

**SUBJECT: PANDEMIC INFLUENZA PREPAREDNESS**

**Agenda item: 13**

**Category: For Decision**

### **Section A: Summary**

- This report presents a detailed briefing on pandemic influenza in response to the June 2018 Board request as part of the Vaccine Investment Strategy (VIS) 2018. It includes a review of the landscape, gap analysis and preliminary assessment of potential options for Gavi engagement.
- The Board is asked to approve a learning agenda (with financial implications of approximately US\$ 4 million from 2019-2022), to be developed with WHO, on the use of routine immunisation of healthcare workers with seasonal influenza vaccines to strengthen countries' pandemic preparedness.

### **Section B: Detailed Briefing on Pandemic Influenza**

#### **1. Introduction**

- 1.1 The Gavi Board approved an approach and set of evaluation criteria for considering vaccine investments for epidemic preparedness and response in June 2018, within the overarching Vaccine Investment Strategy (VIS) 2018.<sup>1</sup> This approach comprises three steps: firstly, identification, with WHO, of vaccines for consideration; secondly, development of a 'living assessment' as vaccine development progresses; and finally, a full investment case for Board consideration. Progression through each stage is determined by pre-defined triggers.<sup>2</sup>
- 1.2 Given that pandemic influenza meets the 'trigger' for an investment case<sup>3</sup>, the Board requested the Secretariat, in consultation with WHO and experts, to prepare an extensive briefing on pandemic influenza preparedness and bring a related investment case if appropriate.<sup>4</sup> As pandemic influenza is an outlier in terms of both the exceptional global threat that it poses and the

<sup>1</sup> <https://www.gavi.org/about/governance/gavi-board/minutes/2018/6-june/minutes/07---vaccine-investment-strategy---short-list/>

<sup>2</sup> A 'living assessment' would be developed once preliminary safety and immunogenicity data is available for the vaccine (Phase 2a/b). An investment case would be developed once there is a defined pathway to vaccine licensure in the short-term (e.g., 1 year), major public health need or update of a WHO use recommendation.

<sup>3</sup> Based on the availability of licensed product(s) and WHO recommendation

<sup>4</sup> The focus of this briefing is on pandemic influenza, however seasonal influenza is important for pandemic preparedness as demand for seasonal influenza supports global manufacturing capacity.

extent of current risk mitigation efforts, this briefing draws from the evaluation framework, but also includes more detail on the role of WHO and the broader pandemic preparedness and response landscape.

- 1.3 Gavi's role in pandemic influenza has been discussed at multiple points in the past. Following the 2005 H5N1 pandemic, the Board recommended that Gavi focus on safeguarding routine immunisation in an influenza pandemic and increasing uptake of vaccines that contribute to secondary infections in a pandemic (e.g., pneumococcal). During the 2009 H1N1 pandemic, WHO did not propose a specific role for Gavi in the response, and following the pandemic WHO initiated a number of activities to improve preparedness. This analysis reconsiders Gavi's potential role in pandemic influenza preparedness based on assessment of current needs and gaps and in the context of Gavi's comparative advantage relative to other actors.<sup>5,6</sup>
- 1.4 Based on extensive consultations<sup>7</sup> and a gap analysis, the Secretariat focused the briefing on consideration of the potential impact of: a) reserving/subsidising production capacity and b) market signals for new vaccine technology **to improve pandemic vaccine supply**; establishing routine immunisation in priority groups **to improve vaccine delivery in a pandemic**. Please refer to Appendix 1 for additional detail beyond what is summarised in this report.

## 2. Disease risk and burden

- 2.1 Influenza viruses pose a global threat because they are highly diverse, evolve rapidly in human and animal hosts, and can cause disease of varying severity (including secondary bacterial infections which may require antibiotics and contribute to antimicrobial resistance). Annually, the circulation of seasonal influenza viruses causes 3-5 million cases of severe illness and between 290,000 and 650,000 respiratory deaths. Influenza pandemics occur with the emergence of a new influenza sub-type to which the human population has limited immunity and which is able to spread efficiently between human hosts. Together with classic public health measures, vaccines play a critical role in reducing the severity and transmission of both seasonal and pandemic influenza.
- 2.2 As exemplified by the 1918 pandemic, which killed between 50 and 100 million people, influenza pandemics represent a major global threat in terms

---

<sup>5</sup> Gavi has also considered support for routine influenza immunisation in the past, focusing on impact on seasonal influenza rather than pandemic preparedness. Most recently, in Phase 2 of the VIS 2018, routine immunisation in pregnant women was assessed but not considered to merit a case for investment based on low projected mortality and morbidity impact.

<sup>6</sup> This briefing focuses on pandemic preparedness. In the event of a pandemic, Gavi would work with WHO and partners to support the response in Gavi-supported countries through existing policies (e.g., reprogramming of HSS through the Fragility, Emergencies, Refugees Policy) or other efforts.

<sup>7</sup> The VIS 2018 Phase 3 country consultations included 96 survey responses and 28 discussions with stakeholders from 17 countries. The VIS Steering Committee provided technical and strategic guidance, and experts were consulted on specific topic areas.

of morbidity, mortality and impact on health systems and economies. The 1918 pandemic killed almost as many South Africans as Americans and was considered the worst natural disaster in the country's history. The single patient group most likely to die was pregnant women with a death rate of 23-71%. Analyses show that the impact of pandemics is disproportionately high in low income countries, exacerbated by weak health systems and limited access to interventions for prevention and treatment.<sup>8</sup> A modelling analysis of a potential future pandemic projects that 96% of deaths would occur in non-OECD countries. To put the overall risk of influenza pandemics in perspective, a recent study estimates that a severe influenza pandemic could have a death toll 2500 times higher than the 2013-2016 Ebola virus disease outbreak.

### 3. Current landscape and strategic context

- 3.1 As the agency responsible for leading global pandemic influenza preparedness and response efforts, WHO oversees a number of activities to: strengthen pandemic and epidemic preparedness (such as the International Health Regulations and the Joint External Evaluation<sup>9</sup>); support the development of global and national influenza programmes (such as the Global Influenza Programme, Global Influenza Surveillance and Response System, National Pandemic Preparedness plans); and strengthen supply security and access to both seasonal and pandemic influenza vaccines (such as the Global Action Plan for Influenza Vaccines 2006-2016, and the Pandemic Influenza Preparedness [PIP] Framework). A new SAGE Working Group on Influenza Vaccines has been established and is expected to report in 2019/2020.
- 3.2 Alliance and broader partners are also engaged in specific efforts to support pandemic influenza preparedness and response that complement WHO's activities. For example, the US Centers for Disease Control and Prevention (CDC) and One Health Partners play a role in influenza surveillance and the links between human, animal and environmental health; the Taskforce for Global Health's Partnership for Influenza Vaccine Introduction (PIVI) programme supports establishment of seasonal influenza programmes in MICs; UNICEF and PAHO procure influenza vaccine for routine immunisation in developing countries; the Bill & Melinda Gates Foundation, Sabin and others are supporting R&D for next generation/universal influenza vaccine candidates; and the World Bank, through its Pandemic Emergency Financing Facility, has a role in financing for pandemic response. Further information on the current landscape of activities and roles and responsibilities of different actors is provided in Appendix 1.
- 3.3 WHO is currently developing a new 'Global Influenza Strategy 2018-2030' (expected by Q1 2019, see Appendix 2 for draft summary) which consolidates existing efforts, focusing on three strategic priorities:

---

<sup>8</sup> Risk mitigation efforts include surveillance (GISRS), risk assessment of new/ emerging strains (PISA), data and sample sharing, and capacity for rapid pandemic vaccine production.

<sup>9</sup> Within the JEE process, 16 of 19 indicators are focused on, or relate to, influenza.

- I. strengthening pandemic preparedness and response for influenza;
  - II. expanding seasonal influenza prevention and control policies and programmes to protect the vulnerable (highlighting health care workers and/or other high-risk groups); and,
  - III. promoting research and innovation to address unmet public health needs.
- 3.4 This briefing has been developed in close consultation with WHO, reflecting both their guidance and experience from existing programmes and the new strategy. The analysis considers how Gavi's efforts could be integral to addressing these priorities, including contributing to equity and sustainability, addressing the bottlenecks described in the 2009 pandemic and expanding WHO's external partnerships.

#### **4. Timely supply of pandemic vaccine**

- 4.1 The 2011 PIP Framework secures, in real time, up to an estimated 425 million doses of vaccine for WHO to distribute in an influenza pandemic to countries without access.<sup>10</sup> However, limitations of current vaccine technology constrains the potential impact of the PIP supply agreements. Since vaccine viruses have to be matched to the pandemic strain, vaccine cannot be produced in advance and stockpiled. In addition, the speed of vaccine production is slow relative to pandemic spread: it can take ~5 months or longer for the first dose of pandemic vaccine to be produced.
- 4.2 Using WHO ideal assumptions for vaccine production speed, the Secretariat analysed the availability of PIP doses relative to the evolution of a pandemic based on data from the 2009 H1N1 pandemic.<sup>11</sup> In an 'optimistic' scenario, only up to ~30 million doses would be available prior to the hypothetical pandemic peak. This is enough to cover the smallest priority group in PIP countries, healthcare workers, but no others. The majority of doses would become available later in the pandemic when the mortality/morbidity impact of vaccination would be substantially less.
- 4.3 One approach to increase the timely availability of pandemic vaccine would be for Gavi to pay manufacturers a fee to hold part of their production and/or to subsidise expanded production to increase total global volume. While this would leverage the Alliance's market shaping expertise, the estimated costs to reserve sufficient capacity for all high priority groups in Gavi-eligible countries are high: ~US\$ 400-US\$ 850 million per year to reserve vaccine production, excluding the costs of pandemic doses, vaccine delivery and production capacity expansion. There is also significant risk that the yield would be less than projected or additional doses would be required. Based on the assessment of costs and risks, the VIS Steering Committee (SC) and PPC supported the view that Gavi should not further explore this approach.

---

<sup>10</sup> WHO PIP Framework website (last accessed August 2018); personal communication with WHO; includes both donated vaccine and vaccine available at affordable pricing

<sup>11</sup> 2009 was widely considered to be a 'best-case' scenario given the subtype, speed of transmission, disease severity and geographic source. See Appendix 2 for additional detail on assumptions.

4.4 Alternatively, Gavi could provide financial incentives (e.g., similar to an Advance Market Commitment) for new technologies such as novel platforms and cross-protective vaccines, which could reduce vaccine production time or enable pre-pandemic stockpiling. Based on expert consultation, this is not recommended at this time given uncertain timeframes and the limited value of a signal given barriers are likely to be technical or scientific rather than due to lack of investment. However, the Secretariat will continue to monitor the landscape including the development of potential alternatives to vaccines in a pandemic.<sup>12</sup>

## 5. Timely delivery of pandemic vaccine

5.1 Even with timely availability of pandemic vaccine through PIP, lack of national systems for regulatory approval and vaccine delivery may delay administration of vaccines in priority groups. This could also limit the future impact of next generation influenza vaccines. A 2011 External Review for WHO<sup>13</sup> emphasised the lack of national capacity to accept, approve and distribute pandemic vaccine to priority groups in the 2009/2010 pandemic. As an indicator of countries' limited capacity to utilise pandemic vaccine, in 2009 only 78 million of 120 million donated doses were delivered to countries.<sup>14</sup>

5.2 One solution is to strengthen routine immunisation programmes for delivery of seasonal influenza vaccine, since key activities for routine immunisation provide the foundation for pandemic response.<sup>15</sup> Preliminary analysis of the 2009/2010 pandemic by WHO/CDC found that countries with functional, public seasonal influenza programmes were over twice as likely to get influenza vaccine before the end of the pandemic as countries without.

5.3 Given the systems impact, a strategy for routine immunisation in one priority group would likely accelerate vaccine delivery to all high priority groups in a pandemic. Of the priority groups for seasonal influenza immunisation, there is a strong case for focusing on healthcare workers: contribution to maintaining health systems; relatively low cost given the small cohort size<sup>16</sup>; link with the Universal Health Care 2030 agenda; and ethical principles of justice, given their increased risk. There is also evidence that healthcare workers' acceptance of influenza vaccine influences community vaccine confidence and uptake. A delivery platform would also enable more efficient immunisation of healthcare workers against other vaccine preventable diseases (e.g., hepatitis B) and emerging diseases (e.g. Ebola).

---

<sup>12</sup> Novel vaccines and antibodies offering cross strain protection or long-term protection and new vaccine, platform and delivery technologies were explored. New therapeutics were not explored.

<sup>13</sup> 2011 Report of the Review Committee on the Functioning of the International Health Regulations (2005) in relation to Pandemic Influenza A (H1N1) 2009

<sup>14</sup> In order to receive doses countries had to provide information to WHO on planning for regulatory approval and vaccine delivery

<sup>15</sup> E.g., regulatory approval, policy development, surveillance, delivery platform, pharmacovigilance

<sup>16</sup> For the period of 2020-2035, the total cost of vaccine procurement for routine immunisation of healthcare workers in Gavi-eligible countries would be ~US\$ 56 million compared with ~US\$ 991 million for pregnant women. This excludes costs for establishing the platform and delivery.

## 6. Learning agenda for routine immunisation of healthcare workers

- 6.1 While routine immunisation in a priority group has significant potential for impact by improving vaccine delivery in a pandemic, there are a number of outstanding issues and open questions. In consultations, country stakeholders anticipated challenges to establishing routine immunisation programmes for healthcare workers. They highlighted the need for: regulatory processes; approaches to define and register the population; development of immunisation policy for adults; and evidence-based approaches to increase vaccine acceptance. There are also questions as to how this approach could best support accelerated vaccine delivery in a pandemic and strengthen epidemic preparedness beyond influenza.
- 6.2 A learning agenda would enable key knowledge and evidence gaps to be addressed and could also inform consideration of any further investment. This would be developed in close collaboration with WHO, in support of the 2018-2030 Global Influenza Strategy objectives, and with other partners working in influenza and epidemic preparedness. Based on preliminary discussions, the learning agenda might include: review of existing policies and programmes for healthcare worker immunisation/occupational health; regulatory processes; policy requirements for the healthcare worker population, including consideration of sub-populations such as pregnant women; approaches to identifying and following-up healthcare workers, recognising that they may be a diverse population; use of vaccine and requirements for timely delivery; and an overarching evaluation programme to understand barriers, facilitators, links with other investments in epidemic preparedness and alignment with other Gavi investments/programmes. Country selection would take into account factors such as vulnerability to outbreaks, size of national healthcare worker population and any previous investment in influenza vaccine delivery (such as PIVI). Learning agenda studies may be focus on sub-national populations. Partners have indicated that Gavi's role in supporting vaccine use and focus on strengthening immunisation systems would be a substantial contribution to broader global efforts.
- 6.3 The scope of the learning agenda, the evaluation approach and alignment with the broader influenza public health research agenda would be explored with partners. Where appropriate, the learning agenda would leverage existing tools and learnings from other efforts (e.g., the work of PIVI to promote seasonal influenza immunisation in MICs).

## 7. Implications

- 7.1 *Financial implications:* The costs associated with the learning agenda are estimated to be approximately US\$ 4 million from 2019-2022<sup>17</sup>. For 2019, resources will be managed within the existing approved budget, while for

---

<sup>17</sup> Of the US\$ 4 million, US\$ 2 million is for 2019-2020, of which US\$ 1 million is for 2019. Projections assume costs associated with vaccine procurement; adaptation of existing tools; technical assistance to support policy and programme development; meetings; and development of evaluation tools.

2020 and beyond, resourcing would be addressed as part of the regular budgeting process.

- 7.2 *Gender implications:* Both seasonal and pandemic influenza cause disproportionate morbidity and mortality burden in pregnant women. Given that the majority of healthcare workers in low income countries are female it will also be important in the learning agenda to consider how the needs of the sub-population that are also pregnant would be addressed. The recommendation in the PREVENT guidelines as to the 'presumptive inclusion of pregnant women' in vaccine research and delivery programmes should be considered in the context of pandemic influenza preparedness and the development of a healthcare worker immunisation programme.<sup>18</sup>

### **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 development of a learning agenda to assess the feasibility and impact of routine influenza immunisation of healthcare workers to support epidemic and pandemic influenza preparedness;
- b) **Note** the financial implications associated with the above approval for 2019-2022 are expected to be approximately US\$ 4 million, comprised of approximately US\$ 1 million in 2019 (which the Secretariat will strive to absorb from the Board-approved Partners' Engagement Framework (PEF) budget for that year), US\$ 1 million in 2020 and US\$ 2 million in 2021-2022.

### **Annexes**

**Annex A:** Implications/Anticipated impact

### **Additional information available on BoardEffect**

**Appendix 1:** Pandemic Influenza Detailed Briefing

**Appendix 2:** Summary of Draft WHO Global Strategy for Influenza 2018-2030

### **Additional reference materials online:**

VIS internet page: <http://www.gavi.org/about/strategy/vaccine-investment-strategy/>

---

<sup>18</sup> Draft Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) guidelines (in preparation); personal communication