991M**
Primary scenario (all boosters)	**~1.5B**

1. Based on Gavi's current eligibility and transition policy
2. Gavi VIS forecast; demand forecast includes full target population (partially & fully vaccinated with primary series and partial and full vaccination with booster series). Drop-off between MCV1-MCV2 used to determine coverage decrease

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 ~1.0B doses between 2021-2035[1]



Nigeria excluded

Countries supported by Gavi for introduction

Scenario: Full target population – partially and fully vaccinated with boosters[2]

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

Gavi-supported demand[2] **~1.0B**

Post-transition demand **~674M**

1. Based on Gavi's current eligibility and transition policy
2. Gavi VIS forecast; demand forecast includes full target population (partially & fully vaccinated with primary series and partial and full vaccination with booster series). Drop-off between MCV1-MCV2 used to determine coverage decrease
3. This demand is used to calculate 'procurement cost to Gavi and countries', which itself is used in the calculation of 'value for money'

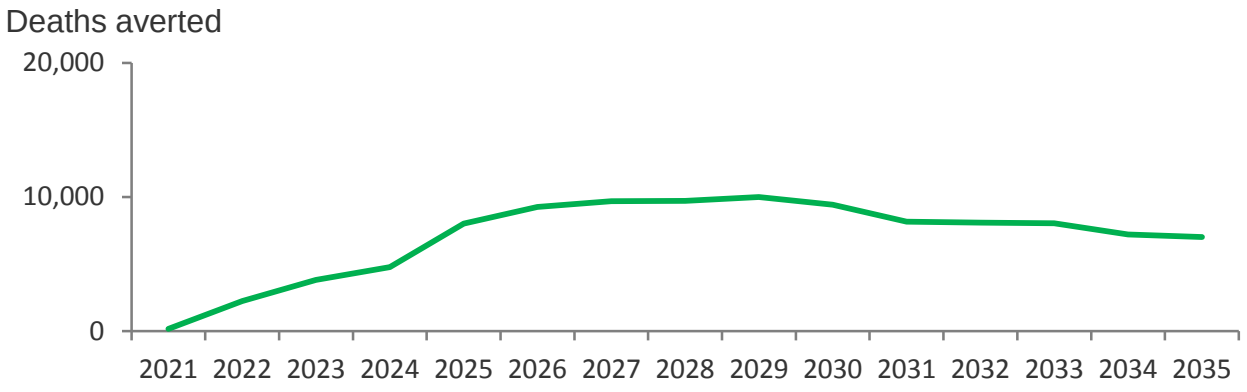
Consideration for Gavi support to Nigeria for VIS candidates would be considered separately through the Nigeria-specific strategy which was approved by the Gavi Board in June 2018

Vaccination could avert ~106K future deaths and ~8.3M future cases through 2035

Nigeria excluded

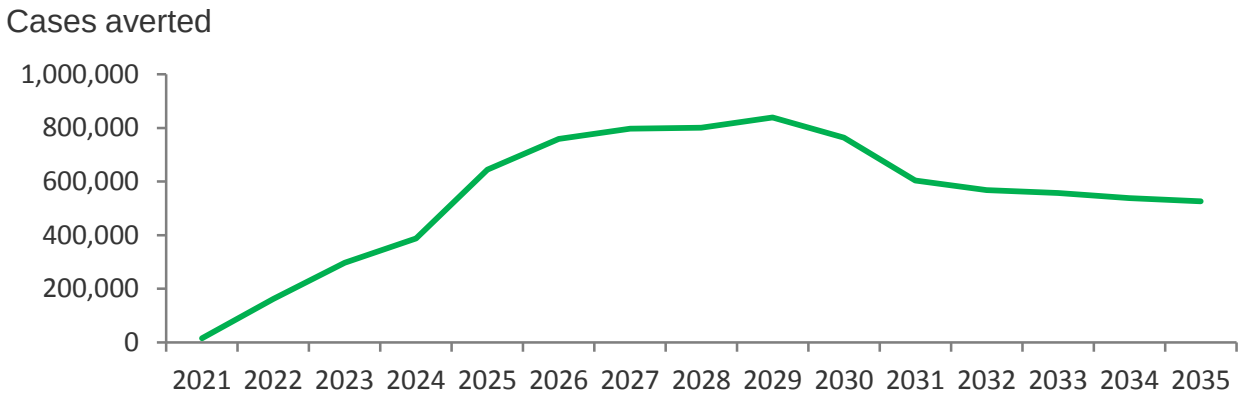
Scenario: Full target population – partially and fully vaccinated with boosters[1]

Deaths



	Total deaths averted (2021-2035)	Deaths averted per 100K vaccinated
Point estimate	~106K	~19

Cases



	Total cases averted (2021-2035)	Cases averted per 100K vaccinated
Point estimate	~8.3M	~1.5K

1. IPM (direct impact only) model; Gavi VIS forecast; demand forecast includes full target population (partially & fully vaccinated with primary series and partial and full vaccination with booster series). Drop-off between MCV1-MCV2 used to determine coverage decrease
Limited data on booster efficacy & likely underestimation in burden for all three diseases drives high uncertainty in impact outcomes and therefore only point estimate presented, as no sensitivity analysis was performed
Consideration for Gavi support to Nigeria for VIS candidates would be considered separately through the Nigeria-specific strategy which was approved by the Gavi Board in June 2018

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

Nigeria excluded

Cost projections are unconstrained. Values do not account for anticipated introduction of current portfolio and other VIS candidate vaccines that may reduce the number of planned D,T&P-containing booster introductions.

Scenario: Full target population – partially and fully vaccinated with boosters[1]

		Primary modelled scenario	
Impact	Fully vaccinated persons	~562M	
	Total future deaths averted	~106K	
		1st booster	*If penta*	*If DTwP*
Cost	Gavi procurement costs	$205M	$0
	Gavi operational costs	$82M	$82M
	Total Gavi cost	$287M	$82M
	Country procurement costs	$420M	$219M
	Country operational costs	$178M	$178M
	Country recurrent delivery costs	$452M	$452M
	Total Country cost	$1,050M	$849M
	Total cost	*$1,337M*	*$931M*
Value for money	Cost per death averted[2]	~$5,912	~$2,074

1. IPM (direct impact only) model; Gavi VIS forecast; demand forecast includes full target population (partially & fully vaccinated with primary series and partial and full vaccination with booster series). Drop-off between MCV1-MCV2 used to determine coverage decrease
2. Calculated using procurement cost only
Consideration for Gavi support to Nigeria for VIS candidates would be considered separately through the Nigeria-specific strategy which was approved by the Gavi Board in June 2018

Assessment of uncertainty in demand and impact analyses

	Comments
Demand	• Uncertainty regarding coverage (lack of good analogues for 4 yo age group; limited data on HPV coverage [10 yo]) • Baseline/existing introduction of boosters difficult to discern precisely (boosters introduced in varying degrees across countries)
Price	• Based on trend-based forecasting of pricing already offered to lower income countries and market intelligence • Pricing based on DTwP or Penta: Hexa would increase the total cost
Health impact	• Uncertainty around efficacy of vaccines in individuals who receive partial vaccination of primary and/or booster series • Effectiveness of booster assumed to be the same regardless of whether the individual is fully or partially vaccinated • Bias in model estimates because waning immunity is not considered, which lowers potential impact estimates • Not every permutation of vaccine combinations is considered, leading to potential underestimate of impact • MCV2 coverage is used as an analogue, which may underestimate school-entry booster-time point and result in lower impact estimates • Uncertainties around burden data (based on expert opinion), and latest data from diphtheria outbreaks not included, leading to underestimation across all three diseases • Models do not include indirect impact, potentially leading to an underestimate in impact estimates

High uncertainty | Medium uncertainty | Low uncertainty

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Implications for demand, health impact and cost when including Nigeria

	% increase if Nigeria included
Demand	~14%
Deaths averted	~15%
Cases averted	~30%
Cost	~14%

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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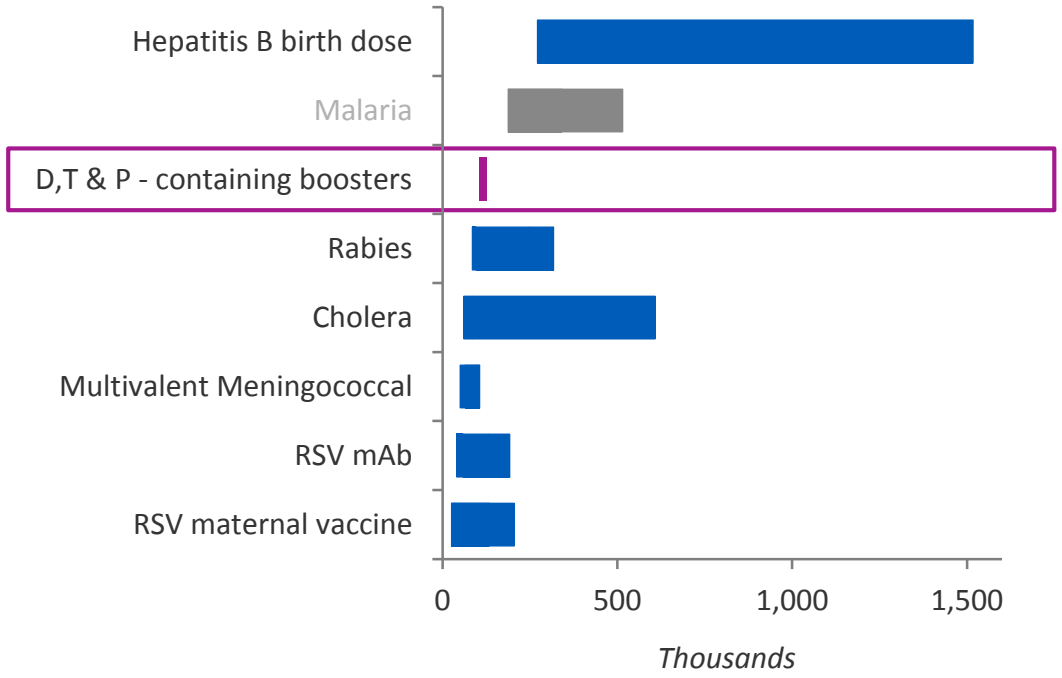
Impact and value for money compared to VIS candidates

Health impact compared to VIS candidates

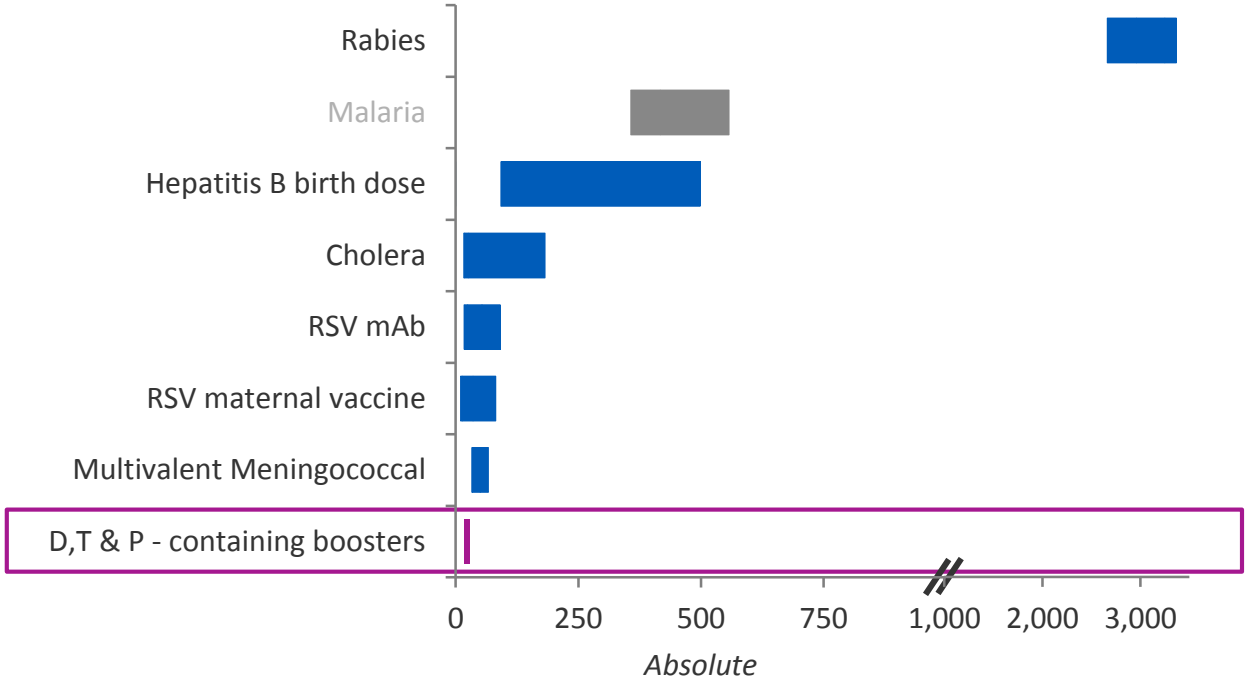
Scenario: Full target population – partially and fully vaccinated with boosters[1]; no range due to single impact model and scenario

Nigeria excluded

Total future deaths averted (K), 2021-2035



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



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Limited data on booster efficacy & likely underestimation in burden for all three diseases drives high uncertainty in impact outcomes

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

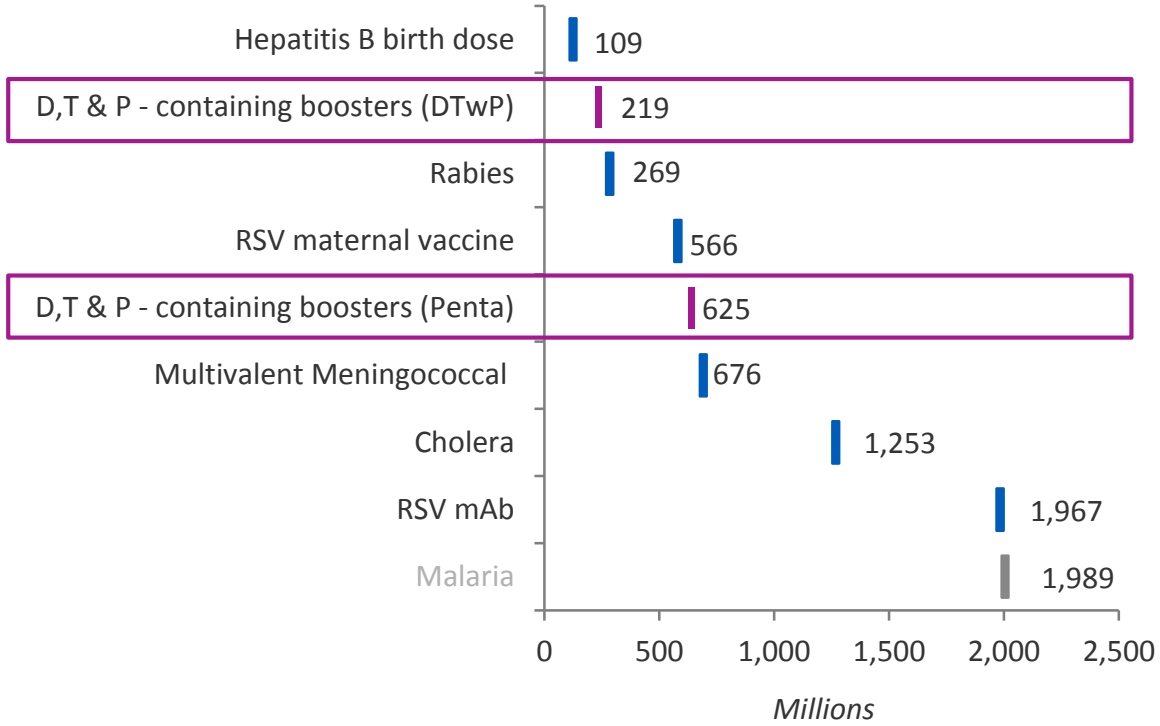
Range of projected impact

Procurement cost and cost per death averted compared across VIS candidates

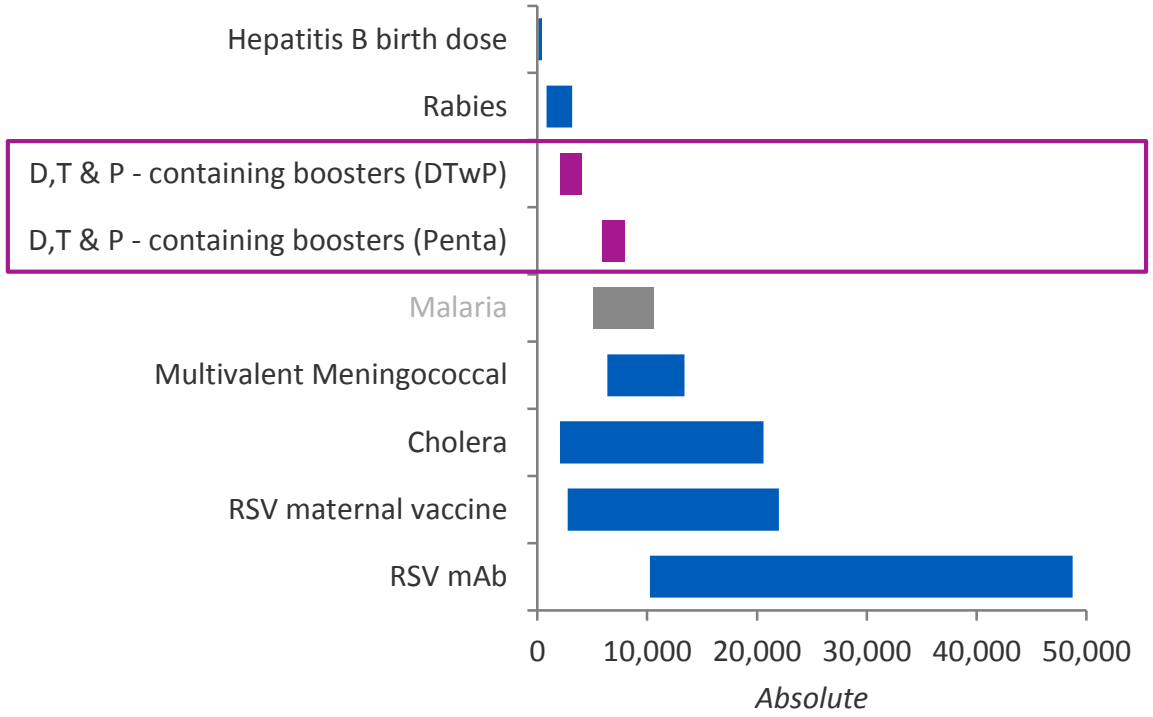
Scenario: Full target population – partially and fully vaccinated with boosters[1] ;no range due to single impact model and scenario

Nigeria excluded

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



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



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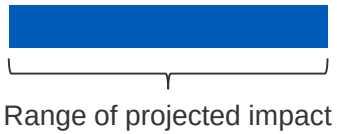

1: IPM (direct impact only) model; Gavi VIS forecast; demand forecast includes full target population (partially & fully vaccinated with primary series and partial and full vaccination with booster series). Drop-off between MCV1-MCV2 used to determine coverage decrease
Limited data on booster efficacy & likely underestimation in burden for all three diseases drives high uncertainty in impact outcomes
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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Country perspective

Interviews with country stakeholders revealed that ease of implementation depends on existing systems

Priorities and approach

- Of mixed priority; in some countries, not yet introduced due to low due to lack of awareness and political will in some countries (and some boosters viewed as more important than others); in other countries, rising priority due to high burden of tetanus and diphtheria outbreaks
- Some countries already include one or more boosters
- WHO recommendations not disseminated clearly: some countries still boosting ever 10 years, some countries not clear on value of 2nd booster

Coordination and expanding to new platforms

- One respondent expressed difficulty in introducing any new vaccines after 12 months of age (including 2nd year of life; others noted that the 1st and 3rd boosters would be easier as those time points exist (measles 2nd dose and HPV)
- In some countries, 2nd and 3rd boosters are given in schools, while in other countries, vaccination is more feasible at the health care facility
- Some respondents noted that bringing vaccines to schools from health care facilities could carry additional operational costs and require additional training

Challenges

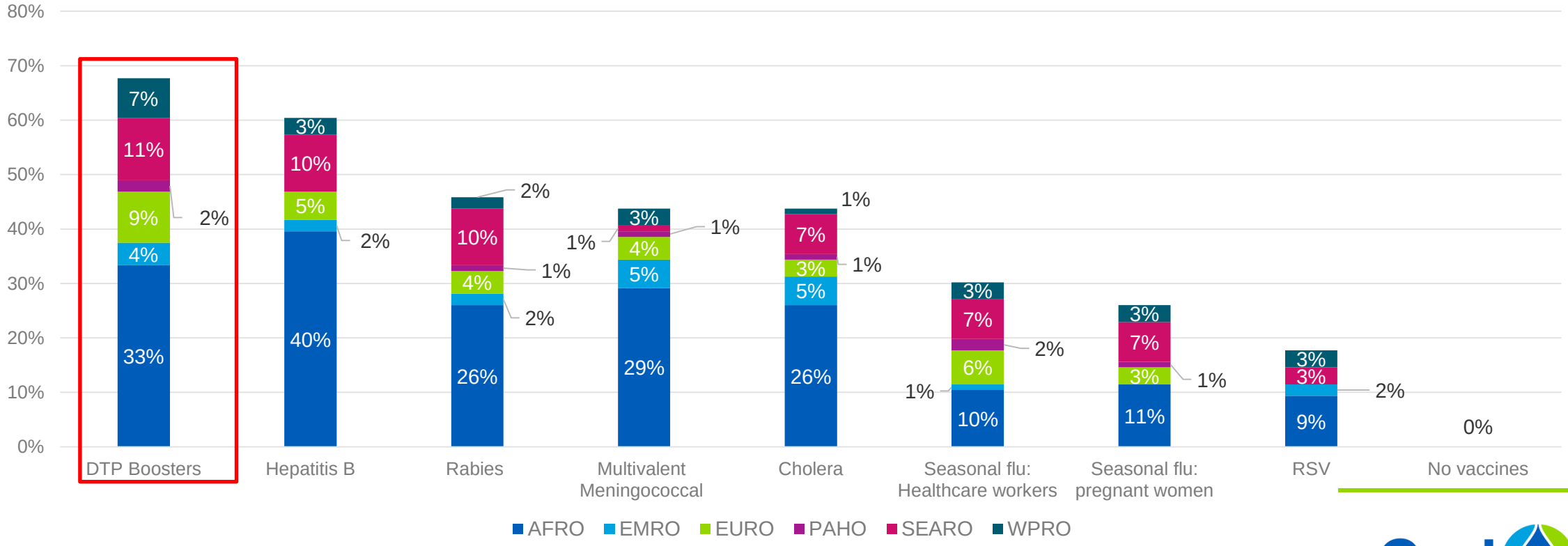
- Determining the optimal location and timing of vaccination of 2nd and 3rd boosters seen as a challenge (eg, health care facility vs schools)
  - One respondent said parents don't often bring children to health facilities over 1 year old except for illness
  - Unclear how to reach children who do not attend school, which in some countries can be significant number
- Lack of communication with communities to build awareness
- Mixed responses on whether the boosters would require additional costs: some respondents cited behaviour change, logistics and demand creation as costing more
- Some interest in using pentavalent for the 1st booster, but will need WHO guidance on what is preferred
  - One respondent said it might be confusing and seen as 'going backward' to use DPT, and there could be mix-ups in administration
- Some concern about cost – individually vaccine price less concern, but country costs are increasingly going up as more vaccines added and countries progress along transition and take up more co-financing

Source: VIS Phase III in-depth country interviews

Boosters were prioritised for introduction by the majority (68%) of respondents

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

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



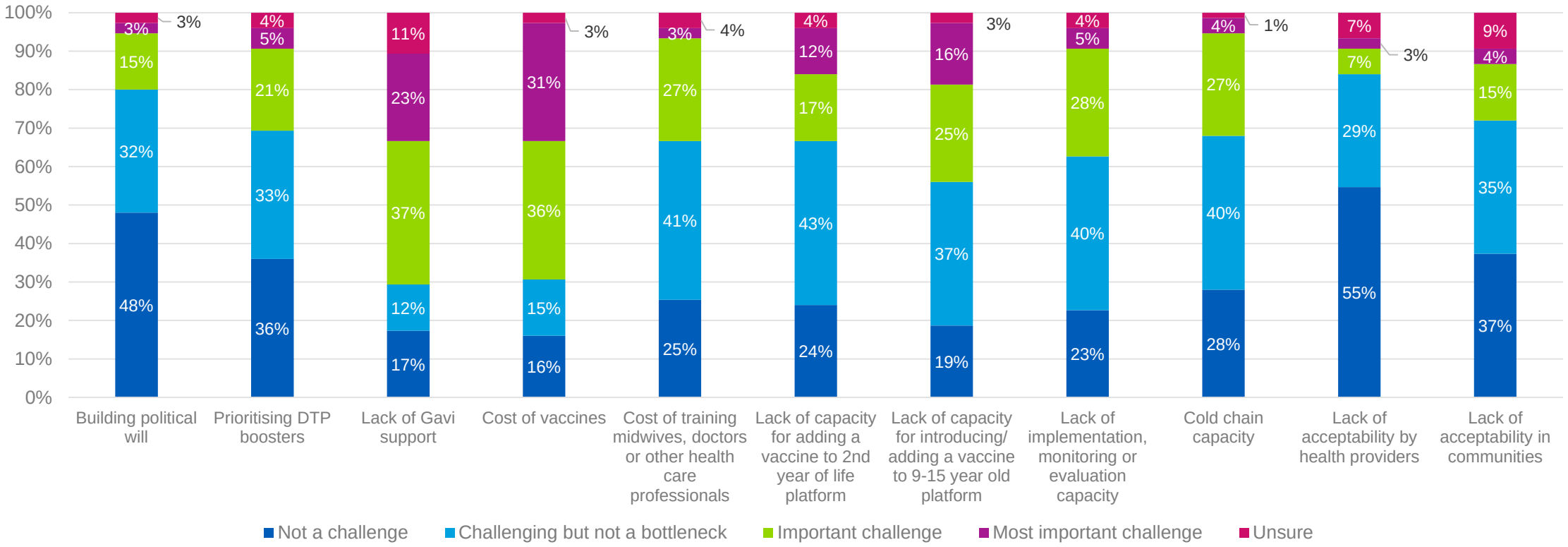
Given limited or regional disease burden, not all vaccines are of relevance for all Gavi-supported countries

Source: VIS Phase III country survey

Cost of vaccines and lack of capacity for adding 9-15yo platform amongst challenges for introduction

WHO recommends three DTP-containing boosters at 12-23 months (DTP or pentavalent), 4-7 years old (Td) and 9-15 years old (Td). What are the main challenges faced in introducing and successfully scaling-up coverage of these vaccines?

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

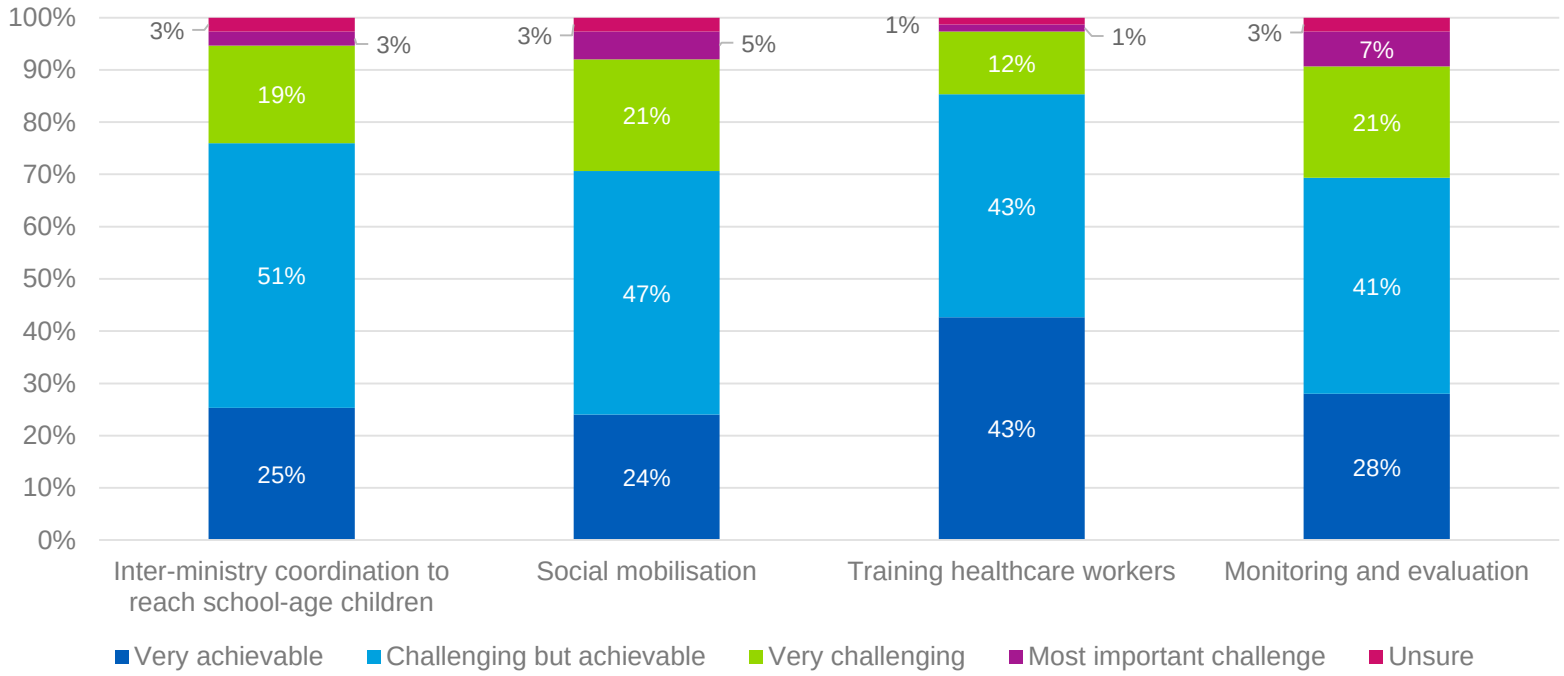


Source: VIS Phase III country survey

Most activities related to establishing 4-7yo platform generally viewed as achievable

How challenging are the following activities that have been/ could be required to establish a successful new vaccination time point at 4-7 years of age?

% respondents indicating level of challenge for each activity



Source: VIS Phase III country survey

7

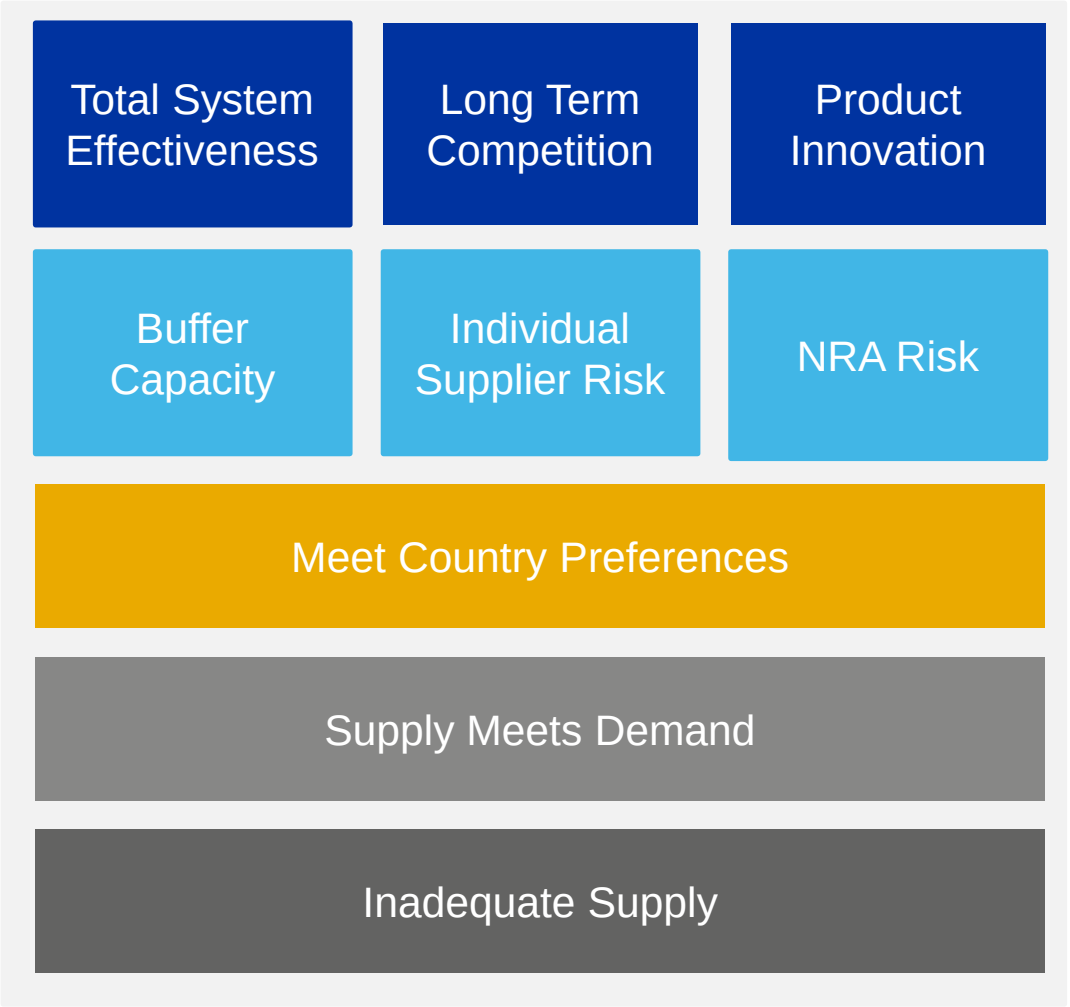
Implementation requirements

Summary of unique implementation requirements

	Area of focus	Unique implementation requirements	Associated costs
Global level	Policies and processes	• Re-labelling Td for use in >4 yo. rather than >7yo. (already underway)	
	Supply	• No supply concerns; pentavalent and Td already procured by most countries • Engagement with countries to understand preference of DTwP vs. pentavalent for 1st booster to ensure these are included in demand forecasting shared with manufacturers	
Country level	Planning, coordination, integration	• Collaboration with the Ministry of Education to coordinate school-based programmes • Microplanning would be required for the boosters, especially if delivered outside of facilities and co-administered with other interventions • Integration into MNTE, ensure switch from tetanus-toxoid (TT) to Td and coordinate vaccine procurement across programmes	• Meetings between ministries and technical assistance for microplanning
	Supply chain infrastructure and logistics	• If DTwP chosen for 1st booster, would represent a new vaccine in most countries, as well as Td if not already used in ante-natal care (ANC) • Updates to data systems to capture and report data at new time-points • Penta as 1st booster requires less updates as already part of the system	• Updates to data systems and expansion of cold chain for increased volumes
	Health workforce	• If school-based vaccination implemented, requires awareness building of teachers and ensuring sufficient health workforce to service schools and facilities	• Awareness building in schools & training of healthcare workers in new schedule
	Social mobilization, education, communication	• Shift towards life-course approach requires strong messaging to policy-makers, healthcare workers and parents to ensure awareness of need for vaccination beyond EPI	• Social mobilisation costs to ensure strong introduction and continued parental support
	Surveillance	• All three antigens currently part of primary series, thus systems could be extended to older age groups	• Training component to track older children from disease and adverse events following immunisation (AEFIs)

Most challenging Unique but manageable Few unique implementation requirements

Healthy market framework analysis implies few market risks



Td used for maternal immunisation, and Penta for primary series thus **procurement and distribution mechanisms are in place in countries**

Td is currently licensed and PQ'd for children >7 years, whereas its intended use in the proposed strategy includes children 4-7 years old. WHO is currently looking to change this, with the expectation it will be solved by 2021

Choice between pentavalent and DTwP vaccines as the 1st booster can be **accommodated** with existing supply; need to signal to manufacturers the expected split between the two

Sufficient supply to absorb additional Penta, DTwP & Td demand generated by Gavi support

Note: Analysis does not take into consideration hexavalent vaccine, please see separate analysis on IPV support post-2020, which considers potential support for hexavalent

Countries have faced barriers introducing booster doses

Planning coordination and integration

44 Gavi-eligible countries have not introduced any diphtheria, tetanus and pertussis-containing boosters despite low cost of vaccine (~$0.20) and clear WHO recommendation

- Where DTP4 is introduced, coverage has been variable, with good levels generally reached in EURO but not in other regions, a trend also seen in the difference between MCV1 and MCV2 coverage levels
- Barriers to introduction have included:
  - **New platforms for vaccination required**: 2YL, school-entry and adolescent, many of which are not already set-up
  - Despite low cost of DTwP and Td vaccine, cost of procurement is still a barrier to use, considering the **increased cost of the full portfolio** and difficulty in securing budget
  - Logistical challenges of **vaccinating children outside of facilities** e.g. at schools
    - 31 of Gavi73 countries have offered school-based immunisation in the last 5 years, usually in primary school and most commonly TTCV or HPV
    - 40 of Gavi73 countries have, or are planning to introduce HPV for girls between 9-18 yo. which provides a platform for the 2nd and 3rd booster provision if integrated

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Additional vaccines and interventions offered at each booster timepoint

	1st booster 12-23 months	2nd booster 4-7 years	3rd booster 9-15 years
Potential platform	• Routine EPI (facility or outreach)	• Routine EPI (facility or outreach) - school-entry screening • School-based	• Routine EPI (facility or outreach) • School-based
Potential vaccines at time-point	• MCV2 *(15-18 mo.)* • MenA conjugate *(9-18 mo.)* • MenC conjugate *(booster in 2YL)* • Meningococcal Quadrivalent *(2 doses at 9-23 mo.)* • PCV *(if using a 2+1 alternative schedule with booster at 9-15 mo.)* • TCV *(2YL)* • JE *(vaccine-dependent)* • Seasonal flu • *Future: malaria 4th dose if required*	• n/a	• HPV – two visits
Illustrative examples of other interventions at time-point	• Vitamin A supplementation • Deworming • Growth monitoring • Insecticide-treated bednet	• Could be linked to school entry screening for vaccination and provision of missed doses • Deworming	• Health education (e.g. menstrual hygiene or physical health promotion) • Insecticide-treated bednet • Deworming

8

Risks and mitigation

Risks of inaction (Gavi investment not approved)

Strategic concern	Risk
Financial	• Countries do not introduce boosters despite relatively low cost of vaccine procurement
Programmatic	• Deprioritisation of boosters among Gavi-supported countries leaving populations unprotected in the longer term due to waning immunity • Continued inequity between Gavi and non-Gavi-supported countries
Reputational	• Gavi support seen as misaligned with WHO recommendations and global priorities

Risk and mitigation plan if Gavi investment approved

Strategic concern	Risk	Mitigation plan
Financial	• Financing of vaccines may not be sustainable in the long term	• Low risk as the vaccine cost is relatively low • Work with countries at time of decision on introduction to ensure planning for long term sustainability
Market	• Fragmented procurement of Td given countries are or will be separately procuring for maternal immunisation	• Package procurement for all Td doses through same UNICEF process
	• More uncertainty around DTwP and pentavalent demand forecasting may negatively impact supply availability	• Engage with countries to understand preference of DTwP vs. pentavalent for 1st booster as part of the planning process, to ensure these are included in demand forecasting shared with manufacturers
	• Inability of countries to use Td vaccine for 2nd booster as it is currently licensed with indication for >7 yrs	• WHO are working with manufacturers to update label and PQ in-line with the recommendation
Programmatic	• Support for platform establishment and strengthening is insufficient to cover all activities countries require to develop new immunisation timepoint, thereby discouraging countries from introducing	• Learning agenda proposed to analyse support structure to identify areas of improvement needed, e.g. bottom-up costing of first several introductions to understand the true cost of introduction to inform future policy reviews • Encourage countries to identify domestic resources for introduction activities not supported by Gavi

9

Investment recommendation

Recommended investment scenario

No Gavi support for D,T & P-containing boosters

Provide support to establish platforms as catalytic support for the introduction of each diphtheria, tetanus & pertussis-containing (D,T&P) booster dose, beginning in 2021[1]

Recommendation

1. In line with current co-financing policy, Gavi would not fund procurement of diphtheria, tetanus and pertussis (DTP) vaccine or tetanus-diphtheria (Td) vaccine as the price is below the minimum country co-financing level within the current co-financing policy, but would provide support for pentavalent vaccines for those countries who choose it as the first booster. Potential Gavi support for use of whole-cell pertussis-containing hexavalent vaccine is being considered within the paper on IPV support post-2020 (Doc 6b)

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Illustrative D, T & P - containing boosters component of a VIS learning agenda

Objective	Key illustrative questions	Indicative cost
Lessons learned around introduction of 2nd and 3rd boosters	• Feasibility of establishing new timepoints and achieving high coverage • School vs. health facility based administration of 2nd and 3rd boosters • Vaccinating boys with 3rd booster using the HPV platform	$1 million/year for 3-4 early introducing countries for ongoing assessment and outcomes monitoring ($3 million)

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

Key experts

Experts consulted

- Peter Strebel (Gavi)
- Azhar Abid Raza (UNICEF)
- Tracey Goodman (WHO)
- Emily Wooton (WHO)
- Ahmadu Yakubu (WHO)
- Heather Scobie (CDC)
- Rania Tohme (CDC)
- Kirstie Clarke (CDC)
- Laura Conklin (CDC)
- Robert Steinglass (JSI)
- Lora Shimp (JSI)
- Rebecca Fields (JSI)
- Liz Miller (Public Health England)

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

Sources

Sources

- WHO Diphtheria Position Paper, 2017
- WHO Pertussis Position Paper, 2015
- WHO Tetanus Position Paper, 2017
- Global Burden of Disease, Institute for Health Metrics and Evaluation (IHME), 2016
- Immunological basis of vaccination: Diphtheria 2009
- Immunological basis of vaccination: Pertussis 2017
- Immunological basis of vaccination: Tetanus draft update 2017
- Brennan et al. 2000. How Many Doses of Diphtheria Toxoid Are Required for Protection in Adults? Results of a Case-Control Study among 40- to 49-Year-Old Adults in the Russian Federation. The Journal of Infectious Diseases 181(Suppl 1):S193–6
- Whole Cell Pertussis Vaccines: Summary of evidence relevant to schedules
- Report of the SAGE Working Group on Maternal and Neonatal Tetanus Elimination and Broader Tetanus Prevention
- Diphtheria Antitoxin: Market Update, UNICEF 2017
- An update of the global burden of pertussis in children younger than 5 years: a modelling study Lancet Infectious Diseases; 2017 Sep;17(9):974-980
- Report from the SAGE Working Group on Pertussis vaccines, 26–27 August 2014 meeting, Geneva, Switzerland

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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: D,T & P-containing boosters *(June 2018)*

Modelled strategy: Three-time booster at 1 yo, 5 yo and 10 yo

VIS criteria	Indicator	Results	Evaluation[1]
Health impact	Total impact averted	~122K-124K future deaths, ~10 million future cases averted, 2020 – 2035	
	Impact averted per 100K	~19 deaths, ~1,500 cases averted, 2020 – 2035, per 100K vaccinated population	
Value for money	Procurement cost	~$ 2,300-2,350 procurement cost per death, ~$30 procurement cost per case averted	
Equity & social protection impact	Impact on vulnerable groups	Relatively even distribution of disease burden across groups[2]	
	Benefits for women and girls	No special benefits of vaccination for women and girls	
Economic impact	Direct medical cost averted	~2.3% of average consumption per capita averted in out-of-pocket medical costs	
	Indirect cost averted	~$ 8 productivity loss averted, 2020 – 2035, per vaccinated person	
Global health security impact	Epidemic potential	Not IHR notifiable; high risk of outbreaks in fragile situations (war, displaced population)	
	Impact on AMR	Not IHR notifiable: Medium impact of vaccination on AMR (2.9/10 points in expert consultation)	
Vaccine cost	Total procurement cost	~$ 285 million total procurement cost to Gavi and countries, 2020 – 2035	
Relevant second. criteria	Vaccine market challenges / Implementation feasibility / Broader health system impact	Low price and multiple suppliers, but also high implementation feasibility and broad health system impact due to multiple access points and paradigm shift to life-course approach	

Additional considerations

- Booster strategy would be a continuation of Gavi's existing work on diphthertia, tetanus and pertussis through pentavalent vaccine
- Three time points (12-23 months, 4-7 years, 9-15 years) open up the possibility to establish new vaccination time points at existing access points
- High interest amongst Gavi supported countries (ranked 2 of 10 in country stakeholder survey)
- Very little data available on addressable burden but experts believe it is underestimated in Gavi countries

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. Maternal and neonatal tetanus important indicator of health inequality, but burden likely due to insufficient coverage

Phase II secondary criteria and financial implications: D,T & P-containing boosters *(June 2018)*

Modelled strategy: Three-time booster at 1 yo, 5 yo and 10 yo

VIS criteria	Indicator	Results	Evaluation[1]
Other impact	U5 deaths averted, total	~101K-104K U5 deaths averted, 2020 – 2035	
	U5 deaths averted, per 100K	~16 U5 deaths averted, 2020 – 2035, per 100K vaccinated population	
	DALYs averted (cost per DALY)	~6.5-6.6 million DALYs averted, 2020 – 2035, ~$ 43-44 procurement cost per DALY	
	DALYs averted, per 100K	~1,010 DALYs averted, 2020 – 2035, per 100K vaccinated population	
Gavi comp. advantage	Vaccine market challenges	Low potential to influence the market (e.g., Gavi experienced suppliers, predictable demand)[2]	
	Catalytic investment	Moderate potential to catalyse additional investments (e.g., strengthen 2nd year, HPV)	
Implementation feasibility	Ease of supply chain integration	Packed volume of 3-15cc; 24-36 months shelf life at 2-8°C; VVM = 14	
	Need for HCW behaviour change	No significant HCW behavior change required: Known vaccine	
	Feasibility of vaccination time point	Existing access points, but new vaccination time-point (4-7 years)	
	Acceptability in target population	Ranked 2/9 in country stakeholder survey, but likely need education among target pop.	
	Long-term financial implications	Falls within the category of price per course <$ 2	
Alt. interventions	Alternative interventions	No alternative interventions for effective disease control	
Broader health system impact[3]	Broader health system impact	Opportunity to improve PNC, child health (nutrition interventions, deworming, treat diarrheal disease, HPV vaccine and reproductive health for older children); new time-point for vaccination increases interaction with HCWs	
Operational cost[4]	Incremental costs per vac. person	Medium incremental cost of ~$ 0.70 per vaccinated person	
Implementation costs	Additional costs for introduction	Medium: Tech. assistance; some demand generation, waste mgmt., and data-related costs	

1. Evaluation based on comparison with other VIS 2018 candidates 2. Possible larger role if considering penta due to possible market shaping role to maintain supply. 3. Contextual information, not evaluated 4. Generic methodology based on routine campaigns. Details on evaluation methodology can be found in Methodology appendix

Rationale for vaccination strategy

Element	Modelled strategy	Rationale / Source
Vaccination schedule	• DTwP/Penta: 1 year olds • Td: 5 and 10 year olds	• WHO recommendation of (1) second year of life, (2) 4-7 years, and (3) 9-15 years • Diphtheria, Tetanus and Pertussis burden is global and vaccination is recommended for everyone
Age group/Target population	• 1 yo., 5yo. and 10yo. • All	

Demand forecasting assumptions

Element	Assumptions	Rationale / Source
Country scope	Countries missing 1-3 booster doses (Gavi-supported in year of introduction based on current policy)	D, T & P burden is global, no specific geographic distribution
Target population	DTwP/Penta: 1 year olds Td: 5 and 10 year olds	WHO recommendation of (1) second year of life, (2) 4-7 years, and (3) 9-15 years
Delivery Strategy	Routine	WHO Position Paper
Introduction dates	First introduction: 2021 Country Introductions to be determined/phased by: • Other new vaccine introductions (e.g., not before PCV, Rota, HPV) • Country governance • GNI • MCV2 and HPV introduction dates (D&T boosters not introduced before MCV2 or HPV)	Vaccines already licensed and PQ, ready for immediate introduction
Vaccine uptake	Standard Gavi assumption of 2-4 years to max uptake, depending on country size	Standard assumption applied to Gavi forecasts of current portfolio
Coverage	MCV2 (or estimated decline from MCV1 based on DTP1 to 3 drop-off) 5% increase/year up to 80%, 1% annual increase up to 95%	Nearest analogue (2017 WUENIC)
Products	PQ Date: DTwP, Penta and Td all currently PQ'd Schedule: 1 dose DTwP/Penta, 2 doses Td (15/56 countries already with 1 or 2 doses in EPI) Presentation: 10-dose vial (DTwP, Penta, Td) and 1-dose vial (Penta – considered for countries currently using 1-dose vial for infant primary schedule)	
Logistics	Wastage factor: 10 dose - 1.2; 1 dose – 1.05 Buffer: 25%	WHO assumption for 1 & 10 dose vials

Impact modelling assumptions

Element	Assumptions	Rationale / Source
Efficacy	We take into consideration the effectiveness and duration of protection if you are fully immunised with the primary series (FVP) and use average values to represent those that have been partially vaccinated with the primary series (PVP) which is represented by 2-doses for diphtheria and tetanus and an average of 1 or 2 doses for pertussis **See following slides for antigen-specific detail**	Effectiveness & duration of protection values were found from publically available documents, and expert opinion Sources are documented in the notes of the following slides
Duration of protection		
Burden of disease	IHME	Only data source available

Only 15 Gavi 73 countries have introduced all boosters

Planning coordination and integration

No Boosters

44 countries

- Afghanistan
- Angola
- Benin
- Burkina Faso
- Bangladesh
- CAR
- Cote d'Ivoire
- Cameroon
- DRC
- Congo
- Comoros
- Eritrea
- Ethiopia
- Ghana
- Guinea
- Guinea-Bissau
- Kenya
- Cambodia
- Liberia
- Madagascar
- Mali
- Myanmar
- Mozambique
- Mauritania
- Malawi
- Niger
- Nigeria
- Nepal
- Pakistan
- North Korea
- Rwanda
- Sudan
- Senegal
- Solomon Islands
- Sierra Leone
- Somalia
- South Sudan
- Sao Tome
- Chad
- Togo
- Tanzania
- Uganda
- Yemen
- Zambia

All Boosters

15 countries

DTwP
- Bhutan
- Cuba
- Georgia
- Guyana
- Honduras
- India
- Kyrgyzstan
- Sri Lanka
- Moldova
- Nicaragua
- Ukraine
- Uzbekistan

Penta
- Armenia
- Indonesia

Partial Booster Introductions

B 1

7 countries

DTwP
- Burundi
- Djibouti
- Gambia
- Haiti
- Viet Nam
- Zimbabwe

DT*
- Lesotho

B 2

0 countries

B 3

1 country

- Laos PDR

B 1&2

4 countries

DTwP
- Azerbaijan
- Tajikistan[2]
- Timor-Leste

Penta
- Bolivia

B 2&3

3 countries

- Kiribati[1]
- Mongolia
- PNG

B 1&3

0 countries

Booster 1 Classification:
DTwP – 20 countries
Penta – 3 countries
DT – 1 countries

*Assumption that countries with DT at booster 1 will upgrade to DTwP before 2020

1. Kiribati provides coverage estimates for DTP4, but it is not listed in its schedule
2. Tajikistan indicates all boosters in schedule, but country consultations indicate 3rd booster is not provided

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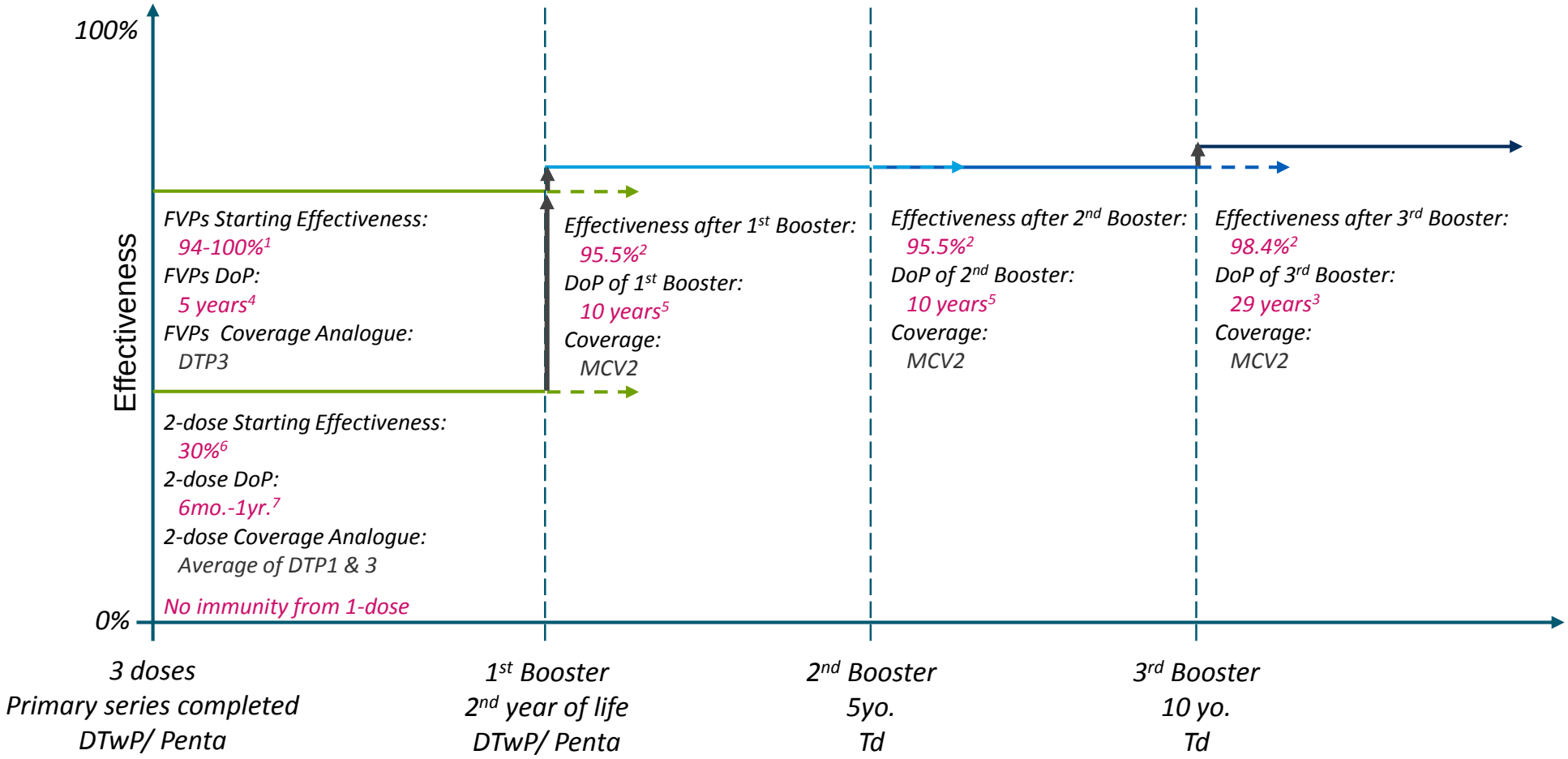
FVP: Fully Vaccinated Person
DoP: Duration of Protection

Diphtheria – Effectiveness & DoP assumptions

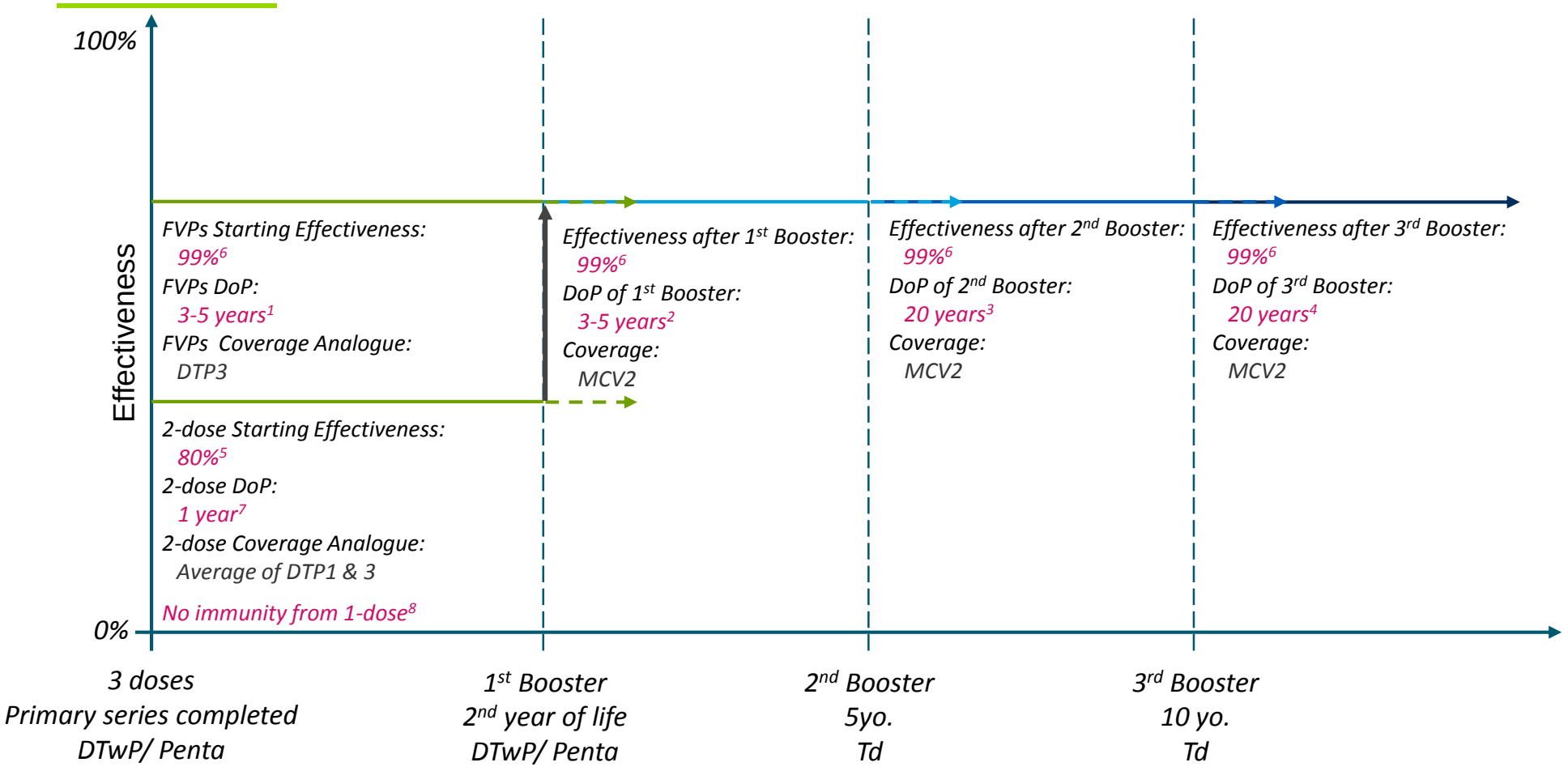


Confirmed by experts

1. Diphtheria Position Paper, page 425 – Immunological basis of vaccination series2. Diphtheria Position Paper, page 426 – case-controls of Soviet Union epidemic in 1990. 3. Diphtheria Position Paper, page 427 – case-controls of Soviet Union epidemic in 1990. 4. Expert Input – Liz Miller. 5. Immunological basis of vaccination, page 14 – inference, some expert doubt that not long enough, but no data source. 6. Brennan et al., 2000. 7. Golaz et al. 2000

FVP: Fully Vaccinated Person
DoP: Duration of Protection

Tetanus – Effectiveness & DoP Assumptions



Confirmed by experts

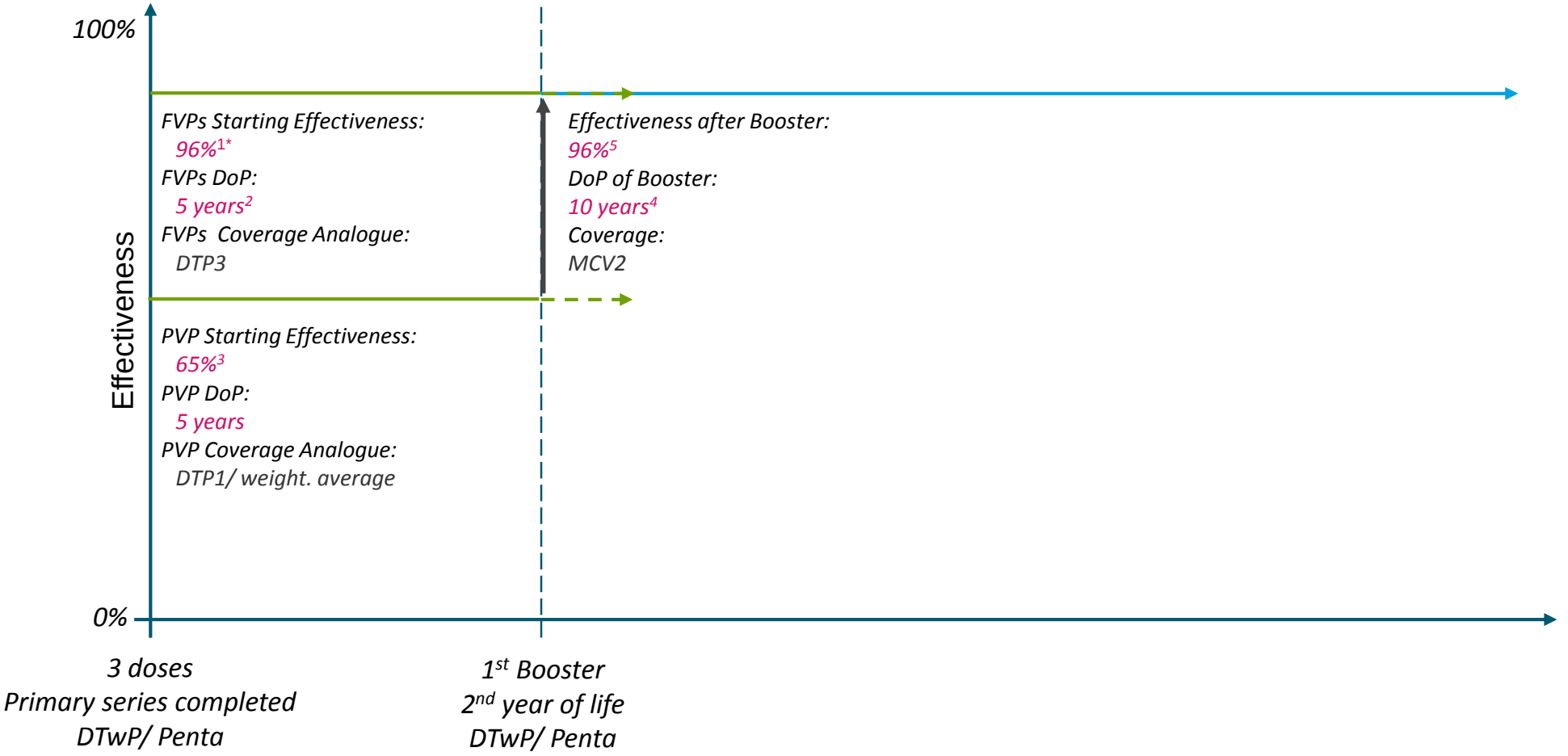
Assumption:

- Not considering the protection derived from TTCVs, e.g., MenAfriVac

1. Immunological basis of vaccination 2017 page 16. 2. Tetanus Position Paper, page 64. 2. Tetanus Position Paper, page 64 3. Tetanus Position Paper, page 65 & Immunological basis of vaccination, page 11. 4. Report of the SAGE Working Group on Maternal and Neonatal Tetanus Elimination and Broader Tetanus Prevention, 2016 page 12 & Expert Opinion to limit range to 20 years. 5. Expert Input. 6. Tetanus Position Paper, page 62, "protective immunity in almost 100% of those vaccinated". 7. Immunological basis of vaccination 2017, page 12, 8. Tetanus Position Paper

PVP: Partially Vaccinated Person (average effectiveness and duration of protection weighted by how many doses of primary series actually received)
FVP: Fully Vaccinated Person
DoP: Duration of Protection

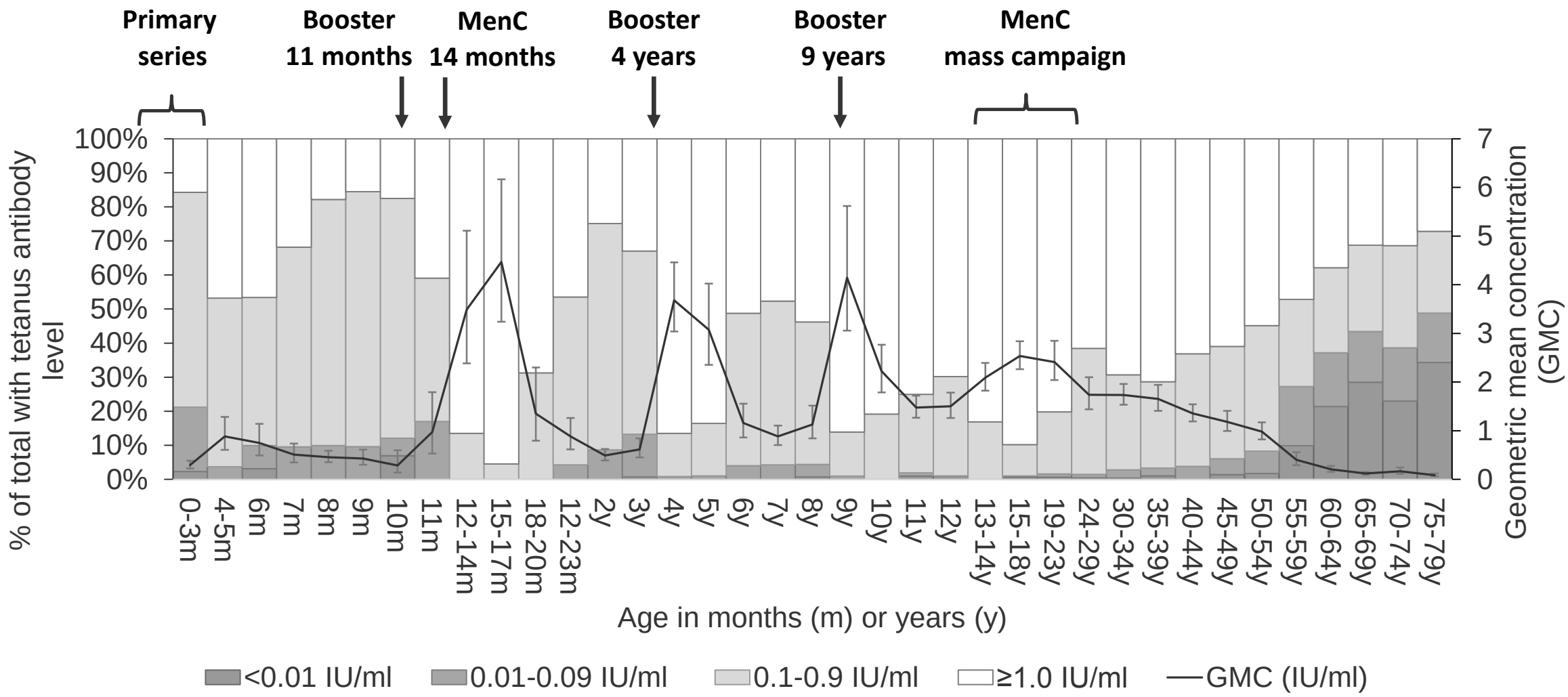
Pertussis – Effectiveness & DoP Assumptions



Confirmed by experts

1. Pertussis Position Paper, page 441. 2. Pertussis Position Paper, page 442 – Sys Review 3. Pertussis Position Paper, page 445. 4. Whole Cell Pertussis Vaccines: Summary of evidence relevant to schedules, p.13. 5. Assumption based on continued effectiveness level as from primary series

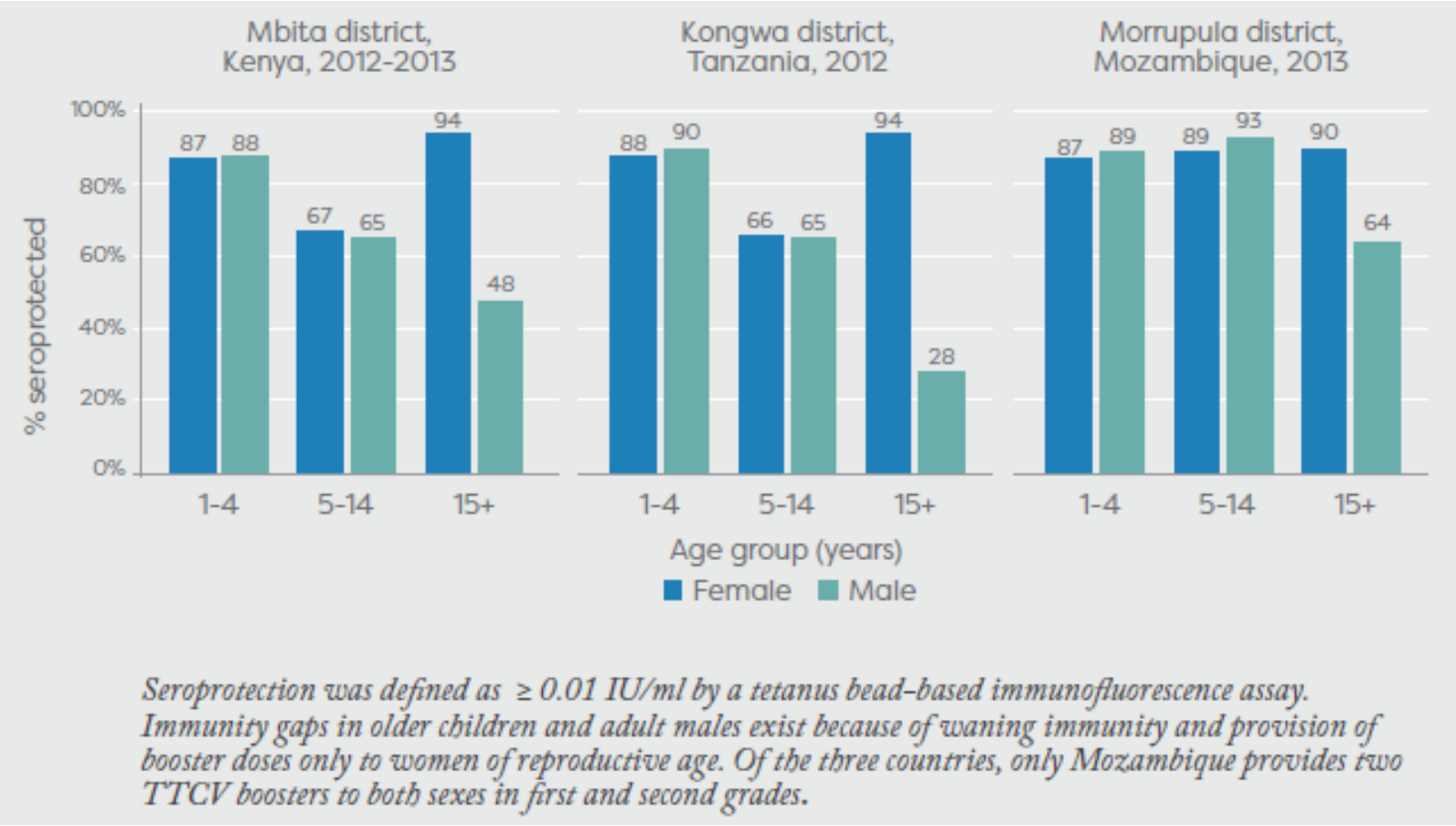
Additional evidence of waning immunity for Tetanus



Source: Steens et al, Vaccine 2010, 28, 7803-7809

Additional evidence of waning immunity for Tetanus

Seroprotection among individuals in districts in three eastern and southern African countries

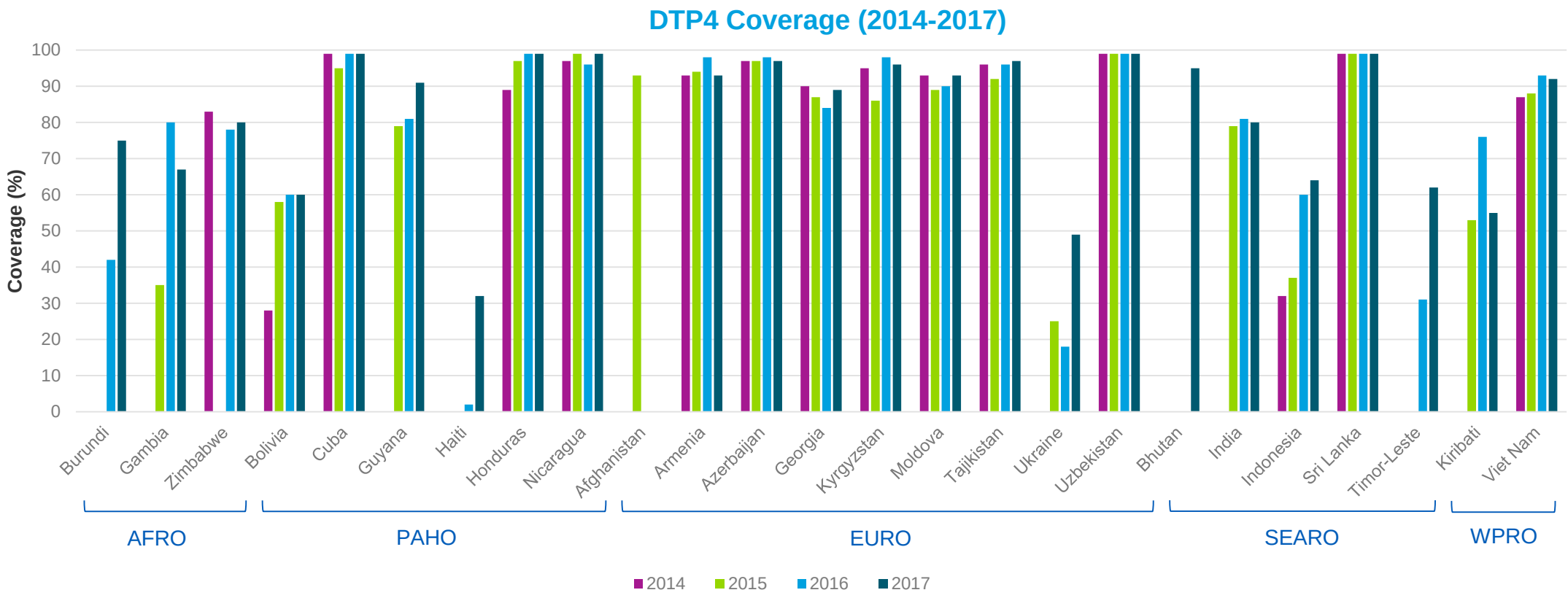


Seroprotection was defined as ≥ 0.01 IU/ml by a tetanus bead-based immunofluorescence assay. Immunity gaps in older children and adult males exist because of waning immunity and provision of booster doses only to women of reproductive age. Of the three countries, only Mozambique provides two TTCV boosters to both sexes in first and second grades.

Source: Annex 2, Vaccine Preventable Diseases, Surveillance Standards, Tetanus Serosurveys

DTP4 coverage has been reported in 25 Gavi countries since 2014

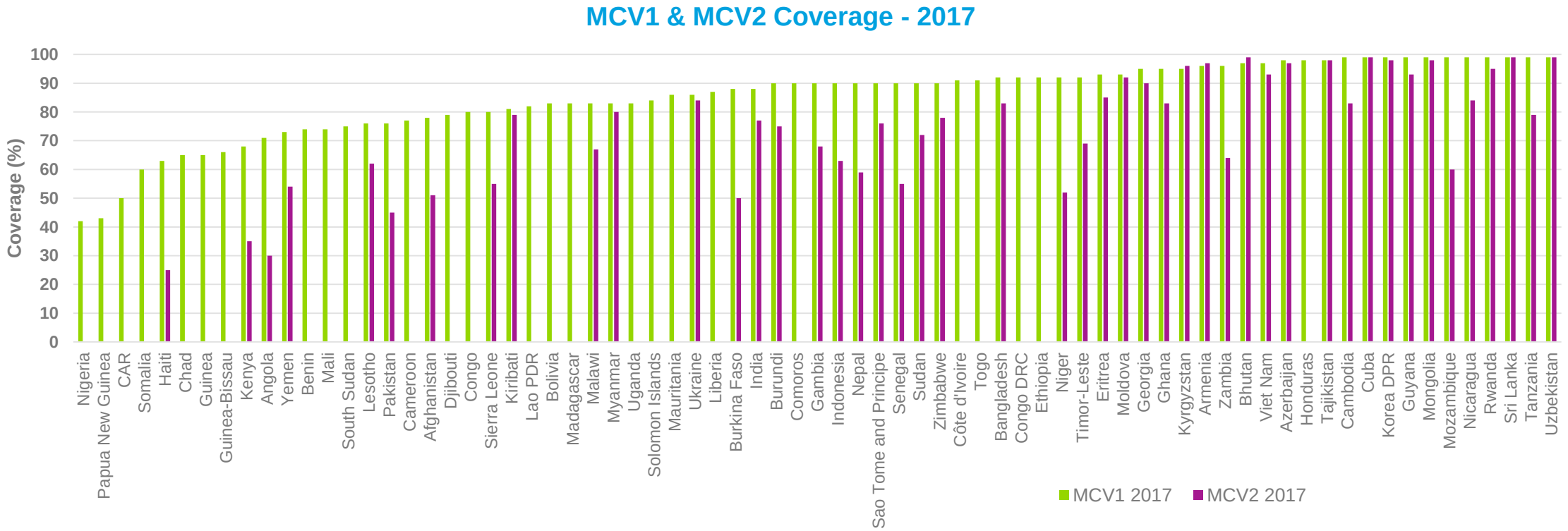
Planning coordination and integration



Coverage of MCV2 is lower than MCV1; the 2YL platform requires strengthening

Planning coordination and integration

Booster 1 – DTwP or Penta



Coverage by 2YL is typically less than that achieved in the first year of life, implying this time point is more difficult to implement successfully; many countries do not yet have a 2YL vaccination time point

MCV2 is provided between 15-18 months, unclear whether WUENIC captures 2nd doses outside this timeframe

31 of Gavi 73 countries have offered school-based immunisation in the last 5 years

Planning coordination and integration

Booster 2 & 3 - Td

- Primary school attendance is typically much higher than secondary, and in some countries offers a good opportunity to reach many children at once
- However, most Gavi countries do not historically use school as a platform for vaccination

In 2017: 23 Gavi73 countries offered school-based immunisation

- TTCV was the most common vaccination delivered in schools, with 11 countries providing Td, 10 providing TT and 3 DT; often provided to girls only
- HPV was the second most commonly delivered vaccine (n=10)
- Other vaccines provided include: typhoid, measles and MR

40 of Gavi73 countries have, or are planning to introduce HPV for girls between 9-18 yo.

Planning coordination and integration

Booster 2 & 3 - Td

- Where HPV is, or is scheduled to be introduced, there is an existing platform for the 3rd booster
- On the 1st school visit, HPV dose 1 is given to 10 yo. girls and Td could be given to both boys and girls at the 4-7 yo. and 9-15 yo. timepoint
- On the 2nd school visit, HPV dose 2 is given to 10 yo. girls and Td could be given to those boys and girls at the 4-7 yo. and 9-15 yo. timepoint who were absent at the time of the first school visit

Age at 1st dose

9 yo.	• Benin • Burkina Faso (demo) • Cambodia (demo) • Georgia (demo)	• Malawi (from 2019) • Senegal (from end 2018) • Sierra Leone • Solomon Islands	• Uzbekistan • Zimbabwe
10 yo.	• Bangladesh • Bolivia • Burundi • Cote d'Ivoire • Laos PDR (from 2019)	• Liberia • Mali • Nepal (from 2019) • Moldova (demo) • Sao Tome e Principe (demo)	• Sri Lanka • Uganda • Zambia
11 yo.	• Ghana • Honduras	• Indonesia (demo) • Niger (demo)	
12 yo.	• Bhutan • Rwanda		
13 yo.	• Armenia (demo)		
14 yo.	• Ethiopia (end 2018) • Tanzania		

9-13 yo.	• Eritrea (demo from 2019) • Gambia (from 2019) • Guinea	• Guyana • Mozambique • Togo (from 2019)
9-14 yo.	• Cameroon (from 2019) • Mauritania (from end 2018)	