Subject	**Vaccine Investment Strategy 2024: Proposed Shortlist**
Agenda item	**11**
Category	**For Decision**

Section A: Executive Summary

In May/June 2023, the Secretariat presented to the Programme and Policy Committee (PPC) and Board the first phase of the Vaccine Investment Strategy (VIS) 2024 including evaluation frameworks to assess a proposed longlist of vaccines for endemic disease prevention, vaccines for epidemic-prone disease and a COVID-19 programme from 2026. The Board approved the longlist of vaccines and evaluation frameworks. The purpose of this paper is to present and seek Board endorsement of the second phase of the VIS 2024 process: the proposed vaccine candidate shortlist. The final decision point on VIS (PPC May 2024, Board June 2024) will consider investment cases on shortlisted candidates in the form of new routine/preventive vaccination programmes, stockpiles, and learning agendas for implementation in Gavi 6.0 (2026- 2030) and beyond. These decisions will be aligned with a decision on the Gavi 6.0 strategy, and implementation will be subject to a successful replenishment.

The PPC recommends to the Board that it approve the following proposals: (1) endemic diseases: develop investment options (including learning agendas) for **tuberculosis** (TB), **group b streptococcus** (GBS), **shigella**, and **dengue** vaccines; (2) epidemic-prone diseases: develop investment options for **hepatitis E** vaccines, and whilst not shortlisting chikungunya and mpox vaccines, develop learning agenda options for consideration; (3) **COVID-19**: develop a time-limited investment option for a COVID-19 programme from 2026.

Section B: Introduction

1.1 The VIS is Gavi's prioritisation process to evaluate vaccines and immunisation products for possible inclusion into the future portfolio. Every five years, through this rigorous, consultative, and transparent process, the Secretariat reviews evidence to identify and assess new and/or under-used vaccines of high public health relevance for Gavi-eligible countries. The VIS facilitates strategic decision-making and provides predictability to countries, and valuable advance signals to manufacturers, and donors for their own planning and future decision- making. It is a fundamental tool in fulfilling Gavi's equity objectives, by shortening the time between life-saving vaccines being available in high-income countries to them being rolled out in lower-income countries.

1.2 The VIS Steering Committee[1] was convened for the third time in Phase 2 to validate the methodology and analysis and recommend vaccines for

1 Provides independent external expert advice to the Secretariat on the strategic questions, methodology and process for the VIS. Chaired by Prof. Helen Rees, it includes 10 independent members with complementary skills selected from an open competitive call and 8 ex officio members representing partners and stakeholders, including a PPC member.

shortlisting. The Steering Committee commended the rigour and comprehensiveness of the analyses as well as the high level of consultation. They acknowledged that the analyses presented were an accurate representation of the vaccines' full value and that any gaps are due to limited data availability at global or regional levels, particularly epidemiological data from affected areas.

1.3 Consultations to reach in-country stakeholders have included a high-level, non-representative survey to Gavi countries in February-March 2023[2] (Phase 1) complemented by in-depth consultations (in-person where possible) with a sub-set of 16 Gavi-supported countries[3] (Phase 2), as well as consultations with civil society organisations (CSOs), one in each phase. In addition, the Secretariat has consulted with disease experts, academics, practitioners, technical partners, and vaccine manufacturers (Appendix 1).

1.4 The PPC reviewed and recommended the VIS proposed shortlist in October 2023. It commended the oversight of the VIS Steering Committee and the multiple opportunities for PPC members to input during the process.

1.5 Further analyses will be carried out to inform final investment cases (and learning agendas) including analyses of the procurement, operational and implementation costs for Gavi and countries, as well as delivery and health system support costs. These will be reviewed by the VIS Steering Committee in March 2024 for final decisions by the PPC/Board in May/June 2024.

Section B: Vaccine Candidates

2. Vaccines evaluated for endemic disease prevention

2.1 Four vaccines were evaluated under the endemic disease prevention evaluation framework (Table 1): **tuberculosis, shigella, group B streptococcus** and **dengue**. Demand, price, health and economic impact were modelled for current Gavi-supported countries and the original 45 countries eligible under Gavi's Middle-Income Country (MICs) Approach[4] to project the impact of future potential Gavi investments for the period 2026-2040.

Table 1. Criteria used for evaluation framework for endemic diseases

Key ranking criteria and weighting used for comparative analysis	Modulating criteria	
• Health impact • Value for money • Equity, social protection • Economic impact • Gavi's comparative advantage	• Global health security impact • Other impact (under 5 health impact) • Broader health system benefits	• Implementation feasibility • Alternate interventions • Contribution to global agenda

[2] Survey to Gavi-eligible countries, yielded 111 responses from 36 Gavi-eligible countries.
[3] Burundi, Cambodia, Cameroun, Chad, Djibouti, DRC, Ethiopia, Kyrgyzstan, Laos, Sao Tome et Principe, South Sudan, Syria, Tanzania, Yemen, Zambia, Zimbabwe.
[4] Gavi's future MICs Approach will be considered in 6.0 strategy design. It currently provides catalytic support for select MICs (including 19 former-Gavi countries) to sustainably introduce rotavirus, HPV and PCV.

2.3 The Secretariat consulted CSOs, the VIS Steering Committee and PPC members to determine how vaccine assessments against the evaluation criteria would be used to prioritise candidates. Based on the information presented and subsequent discussions, the VIS Steering Committee and **PPC recommended to shortlist all four vaccines**, to develop full investment cases including options for accompanying learning agendas.

2.4 **Tuberculosis** vaccines (for adolescents and adults, expected ~2029) were assessed to have high health impact in current Gavi-supported countries. Good data is available on TB burden compared to other diseases and most of the uncertainty is driven by the lack of clarity on the vaccination strategy that will be employed. TB vaccines show good value for money based on procurement cost only but are likely to have large cohort sizes. Gavi is well positioned to work with manufacturers and Alliance partners to proactively shape market outcomes and to address potential market shaping risks that may arise depending on which vaccine is licensed and has a policy recommendation, with the most relevant candidate, GSK and Gates Medical Research Institute's M72/AS01, currently expected around 2029. Bacillus Calmette-Guérin (BCG) vaccines were excluded from the VIS scope as they are already well-used vaccines with a low price. However, second generation BCG vaccines for adults are in scope. The VIS Steering Committee recommended monitoring BCG re-vaccination trials, noting the likely lower price and programmatic feasibility. Whilst TB vaccines are only likely to be licensed towards the end of the 6.0 period with most introductions likely in the Gavi's 7.0 period, programme design, in close collaboration with partners such as The Global Fund, would need to be considered in 6.0. Interest in TB vaccines is high, with WHO initiating a committee to accelerate efforts. A key question for Gavi will be country eligibility given the high burden of disease in middle-income countries (MICs).

2.5 **Group B streptococcus** vaccines (for pregnant women in 2nd-3rd trimester, expected ~2028) represent high health impact with relatively good value for money, providing protection for pregnant women and their babies. The overall strength of evidence available is good, although gaps on burden in low- and middle-income countries remain. There are two leading vaccine candidates in the pipeline, Pfizer's GBS6 and MinnervaX's GBS-NN/NN2. Licensure may be based on a correlate of protection[5], which may pose challenges for regulators and policymakers, and may ultimately require additional effectiveness studies to support a policy recommendation from WHO's Strategic Advisory Group of Experts on Immunisation (SAGE). Gavi investment could help ensure demand generation and could contribute to strengthen antenatal care and maternal services overall.

2.6 **Shigella** vaccines (for infants <1y of age, expected ~2030) could have moderate health impact based on current estimates however, there continues to be uncertainty around disease burden and vaccine data given ongoing

[5]Licensure based on indirect evidence of protection, such as immunological readouts, rather than a direct demonstration of efficacy. Generation of evidence for GBS vaccine licensure through a traditional efficacy trial is not considered feasible due to the very large sample size requirements.

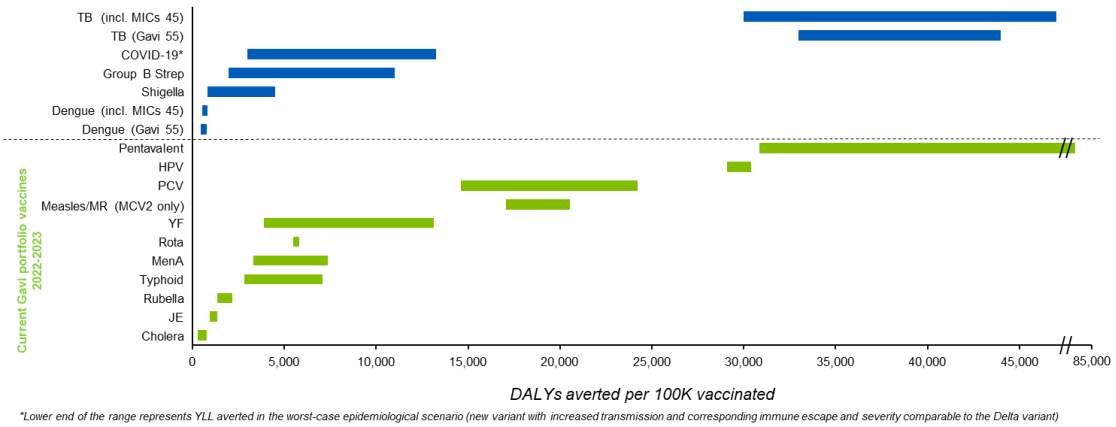
clinical trials. The most advanced quadrivalent Shigella vaccines are currently in Phase 2b, Limmatech's S4V-EPA and GSK's altSonflex. The VIS Steering Committee noted that Shigella is a disease of importance for current Gavi-supported countries, and the continued development of standalone vaccines that will lead to potentially more preferrable combination products is highly encouraged, as well as further consideration of the policy pathway through the development of, for example, an Evidence Considerations for Vaccine Policy (ECVP) document by WHO. Further evidence of a vaccine's potential impact on reducing stunting (and its associated impact on productivity) and anti-microbial resistance (AMR) are important considerations that should be measured in Phase 3 trials.

2.7 **Dengue** vaccines (for children, age of vaccination varies based on transmission intensity in country, already licensed) are estimated to have the lowest health impact compared to TB, GBS and Shigella[6], however significant data gaps in the analysis should be noted: African countries and Yemen were excluded from the health impact modelling due to lack of epidemiological data. The principal analysis is therefore based on only six Gavi-eligible countries[7] where the vaccine could have important regional impact. The VIS Steering Committee noted that the evaluation was not able to capture more recent outbreaks of dengue in Africa and elsewhere[8], and highlighted the increasing risk of outbreaks due to climate change. Disease burden data is better in MICs, and anecdotal evidence and ongoing outbreaks indicate high demand for the vaccine, since outbreaks have a high economic impact and place a significant burden on health systems[9]. Takeda's TAK-003 is licensed by the European Medicines Agency. In the September 2023 SAGE meeting, WHO recommended that the vaccine is introduced for children aged 6-16 years in settings with high dengue transmission intensity. WHO does not recommend the use of this vaccine in low to moderate transmission settings. Merck`s TV003 is in the late stage of a 5-year Phase 3 trial with results expected by end 2024. If not shortlisted, Gavi-eligible countries would not have access to the vaccine at the same time as non-Gavi-eligible countries.

2.8 Vaccines for endemic disease prevention were also compared to current Gavi portfolio vaccines.[10] Health impact of the VIS 2024 candidate vaccines is shown to be within the ranges of those that are in the current Gavi portfolio (Figure 2).

[6] The ranking methodology was used to compare the four vaccines against each other and favoured the extremes. Thus, a score of 0 does not imply no impact, only that it scores lowest of the four vaccines assessed (Annex B).
[7] Cambodia, Haiti, Laos, Papua New Guinea, Solomon Islands, and Timor-Leste.
[8] In 2023, dengue outbreaks have been reported in 12 African countries, including 9 Gavi countries: Burkina Faso, Chad, Côte d'Ivoire, Ethiopia, Guinea, Mali, São Tomé and Príncipe, Senegal, and Sudan.
[9] The methodology employed to capture economic impact does not capture the complete burden on a health system.
[10] Health impact of current Gavi portfolio vaccines was modelled for 2022-2030, except for the malaria vaccine (2021-2035), while that of the VIS candidate vaccines was modelled for 2026-2040 (except for COVID-19, 2026-2030).

Figure 2. VIS 2024 candidate vaccines vs. current portfolio of Gavi-supported vaccines: DALYs averted per 100K vaccinated



**Lower end of the range represents YLL averted in the worst-case epidemiological scenario (new variant with increased transmission and corresponding immune escape and severity comparable to the Delta variant)*

3. Vaccines evaluated for epidemic disease prevention

3.1 Three vaccines were evaluated with the epidemic disease prevention framework for stockpile investments[11]: **hepatitis E, chikungunya** and **mpox.** The VIS Steering Committee and **PPC recommended that the Secretariat develop an investment case for hepatitis E** and continue to monitor mpox and chikungunya and present learning agendas for potential investment.

3.2 In 2018 the Board requested that the Secretariat develop living assessments to monitor the development of vaccines for epidemic preparedness and response. When there is a defined pathway for vaccine licensure or major public health need, the living assessment is developed into an investment case in real time or through VIS if timelines align. The VIS epidemic framework builds on the living assessments and is structured around four key areas: a) disease risk and burden; b) vaccine impact and feasibility; c) fit for Gavi and partners; and d) overall financial cost. In this phase of the VIS, the Secretariat has analysed areas (a)-(c). Given differences in availability of data and greater uncertainty for these vaccines were assessed individually drawing widely on expert input and partner expertise to fill evidence gaps. An indication of data quality is provided as part of the assessment.

3.3 **Hepatitis E** vaccine is **recommended** for development of an investment case. This is the third time hepatitis E is evaluated through a VIS process, with new data now available on efficacy and safety, and evidence from the first vaccine use in Bentiu, South Sudan in a displaced person camp. The Governance Oversight Committee of the International Coordinating Group (ICG) on Vaccine Provision recently agreed to establish a "proof-of-concept" hepatitis E vaccine stockpile for three years with support from the Bill and Melinda Gates Foundation. A hepatitis E vaccine with WHO prequalification (PQ) could be available by end of 6.0[12]. The VIS Steering Committee noted the strong impact

[11] Stockpile investments can include physical stockpiles as well as fungible investments, for example ring-fenced financing or manufacturing capacity for vaccine doses.
[12] A hepatitis E vaccine is available currently but does not have WHO PQ.

that an investment in a relatively small stockpile would have on equity and vulnerable populations, particularly pregnant women with a higher risk of mortality. It also suggested that the Secretariat consider a learning agenda to assess the delivery needs and ongoing effectiveness and safety monitoring on high-risk groups.

3.5 **Chikungunya** vaccines are **not recommended** for the development of an investment case at this time due to the insufficient epidemiological evidence in current Gavi-supported countries and uncertain demand. However, the VIS Steering Committee recommended continued monitoring through a living assessment and that a learning agenda should be considered to help address data gaps. Evaluation of impact is challenging due to poor surveillance and understanding of clinical presentation in Africa. Several vaccines are in Phase 3, including a Coalition for Epidemic Preparedness Innovations (CEPI)-funded candidate, with the earliest expected PQ of a suitable presentation in ~2027.

3.6 **Mpox** vaccines are **not recommended** for the development of an investment case due to insufficient evidence on epidemiology in current Gavi-supported countries and uncertain demand. However, the VIS Steering Committee recommended a living assessment to monitor any changes to the epidemiology and emergence of increased outbreaks of more virulent clades, and a learning agenda to better understand the epidemiology, feasibility of implementation and potential uptake. The VIS Steering Committee noted the ethical and equity implications of not investing in a stockpile at this time, which would deprive access to countries historically reporting and continuing to experience mpox outbreaks.

4. COVID-19 programme from 2026

4.1 In June 2023, the Board approved a COVID-19 programme for 2024-2025, focusing on high priority groups as per the SAGE recommendation. Through the VIS 2024, the Secretariat is evaluating the value of continued investment in COVID-19 from 2026. Health impact modelling estimated impact of an annual booster dose programme with an mRNA product targeting both the over 60 and health worker population from 2026-2030 (as a proxy for all high priority groups). Two epidemiological scenarios were considered, the first assuming a gradual evolution of the virus with consistent severity and the second assuming a new variant with increased transmission and severity. Significant limitations should be noted due to limited availability of current epidemiological data, ability to predict vaccine effectiveness and evolution of emerging variants, severity of disease, transmission, country demand and coverage levels.

4.2 The VIS Steering Committee and **PPC recommended the Secretariat develop a time-limited programme** and take an iterative approach due to the changing nature of the virus and immunity. The Secretariat is currently updating the health impact modelling and considering a ~2-3-year approach balancing the need to manage this uncertainty while providing predictability to countries and manufacturers.

5. Tailored support to reach priority populations with vaccines

5.1 In June 2023 the Board requested that the Secretariat undertake further analyses to evaluate the potential value of providing support to develop, strengthen and deliver vaccines at new and existing touchpoints for specific target populations. In October, the Secretariat presented to the PPC an approach to analyse the value of tailored support to reach two high-priority target groups: pregnant women/newborns and health workers, including prioritised vaccines. The PPC saw merit in taking a tailored health systems approach for priority target groups recognising the challenges and opportunities of integrating maternal vaccines into antenatal care, and opportunity to build on prior COVID-19 investments and support pandemic preparedness efforts through a health worker immunisation programme. However, in order to provide a more holistic review of the value of supporting other target groups and to better understand trade-offs, the PPC requested that this be reviewed as part of the development of Gavi's 6.0 Strategy through the revised Health Systems Strengthening strategy (Appendix 3). This request is in line with the discussion of a proposal for a health worker immunisation platform as part of Gavi's Pandemic Prevention Preparedness and Response (Paper 10a), which was not supported by the PPC but will be considered alongside other potential investments as part of the 6.0 design process.

Section C: Actions requested of the Board

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

For vaccines for endemic disease prevention:

a) **Request** the Secretariat to develop possible investment options for further consideration for tuberculosis, group B streptococcus, shigella and dengue vaccines;

For vaccines for epidemic-prone diseases:

b) **Request** the Secretariat to develop possible investment options for further consideration for hepatitis E vaccines;

c) **Request** the Secretariat to monitor and update living assessments for Chikungunya and Mpox vaccines, including potential investments in learning agendas in consultation with WHO and other partners, and;

For COVID-19 from 2026:

d) **Request** the Secretariat to develop possible investment options for further consideration of a continued time-limited COVID-19 vaccine programme from 2026.

Annexes

Annex A: Implications and Anticipated impact

Annex B: Vaccines for endemic diseases – Summary of cross-vaccine analyses

Additional information available on BoardEffect

Appendix 1: (in PPC Library – Additional materials for October 2023 PPC meeting): Appendix 1 to Doc 7 Evaluation methodologies and consultation approach for vaccines

Appendix 2: (in PPC Library – Additional materials for October 2023 PPC meeting)**:** Appendix 3a-3h to Doc 7 Vaccine-specific analyses

Appendix 3: Evaluation of tailored support to reach priority populations with vaccines