Annex A: Implications and Anticipated Impact

1. Anticipated impacts of a potential Hexavalent support decision

1.1 Financial impacts

Financial impact on the Gavi Alliance

Table 1: Additional cost of Hexavalent to Gavi versus currently used (Pentavalent+IPV)

Gavi vaccine costs (US$M) as per latest financial forecast (v20.1)	**Gavi 5.1**	**Gavi 6.0**	**Total**
IPV	$874M	$773M	$1,647M
Pentavalent	$492M	$425M	$917M
Total	**$1,366M**	**$1,198M**	**$2,564M**
Additional cost to Gavi if Hexavalent supported[(a,b)]	**$29M-$63M**	**$357M-$430M**	**$387M-$492M**
% Increase versus [Pentavalent + IPV]	2%-5%	30%-36%	15%-19%

(a): the range of additional cost reflects the base and high demand scenarios and includes the saved ancillary costs to Gavi

(b): the additional cost includes a one-time switch grant based on US$ 0.25/child in birth cohort in the year of introduction or US$ 30,000 (whichever is higher)

- The main driver of the increase in cost to Gavi is Hexavalent's price premium[1].
- In a highly unlikely scenario where all Gavi54 eligible countries gradually switch to Hexavalent by 2030, the additional cost to Gavi is estimated to reach US$ 115 million in Gavi 5.1 and US$ 700 million in Gavi 6.0.
    - This scenario assumes an optimistic supply availability outlook and a gradual linear uptake of Hexavalent demand[2].
    - Hexavalent price used in this scenario is lower than the base demand scenario because we expect that higher demand would lead to improved economies of scale and a more competitive environment[3].

[1] This cost of this programme includes two additional doses of IPV (as part of a combination vaccine) that are not currently supported. There may also be additional service delivery costs that are not currently reflected in the forecast.
[2] The uptake of Hexavalent demand was assumed as a linear increase, constrained by supply availability. This approach is different than the base/high demand forecasts used to estimate the financial implications in Table 1, which are based on a bottom-up model that assesses the likelihood of a country switching to Hexavalent (see Appendix 1 – Table 2).
[3] Using the known cost of Hexavalent (not assuming competition), the additional cost to Gavi is estimated to be US$ 117million in Gavi 5.1 and US$ 793 million in Gavi 6.0.

- This scenario is highly unlikely because we expect some Gavi-supported countries to remain on Pentavalent and standalone IPV.

Financial impact on countries

- Countries would benefit from saved ancillary costs (cold chain, in-country transportation and labour) resulting from the use of four instead of five injections to immunise children against the six diseases covered by Pentavalent and standalone IPV (or Hexavalent). The total financial and opportunity ancillary costs that countries are expected to save is on average US$ 0.89/course[4] of Hexavalent versus (Pentavalent+IPV) which would result in a total of US$ 2-6 million in Gavi 5.1 and US$ 70-95 million in Gavi 6.0 based on the Hexavalent demand scenarios.

Table 2: Saved financial and opportunity ancillary costs per fully vaccinated child (4Hexavalent versus 3Pentavalent + 2IPV) calculated based on PATH's Vaccine Technology Impact Assessment model (VTIA) model

Saved ancillary costs – Gavi		Saved ancillary costs – Countries	
• Syringes	US$0.06	• Cold chain	US$0.02
• Safety box	US$0.01	• Transport	US$0.11
		• Administration	US$0.02
		• Other labor costs	US$0.74

- The saved in-country ancillary costs will reduce the impact of the additional co-financed vaccine cost by countries due to Hexavalent's price premium. The evaluation of Hexavalent in a specific country will depend on the country's co-financing share and the saved in-country ancillary costs in its specific context noting that a distinction is needed between the financial and opportunity cost impacts.

2. Risk implications of a potential Hexavalent support decision

2.1 Demand-related risks and mitigation actions

- Low demand: Countries will need to decide if they have the willingness, capacity, and resources to switch to Hexavalent, given their many competing priorities and economic circumstances. As with other Gavi-supported switches, countries will be provided with the tools they need to make an informed decision, including portfolio optimisation input, and resources to facilitate these programmatic changes in the form of a switch grant, as well as targeted country assistance, when available and possible.

- High demand: With an unconfirmed number of countries that are interested in switching to Hexavalent, there is a possibility that demand could be higher than supply, at least in the beginning of the programme. If this happens, Gavi Alliance partners will work together to develop and

[4] Estimation based on a comparative economic evaluation of ancillary costs between a 4-Hexavalent schedule and a [3-Pentavalent + 2-IPV] schedule used in most Gavi-supported countries. An analysis using real-life data (when available) should be done by a country when assessing the option to switch to Hexavalent, taking into account the different nature of the saved costs (financial and opportunity costs).

implement a country prioritisation plan with appropriate communication materials.

- Given that there are still 29 Gavi-eligible countries that have not introduced IPV2 (see below), it is important that countries with the willingness and capacity to introduce IPV2 are not deterred from doing so in anticipation of introducing Hexavalent instead. There will need to be clear guidance for and communication with countries about timelines and supply to avoid the possibility of delays.

- Out of the Hexavalent programmatic benefits outlined in the paper, improving the reach of zero-dose children and catch-up of missed children in the context of backsliding routine immunisation will be the most challenging due to the additional immunisation activities that need to be implemented to achieve these objectives. Hexavalent's benefit in this regard comes from its logistical advantage versus Pentavalent and standalone IPV in these settings. A close alignment with the teams in charge of mapping countries with zero-dose children and supporting immunisation activities is needed to identify countries that would benefit most from Hexavalent and ensure the vaccine is evaluated and introduced by these countries, if appropriate.

2.2 Supply-related risks and mitigation actions

- Currently, six manufacturers have developed or are developing Hexavalent vaccines.
    - A first Hexavalent vaccine was prequalified in November 2022; however, the vaccine was delisted in March 2023 following a decision by the manufacturer to stop its production and commercialisation.
    - Two other vaccines have been licensed in India with potential plans to seek WHO prequalification.
    - Two other manufacturers are developing Hexavalent vaccines that are currently in clinical trials.
    - Finally, a sixth manufacturer based in Africa has signed an agreement with one of the manufacturers cited above to use its Hexavalent bulk to fill-finish the vaccine.

- Based on the expected timelines of WHO prequalification and supply availability, the Hexavalent market will evolve from a **low competition period** in 2023-2026, to a more **competitive period** starting 2027.

Low competition period

- Up to three manufacturers could supply Hexavalent to Gavi-supported countries in 2023-2026; however, they operate in a low competition market

as they share the same bulk source for one or more antigens which increases the risk and impact of potential supply disruptions.

- While this is not ideal for market health, a programme could be launched under these conditions[5], especially in the context of a sustained access to Pentavalent and standalone IPV as a fallback option in case of a supply disruption impacting all three manufacturers at once. Furthermore, increased frequency of onsite diligence visits by UNICEF would help ensure better visibility on production progress and supply availability, and early detection of possible delays.

- Manufacturers producing Hexavalent are not expected to stop supplying Pentavalent and standalone IPV to Gavi-supported countries. Based on the assessment of Hexavalent support condition 3 (see Appendix 2), the supply of Pentavalent and standalone IPV is expected to cover demand even if some of it is diverted to produce Hexavalent. The approach of phased awards implemented by UNICEF in the Pentavalent / Hexavalent / DTP tenders provides visibility to manufacturers to plan their production and helps ensure availability of DTP/Pentavalent during this period. The Gavi Alliance partners would also implement targeted market shaping interventions to mitigate any potential additional risk impacting the availability of standalone IPV and DTP/Pentavalent.

- Hexavalent prices that were reviewed by the MSDC and considered as commensurate with the vaccine's benefits and savings are expected to remain valid during this period. Furthermore, Pentavalent and standalone IPV prices are not expected to increase during this period due to existing competitive dynamics and limited impact of Hexavalent on Pentavalent and standalone IPV demand during the initial years of the programme.

Competitive period

- Starting 2027, the Hexavalent market health should start to improve following the expected prequalification of vaccines from two additional manufacturers dependent on two different national regulatory agencies (NRA) and using different antigen bulk sources.

- The estimated Hexavalent production capacity of one of these manufacturers is enough to improve overall supply availability and to cover a base Hexavalent demand scenario for Gavi-supported countries, while the second manufacturer is needed to cover a high demand scenario and improve supply diversity.

- Supply disruptions during the initial years of production are a risk for these new manufacturers. The supply uncertainty could be mitigated by the

[5] 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.

increased frequency of onsite diligence visits by UNICEF, as advised during the previous period as well.

- These manufacturers are also expected to offer Hexavalent at a price that is commensurate with its benefits and savings, based on the MSDC review and their current Pentavalent and IPV pricing approaches compared to other manufacturers.

- The price dynamics are uncertain beyond the tender period (i.e., 2028+); however, Hexavalent price will probably decrease further as competitive dynamics and economies of scale improve. This trend has been seen in other vaccines such as Pentavalent whose weighted average price (WAP) decreased by 30%, ten years after Gavi started to support it (see Appendix 3 – Graph 1).

- On the other hand, Pentavalent and standalone IPV prices could increase due to a reduction in demand. A consolidation in the Pentavalent and standalone IPV markets may be the most efficient outcome to manage this risk and to ensure market dynamics are viable for the remaining suppliers. This intervention is facilitated by the fact that Hexavalent suppliers are also the ones providing Pentavalent and standalone IPV to Gavi-supported countries.

- Some suppliers might decide to stop offering Pentavalent and standalone IPV to Gavi-supported countries and focus all their production capacity on Hexavalent. In this low likelihood scenario, the development and prequalification of pipeline standalone IPV vaccines would be key to ensure supply of standalone IPV covers demand. The Alliance partners are currently assessing further mitigation actions to address these specific risks.

3. Risk implications of a potential delayed Hexavalent support decision

3.1 Market-related risks

- From a supply perspective, the potential Board decision to support Hexavalent in June 2023 is an opportunity to ensure availability of Hexavalent to Gavi countries and improvement of market health in the medium and long term.

- Any further delay in opening a funding window for Hexavalent could lead manufacturers to deprioritise it in favour of other vaccines in their pipeline by postponing or cancelling Hexavalent development plans and production scale-up. This would negatively impact Hexavalent market health by reducing supply availability to Gavi-supported countries and competitiveness. Furthermore, UNICEF will not be able to consider the implementation of awards within the first phase (2024-2025) of the Hexavalent tender if a funding window is not approved by the Board in the current cycle.

- A delay could also negatively impact efforts to advance vaccine manufacturing in Africa, as Hexavalent is one of the vaccines that could be fill-finished and commercialised in African countries by a manufacturer based in Africa (with bulk from another manufacturer).

- Finally, a delay in the Hexavalent programme launch could result in the longer term in deprioritising other combination vaccine projects that include Pentavalent and Hexavalent, such as combination with injectable next generation Rotavirus vaccines (iNGRV) and with Polio virus-like particles (VLP) vaccines that could replace IPV in the polio post-eradication phase.

3.2 Credibility risks

- The Gavi Board's "in principle" support decision in 2018 was a strong signal that incentivised multiple manufacturers to pursue their Hexavalent development plans which will help create a healthier and more competitive market in the medium and long term. Additional engagement by Alliance partners has improved several market attributes to ensure a successful launch of Hexavalent, especially price that was optimised in the latest UNICEF tender owing to a cross-Alliance effort.

- While the Gavi Board was clear that support conditions should be met in order to open a funding window, deprioritising Hexavalent after giving an indication of the pathway in 2018, should be considered as a risk to Gavi's credibility which could impact its market shaping model and may have unintended negative consequences on other antigens where Gavi Alliance has been signalling to manufacturers to develop and produce vaccines to improve market health.

3.3 Programmatic risks

- If a Hexavalent support decision is not made in this governance cycle, the access of Gavi-supported countries to Hexavalent will be delayed and first introductions in 2024 will be unlikely.

- While countries still benefit from Gavi's support for Pentavalent (based on their co-financed status) and IPV, they would miss out on Hexavalent's programmatic benefits, which could be key for some of these countries that have challenges in terms of IPV coverage and a high concentration of zero-dose children.

4. IPV Programme Update

- Significant investments by vaccine manufacturers and concerted efforts from the global community tipped the balance from a supply constrained IPV market in 2018 to a much healthier state in 2023.

- In the 2022 UNICEF tender for IPV supply covering the period 2023-2025, seven manufacturers offered over 350 million doses, up from two

manufacturers and 70 million doses in 2018. The prices of IPV had significantly increased at the start of the 2019-2022 tender but have since been driven down with the arrival of new manufacturers offering the vaccine at more affordable prices.

- Building on improved supply and SAGE recommendations, Gavi's IPV programme has made significant progress over the last four years. Since April 2019, all countries have one dose of IPV into their routine schedules - reaching a coverage rate of 75% in 2021 - and all but 6 countries have implemented catch-up vaccination activities for birth cohorts missed during the period of supply constraints[6].

- Support for the introduction of second dose IPV (IPV2) in routine programmes is progressing. To date, 34 Gavi IPV-eligible countries have introduced IPV2.

- However, the impact of COVID-19, capacity gaps, and multiple competing priorities have resulted in introduction delays for the already approved countries and fewer submissions of new applications for IPV2 and IPV catch-up support. There are 24 countries that have not yet applied or completed the full application cycle[7] - and 5 countries have been approved to introduce IPV2 but have not yet done so[8].

[6] Democratic People's Republic of Korea, Djibouti, the Gambia, Guinea-Bissau, Lesotho and Nepal
[7] Benin, Burundi, Cambodia, CAR, Comoros, Congo, DPRK, Ethiopia (awaiting IRC approval), Ghana, Guinea, Guinea-Bissau, Haiti, Kenya, Kiribati, Lao, Lesotho, Liberia, Malawi, Mauritania, Mongolia, Sao Tome and Principe, Solomon Islands, Tanzania, Zambia
[8] Djibouti, Cote d'Ivoire, Myanmar, Timor-Leste, Mozambique