Subject	**Hexavalent Investment Case**
Agenda item	**06**
Category	**For Decision**

Section A: Executive Summary

Content

In November 2018, the Board approved in-principle support for whole-cell Pertussis Hexavalent vaccine (Hexavalent), a combination vaccine that includes six antigens already covered by Gavi support via Pentavalent and standalone Inactivated Polio Vaccine (IPV). This approval was subject to a vaccine being licensed, recommended for use by WHO, WHO prequalified, and with market attributes met that support the successful implementation of Hexavalent. This topic is now being brought back to the Board, since the support conditions laid out in the 2018 decision are now evaluated as having been *met*, based on current market information (see Appendix 2 to May 2023 Doc 06) – and the programme was endorsed unanimously by the PPC during its May 2023 convening.

Support for Hexavalent (4-dose series)[1] is expected to provide considerable programmatic ease and reduce ancillary costs, among other benefits. Furthermore, the shift to this combination vaccine would support Gavi 5.1 and polio eradication objectives. These benefits need to be weighed against estimated additional costs to Gavi of US$ 29-62 million in Gavi 5.1 and US$ 357-430 million in Gavi 6.0 and increased co-financing obligations of countries of US$ 0.2-2 million in Gavi 5.1 and US$ 34-60 million in Gavi 6.0 compared to the currently supported (3Pentavalent+2IPV) schedule[2].

Conclusions

This governance cycle is a critical window of opportunity to ensure the availability of Hexavalent to Gavi-supported countries. Declining or delaying support for Hexavalent could lead to unrealised programmatic benefits and negative consequences for any future Hexavalent product and other combination vaccine markets – and potentially jeopardise Gavi's credibility with the manufacturer base.

Given that the favourable analysis of the value of Hexavalent demonstrates that it is commensurate with its financial implications, the Programme and Policy Committee (PPC) recommends to the Board that Gavi opens a funding window starting Q3 2023.

[1] See Table 1 below for WHO-recommended schedules and Appendix 1 to May 2023 PPC Doc 06 for additional details.
[2] The lower figure in each range is the base scenario costs currently reflected in the financial forecast. The higher figure in each range is based on the high demand scenario. See Appendix 1 to May 2023 PPC Doc 06 for details.

Section B: Content

1. Hexavalent partnership alliance and governance pathway

1.1 Following its first IPV support decision in November 2013, in June 2018, the Board approved support for IPV from 2019-2020 based on the rationale that polio eradication is a global public health good, and routine vaccination with IPV plays a fundamental role in the polio eradication strategy. Furthermore, IPV is the only vaccine in national routine immunisation programmes to provide protection against all three poliovirus types.

1.2 In December 2022, the Board approved continuation of its June 2019 IPV decision: countries are exempt from Gavi eligibility and co-financing policies until polio eradication and after the withdrawal of bivalent oral polio vaccine (bOPV) from routine immunisation schedules.

1.3 In 2018, Gavi Alliance partners formed the **Hexavalent Strategic Alignment Group**[3], which assessed the programmatic benefits of Hexavalent and recommended a decision pathway to Gavi's potential support.

*Table 1: Hexavalent schedule compared with Gavi-supported (Pentavalent + IPV) schedule**

		Primary immunization schedule				Booster
		6w	10w	14w	9m	12m-24m
1. Base schedule	Pentavalent	1st dose	2nd dose	3rd dose		DTP/Penta
	IPV (full or fIPV)			1st dose	2nd dose	
2. Full Hexa schedule (3+1)	Hexavalent	1st dose	2nd dose	3rd dose		Hexa [1]

Colour code
- Supported by Gavi
- Approved for support by Gavi's Board - Roll-out on hold due to COVID
- In principle support by Gavi

[1] A Hexavalent booster is needed in countries using Hexavalent in primary series starting at 6 weeks based on WHO Polio vaccine position paper.

(*) These schedules are illustrative.

1.4 Based on this recommendation, in November 2018, the Board was asked to consider support for IPV and Hexavalent. The Board approved:

a) Support for IPV post 2020, subject to the availability of funding;

b) **In-principle support for Hexavalent**, subject to five conditions.

1.5 This "in-principle" decision demonstrated Gavi's interest in supporting Hexavalent vaccine, while acknowledging that a prequalified product was not yet available and that some conditions that define desired market attributes needed to be met before Gavi's support was made available.

1.6 In 2022, the Hexavalent Strategic Alignment Group evaluated the support conditions and determined that four out of five conditions are met[4]. In February

[3] Gavi partners as part of a Hexavalent dedicated working group, which includes WHO, UNICEF, The Bill & Melinda Gates Foundation, and Gavi Secretariat.
[4] See Appendix 2 to May 2023 PPC Doc 06 for details on the support conditions.

2023, the Market Sensitive Decisions Committee[5] (MSDC) assessed whether the price aligns with Hexavalent's expected benefits. The **MSDC confirmed that this fifth condition is now met**: *Hexavalent's price is in line with its value*. It is now determined that all five conditions are met.

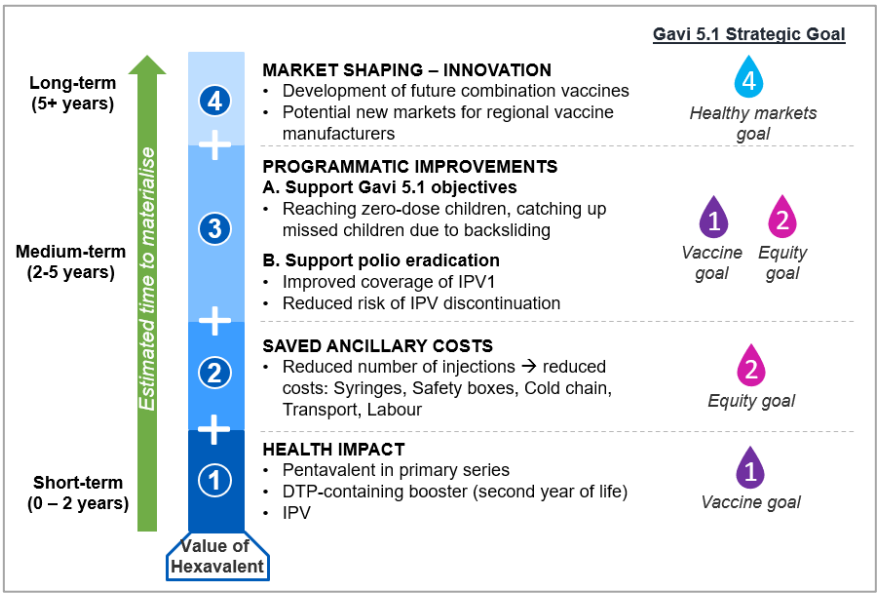
2. Update on polio eradication

2.1 The Polio Eradication Strategy 2022-2026 targets the interruption of poliovirus transmission by the end of 2023. This means the earliest global certification of eradication would occur is 2026, followed by the cessation of bivalent oral poliovirus vaccine (OPV) use starting in 2027.

2.2 This year, there have been four confirmed cases of wild poliovirus type 1 (WPV1) in Afghanistan and one case in Pakistan[6]. This signals that progress continues to be made to interrupt all remaining WPV transmission in 2023. While there has been a recent decline in the number of circulating vaccine-derived poliovirus (cVDPV) cases, outbreaks continue in 2023. Use of type 2 novel OPV is helping to bring these outbreaks under control and limit the number of new emergences.

2.3 Despite these positive trends, timelines for eradication have changed numerous times over the last 20 years, so further delays in eradication targets can be expected.

3. Value of Hexavalent



3.1 **Health impact:** Switching to Hexavalent is expected to provide considerable programmatic benefits and have a catalytic effect on innovation, which would amplify its health impact and support reaching Gavi 5.1 strategic goals. This

[5] Even though MSDC does not typically review this type of request, it was selected as the most appropriate committee due to the market-sensitive nature of the price and supply information.
[6] Update as of 7 June 2023.

value proposition was vetted by Gavi Alliance partners through a series of rigorous analyses[7].

3.2 **Saved ancillary costs, improved injection safety:** This streamlined vaccination schedule with Hexavalent would reduce the number of vials and injections, which would result in saved ancillary costs for Gavi and countries[8].

3.3 **Programmatic improvements**

3.3.1. **Support for Gavi 5.1 objectives**

a) In support of Gavi's Equity Goal, the use of a Hexavalent combination vaccine would facilitate extending immunisation services to reach zero-dose children and catch-up of missed children.

b) Furthermore, Hexavalent could increase the opportunities to provide more IPV doses and better protection to under-immunised children in case they miss one of their immunisation visits.

c) The fourth dose of Hexavalent provides an opportunity to strengthen the second year of life (2YL) platform as part of a life-course approach to immunisation, as described under Gavi's Vaccine goal.

d) The consolidation of the immunisation schedule at 6/10/14 weeks[9] would create efficiency and ease the burden on clients and health workers.

3.3.2. **Support for polio eradication**: Hexavalent is an important tool to sustain polio eradication, as it is anticipated that IPV will remain a core routine antigen.

a) As seen with other combination vaccines, such as Pentavalent, IPV1 coverage is expected to improve, especially where IPV1 and DTP3 are both given at 14 weeks and IPV1 rates are lower[10].

b) Using Hexavalent would reduce the risk of IPV discontinuation in the post-eradication period, as countries are not expected to revert to Pentavalent once they have introduced Hexavalent.

c) A primary 3-dose Hexavalent schedule starting from 6 weeks of age initiates early-in-life protection compared to a two-dose IPV schedule starting at 14 weeks of age or older.

d) Offering Hexavalent could provide a preferred option for countries that have not yet introduced IPV2 into their routine schedule[11].

[7] See Appendix 2 to May 2023 PPC Doc 06 for details on the Hexavalent Strategic Alignment Group's analyses.
[8] Saved costs analysis conducted by PATH, using their Vaccine Technology Impact Assessment Tool
[9] This schedule is used as an illustration. There are other WHO-recommended schedules (see Appendix 1 to May 2023 PPC Doc 06).
[10] It is estimated that ~500,000 additional children could benefit annually from improved IPV1 coverage, based on studies about the impact of adoption of wP-Pentavalent on paediatric vaccine coverage rates, and on the analysis of historical WUENIC data showing an improvement of HepB and Hib coverage in Gavi74, with Penta.
[11] Partners would take deliberate measures, including clear communication on timelines and supply, to ensure the anticipation of Hexavalent would not deter for countries with the willingness and capacity to introduce IPV2.

3.4 Market shaping – support of innovation

a) Other vaccine combination projects are in the pipeline[12]. A decision to support Hexavalent would send a positive signal to manufacturers, which would positively impact the development of this type of innovation.

b) New regional vaccine manufacturers could play an important role in improving supply availability and diversity in the Hexavalent market. Hexavalent could become an important part of their portfolio, providing a steady revenue stream that supports future investments.

4. Demand materialisation

4.1 As part of the VIS 2024 process, governments and in-country partners from Gavi-eligible countries were surveyed in March 2023. Among the respondents[13] from 36 countries, Hexavalent was ranked second (among 18 options) in the *Priority diseases with country likelihood to introduce vaccine programme* category. In addition, some Gavi-eligible countries have expressed interest in Hexavalent.

4.2 This is a promising indication that there is awareness of and interest in Hexavalent at the country level. However, there has not been systematic engagement with countries to present the Hexavalent vaccine programme and gauge their potential interest.

4.3 To determine an accurate demand forecast, the programme design process would include a robust demand materialisation plan, requiring close collaboration with Alliance and expanded partners, to support country prioritisation and portfolio optimisation,[14] including an assessment of co-financing requirements and saved costs, fit and feasibility, and possible operational and communications challenges, among other considerations. Country demand will be driven by their capacity and the availability of resources necessary to switch to Hexavalent, given their many competing priorities and economic circumstances[15].

4.4 The demand scenarios used to inform the programme's financial implications (outlined below) are based on a model that estimated the likelihood of countries to switch to Hexavalent (see Appendix 1 to May 2023 PPC Doc 06). The financial impact assumes that 30 Gavi-eligible countries would introduce Hexavalent by 2030, including 23 initial self-financing countries, which were deemed to be more likely to introduce due to the lower cost implications, based on Gavi's co-financing policy[16].

[12] Future potential combination vaccine projects include (non-exhaustive list): Pentavalent and Hexavalent in combination with injectable next generation Rotavirus vaccines (iNGRV) and Pentavalent in combination with Polio virus-like particles (VLP) vaccines that could replace IPV in the polio post-eradication phase.
[13] These are individual responses and non-representative, not an official government or partner position.
[14] See Annex B to May 2023 PPC Doc 06 for the Theory of Change and learning questions related to the Hexavalent Programme.
[15] See Annex A for more information on demand-related risks.
[16] Countries that choose to retain standalone IPV in their schedule will continue to receive this exemption.

5. Financial implications[17,18]

5.1 **Financial impact on Gavi:** The additional cost to Gavi of supporting Hexavalent is estimated at US$ 29 million in Gavi 5.1 and US$ 357 million in Gavi 6.0 in the case of a base demand scenario. In the event of an accelerated rate of Hexavalent uptake, this cost is estimated at US$ 62 million in Gavi 5.1 and US$ 430 million in Gavi 6.0.

a) These costs are based on a fully loaded vaccine price and include the saved ancillary costs of freight, safety boxes, and syringes. Costs also include a one-time switch grant based on US$ 0.25 per child[19].

b) Additional costs, such as those related to Health System and Immunisation Strengthening (HSIS), Partners' Engagement Framework (PEF), and additional technical and operational support, are unknown at this time and would need to be reflected in the next forecast, in close consultation with partners.

c) These figures include the cost of two additional doses of IPV (embedded in Hexavalent) currently not supported by Gavi, as well as a diphtheria-tetanus-pertussis (DTP)-containing booster dose.

5.2 **Financial impact on countries:** The additional co-financed vaccine cost to countries is estimated at US$ 0.2 million in Gavi 5.1 and US$ 34 million in Gavi 6.0. In the event of an accelerated rate of Hexavalent uptake, this cost is estimated at US$ 2 million in Gavi 5.1 and US$ 60 million in Gavi 6.0.

a) These figures do not include saved in-country ancillary costs related to cold chain, in-country transportation, and labour estimated at US$ 2-6 million in Gavi 5.1 and US$ 70-95 million in Gavi 6.0.

5.3 **Co-financing**: The proposed co-financing policy for Hexavalent is based on the regular co-financing policy applied to countries eligible for Pentavalent support. In addition, countries that decide to switch to Hexavalent will continue to benefit from the IPV co-financing subsidy[20]. Additional information about the co-financing proposal, including the co-financed share for countries by transition status, can be found in Appendix 1 to May 2023 PPC Doc 06. This may need to be reassessed for the Gavi 6.0 strategic period.

[17] See Annex A for detailed information on the financial implications.
[18] The additional cost of 4 doses of Hexavalent versus the currently supported schedule was included in the financial forecast v20.1, presented to the Audit and Finance Committee (AFC) on 11 May, noting that the cost of Hexavalent support was not included in the financial forecast v20 approved by the Board on 7-8 December 2022.
[19] Switch grants provide US$ 0.25 per child or US$ 30,000 (whichever is higher).
[20] Based on the IPV co-financing policy approved by the Board in June 2019 and December 2022, Gavi fully finances two doses of IPV until bOPV cessation. After bOPV cessation (not expected before 2027), countries in preparatory and accelerated transition phase and fully self-financing countries will have to co-finance a share of IPV - equivalent to US$ 0.60/child.

6. Supply health and risks

6.1 The success of manufacturers developing Hexavalent vaccine, obtaining WHO prequalification for the primary and booster indications, and meeting the product portfolio management principles[21] (PPM) are important steps in ensuring supply availability and diversity, which would support Hexavalent's market health, demand materialisation, and predictability.

6.2 Furthermore, as defined in the 2018 Hexavalent support conditions and in the Pentavalent/IPV/Hexavalent market shaping roadmap[22], Gavi Alliance partners will continue to assess and intervene, as necessary, to ensure the Pentavalent and standalone IPV markets remain healthy, and access to these vaccines is secured for countries that decide to remain with Pentavalent and IPV. Based on the expected timelines of WHO prequalification and supply availability, the Hexavalent market would evolve from a low competition period in 2023-2026, to a competitive period in 2027.

6.3 During the 2023-2026 period, up to three manufacturers could supply Hexavalent; however, they currently share the same bulk source for one or more antigens. A programme could be launched under these supply conditions[23], especially with sustained access to Pentavalent and standalone IPV as a fallback option in case of Hexavalent supply issues.

a) Hexavalent prices reviewed by the MSDC are expected to remain valid during this period. While IPV prices beyond 2025 are not known at this stage, Pentavalent and standalone IPV prices are not expected to increase during this period due to existing competitive dynamics.

b) Gavi Alliance partners will use targeted market shaping interventions, including procurement strategies for UNICEF tenders, to mitigate supply risks.

6.4 Starting in 2027, the health of the Hexavalent market is anticipated to improve following the expected prequalification of vaccines from two additional manufacturers dependent on two different national regulatory agencies and using different antigen bulk sources.

a) Hexavalent price dynamics are uncertain beyond the tender period (2028+). However, it is anticipated that the price of Hexavalent will decrease further with competitive dynamics and economies of scale[24].

[21] Principles approved by the Board in June 2016, part of the Supply and Procurement Strategy 2016-2020, which guide the Gavi Secretariat for adding a new vaccine presentation or product to the Gavi "product menu".
[22] https://www.gavi.org/sites/default/files/document/supply-procurement/Penta-IPV-Hexa-Roadmap-Public-Summary-2020.pdf
[23] Gavi-supported immunisation programmes that started with one supplier include Pentavalent, Meningococcal A, Measles-Rubella, HPV, TCV. In the case of Pentavalent, GSK was the only supplier to offer prequalified Pentavalent to Gavi-supported countries between 2001-2005 while DTP, DTP-HepB, and standalone HepB and Hib were available.
[24] This trend has been previously seen with other vaccines such as Pentavalent whose weighted average price (WAP) decreased by 30%, ten years after Gavi started to support it (see Appendix 2 to May 2023 PPC Doc 06 for more details).

b) The prices of Pentavalent and standalone IPV could increase due to a reduction in demand, and some suppliers might decide to stop offering these vaccines to Gavi-supported countries and focus their production capacity on Hexavalent.

c) A carefully managed consolidation in these markets in the long run may be the most efficient way to mitigate these risks and ensure Pentavalent and IPV market dynamics are viable for suppliers. This intervention is facilitated by the fact that Hexavalent suppliers are also the ones providing Pentavalent and standalone IPV to Gavi-supported countries.

7. Interdependencies with DTP-containing boosters

7.1 In May 2023, the PPC provided guidance on DTP-containing boosters, recommending that the decision on next steps for this introduction be done in broad consultation with partners. The Hexavalent and DTP-containing booster programmes will be designed to ensure full programmatic and financial alignment.

8. Timing of governance decision

8.1 At the request of the Board in 2018, Hexavalent is being submitted during this governance cycle now that all five support conditions are met. The PPC, at its meeting in May 2023, unanimously recommended that the Board approve the opening of a funding window for a Hexavalent programme in Q3 2023. This would allow the Gavi Secretariat and partners to develop and finalise Hexavalent's programme design and countries to start assessing Hexavalent, in time for first introductions starting in 2024.

8.2 Any further delay in opening a funding window for Hexavalent would likely lead to negative consequences. The Hexavalent **market** could be impacted by a risk of deprioritisation or discontinuation of i) Hexavalent development programmes and production scale-up, and ii) investments in vaccine manufacturing in Africa where Hexavalent was identified by some manufacturers as a candidate for production and/or fill-finish on the continent. This would result in a longer period of supply dominance and limited diversity in the Hexavalent market and exacerbate the supply-related risks described in the previous section.

a) In the longer term, such a delay could also limit future investments in the next generation of combination vaccines.

b) Furthermore, a delayed Board decision would prevent UNICEF from being able to consider implementation of awards within the first phase (2024-2025) of the Hexavalent tender.

8.3 Hexavalent vaccine developers have been closely following Gavi's funding pathways since 2018 and expect a programme launch in 2024. Deprioritising Hexavalent after giving an indication of this pathway in 2018 risks Gavi's **credibility**. This could jeopardise Gavi's market shaping model and may have

negative consequences on other antigens that Gavi Alliance has been signalling to manufacturers to develop and produce to improve market health.

8.4 Pentavalent and standalone IPV would remain available to Gavi-supported countries; but countries, health workers, and children would miss out on the considerable **programmatic** benefits brought by Hexavalent.

Section C: Actions requested of the Board

The Gavi Alliance Programme and Policy Committee **recommends** to the Gavi Alliance Board that it:

a) **Approve** the opening of a funding window for combination Hexavalent vaccine for the administration of diphtheria, tetanus, whole-cell pertussis, hepatitis B, Haemophilus influenza b, and IPV antigens;

b) **Note** that the initial estimates of the financial implications associated with the above approval for 2023-2025 are expected to be up to US$ 62 million, and the US$ 29 million estimated costs associated with base demand has been taken into account in the financial forecast being presented during this Board meeting; and

c) **Note** that the initial estimates of the financial implications associated with the above approval for 2023-2025 for additional operational cost support and Secretariat and partner resources will be accounted for in the financial forecast to be presented to the Board in December 2023, following consultations with partners and countries; and

d) **Note** that the initial estimates of the financial implications associated with the above approval for the strategic period 2026-2030 are expected to be up to US$ 430 million and contingent on financial resources being made available for the next strategic period; and

e) **Note** that the initial estimates of the financial implications for both time periods are based on a fully loaded vaccine price and include saved ancillary costs and a one-time switch grant.

Annexes

Annex A: Implications and Anticipated Impact

Additional information available on BoardEffect

Appendix 1 (in May 2023 PPC meeting book): Annex B to Doc 06 Hexavalent Investment Case – Theory of Change and Learning Questions

Appendix 2 (in PPC Library – Additional materials for May 2023 PPC meeting): Appendix 1 to Doc 06 – Programmatic Considerations

Appendix 3 (in PPC Library – Additional materials for May 2023 PPC meeting): Appendix 2 to Doc 06 - Assessment of the 2018 Hexavalent Support Conditions

Appendix 4 (in PPC Library – Additional materials for May 2023 PPC meeting): Appendix 2 to Doc 06 - Pentavalent Historical Data

Appendix 5 (in PPC Library – Additional materials for May 2023 PPC meeting): Appendix 2 to Doc 06 - Board Decisions Related to IPV and Hexavalent