

**SUBJECT: TYPHOID CONJUGATE VACCINE SUPPORT WINDOW**

**Agenda item: 08**

**Category: For Decision**

### **Section A: Introduction**

The purpose of this paper is to review the case for typhoid conjugate vaccine (TCV) and summarise the discussions of the Programme and Policy Committee (PPC) on TCV to request the Board to approve the opening of a country support window for TCVs.

TCVs have a long history:

- TCVs were prioritised in the 2008 Vaccine Investment Strategy (VIS);
- TCV was not reviewed in the 2013 VIS as it was already prioritised and included in Gavi's financial forecast. The Board was reminded that a support window would be opened once a suitable vaccine obtained WHO pre-qualification (PQ);
- At the 2017 June meeting, the Board was informed that the Secretariat would update analyses if WHO recommendations and PQ were obtained before the end of 2017; and
- The Strategic Advisory Group of Experts on Immunization (SAGE) October 2017 meeting provided strong recommendations on TCV use and one vaccine is anticipated to receive WHO PQ in Q4 2017. As WHO PQ is imminent and to avoid delays in opening a funding window, the Secretariat presented updated analyses and proposed to the October 2017 PPC the opening of a funding window.<sup>1</sup>

The October 2017 PPC recommends to the Board to approve the opening of a country support window given that TCV is comparable to current Gavi funded vaccines on measures of health impact and costs per deaths averted<sup>2</sup> and is strongly aligned to Gavi's mission and strategic goals focusing on health impact, equity, new vaccine uptake and market shaping.

The Audit and Finance Committee at its meeting on 19 October 2017 noted that it had reviewed the financial implications of this and other potential funding decisions that may be considered by the Board and concluded that these decisions could be approved by the Board in accordance with the Programme Funding Policy.

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<sup>1</sup> Previous decisions were made on the condition of obtaining WHO PQ (e.g. Japanese encephalitis) to avoid delays in opening a funding window.

<sup>2</sup> These metrics were used in the 2013 VIS and are planned to be used in the 2018 VIS.

## **Section B: Facts and Data**

### **1. Typhoid Overview**

- 1.1. Typhoid fever has been eliminated from industrialised nations but still remains a serious public health concern for Gavi countries. Those without access to clean water, food and sanitation remain at highest risk. Current estimates show annual typhoid deaths ranging from 145,000 to 223,000 and annual cases from 11-22 million.<sup>3,4,5,6</sup> New evidence indicates that a major burden of severe disease occurs in the younger age, meaning vaccination at an earlier age (< 2 years of age) is key to controlling this disease.
- 1.2. Although treatable through the use of appropriate antibiotics, there is an increasing number of typhoid infections that are antimicrobial resistant (AMR), including strains resistant to multiple drugs. The AMR threat creates additional complications, ultimately increasing treatment costs and complexities around treatment administration (e.g. intravenous), limiting access to treatment, and potentially increasing case fatality rates. Prior to the availability of antibiotics, case fatality rates were as high as 20%, so with increased AMR we can expect to see increasing mortality. WHO has released an objective tied to Strategic Development Goal 3 focused on “reduc[ing] incidence of AMR for at least one organism by 10% by 2023”, and TCVs represent an important opportunity to achieve this objective.
- 1.3. One TCV product has been licensed in India since 2013 and is expected to obtain PQ by the end of 2017. There are five additional products in the pipeline with anticipated PQ timelines from 2019-2022. The Alliance has an opportunity now to catalyse the market, increasing both supply and demand for TCVs, thus creating supply security and long-term competition to ensure appropriate products and prices for Gavi countries. The Secretariat has initiated the development of a typhoid supply and procurement roadmap to guide market shaping efforts to be completed by early 2018. See Appendix 1 or Annex B for additional details on disease overview and market analysis.
- 1.4. In October 2017, SAGE reviewed evidence and noted the continued high burden of typhoid fever and the alarming increase in AMR of *Salmonella* Typhi (S. Typhi) in low- and middle-income countries. SAGE re-emphasised the importance of programmatic use of typhoid vaccines in controlling endemic disease and the need for countries to strengthen surveillance of typhoid fever and monitor AMR strains and epidemic disease.

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<sup>3</sup> Crump JA et al. The global burden of typhoid fever. Bull WHO 2004;82:346–53

<sup>4</sup> Mogasale V et al. Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment. Lancet Glob Health 2014;2(10):570-80

<sup>5</sup> GBD 2016 Global, regional, and national under-5 mortality, adult mortality, age-specific mortality, and life expectancy, 1970-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1058–1150

<sup>6</sup> Antillon M et al. The burden of typhoid fever in low- and middle-income countries: A meta-regression approach. PLoS Negl Trop Dis 2017;11(2): e0005376

- 1.5. SAGE indicated that TCVs were safe and recommended use for infants and children over 6 months of age as a single dose and if feasible, a catch-up of up to 15 years of age. SAGE did not recommend a booster. At the country level, decisions on the preferred immunisation strategy should be based on disease burden analysis, availability and quality of surveillance data, affordability, and operational feasibility. SAGE also recommended prioritisation of TCV to countries with the highest burden of disease or AMR S. Typhi as well as the use of typhoid vaccines to respond to confirmed outbreaks.
- 1.6. Although co-administration data exists for Measles and Measles-Rubella, SAGE noted the need for co-administration data with other routine childhood vaccines.<sup>7</sup> During the PPC discussions, WHO indicated that the lack of additional co-administration data should not be a barrier to introducing TCV as the data can be generated with early vaccine introductions, which has been done with other new vaccines. However, the data is desirable and all efforts should be made to generate the data as part of the TCV use learning agenda.

## **2. Demand Forecast, Impact Analyses and Estimated Financial Implications**

- 2.1. The Secretariat developed demand forecasting scenarios through applying the same methodology used for its current portfolio of vaccines and Board approved policies<sup>8</sup>. The Vaccine Implementation (VI) Typhoid Sub-team (see Appendix 2 for Terms of Reference) served as the expert group.
- 2.2. The vaccination strategy modelled follows SAGE recommendations and assumes 1 dose routine administered at 9 months of age and catch-ups of up to 15 years of age<sup>9</sup>. Both national and sub-national strategies were modelled. This paper presents the estimated financial implications and impact for the national strategy assuming supply constraints.
- 2.3. It is anticipated that the first country applications can be submitted in the first half of 2018 followed by the first introduction in the first half of 2019. To develop the forecast, the Secretariat used all information available; however as TCV is a new programme, this information is limited and subsequent forecasts incorporating newer information may have significant variances.
- 2.4. The demand forecast scenarios were used as a key input for the Integrated Portfolio Management (IPM) Tool<sup>10</sup> and analyses by Yale University to estimate the health impact of Gavi-supported TCV introductions. Both models estimated Gavi's investment in TCV to be comparable to current

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<sup>7</sup> [http://www.who.int/immunization/policy/sage/SAGE\\_oct\\_2017\\_meeting\\_summary.pdf?ua=1](http://www.who.int/immunization/policy/sage/SAGE_oct_2017_meeting_summary.pdf?ua=1)

<sup>8</sup> Current policies on Eligibility and transition, co-financing, and Health System and Immunisation Strengthening Support (HSIS) were used.

<sup>9</sup> SAGE recommends TCV use over 6 months of age and programmatically suggested incorporation at existing touchpoints (e.g. 9 months or second year of life); however exact timing should be a country-driven decision.

<sup>10</sup> IPM tool is being used for 2018 VIS analyses.

Gavi funded vaccines from both health impact and value for money (costs per deaths averted)<sup>11</sup>. Please refer to Annex B for more information on demand forecast and impact modelling.

- 2.5. Although supply is initially anticipated to be constrained, forecasted new market entrants are expected to significantly increase supply availability by 2022-2023. The timing of India's self-financed introduction could affect supply availability to Gavi supported countries, thus it is important to maintain an ongoing understanding of country plans and a focused effort on market shaping activities.
- 2.6. For the supply constrained scenario, following the national immunisation strategy and assuming a public price of US\$ 2 per dose<sup>12</sup>, the opening of an application window has forecasted financial implications of approximately US\$ 85 million from 2019-2020.<sup>13</sup>
- 2.7. As the typhoid programme continues to be rolled out in 2021-2025, TCVs will account for a larger percentage of Gavi's total programme spend. The 2021-2025 estimate is US\$ 865 million<sup>14</sup>. However, these values rely on a number of assumptions creating uncertainty and significant potential variance. We expect the level of uncertainty to decrease as the programme is implemented.

### 3. Implementation Considerations

- 3.1. As with any new vaccine entering into Gavi's portfolio, there is a high level of uncertainty on demand and supply forecasts. This uncertainty is anticipated to continue until a long term investment is approved and discussions on country interest and market shaping efforts can begin.
  - (a) It is proposed that Gavi and countries will co-finance a single dose routine programme, paying for the vaccine procurement costs. Gavi will provide a vaccine introduction grant (VIG)<sup>15</sup>.
  - (b) It is also proposed that Gavi will fund a one time, single dose catch-up vaccination administered to children up to 15 years of age, paying for the vaccine procurement costs and related operational costs<sup>16</sup>.

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<sup>11</sup> Gavi's investment in TCVs are estimated to avert between 0.3 and 0.7 deaths per 1,000 fully vaccinated person, similar to Japanese Encephalitis (JE) and Rotavirus and with an estimated cost per deaths averted of US\$ 6,580 and US\$ 4,190, similar to Rotavirus, JE and Pneumococcal Conjugate Vaccine. Note these are point estimates provided per IPM and Yale, respectively, and more information can be found in Annex B.

<sup>12</sup> Final price will be determined upon completion of the tender.

<sup>13</sup> These amounts are linked to programmatic years. Per the Financial Forecast Update to be presented to the Audit and Finance Committee on 19th October 2017, the amount is approximately US\$ 102 million for 2016-2020 strategic period based on an anticipated disbursement basis (i.e. cash flow year).

<sup>14</sup> Assuming US\$ 2 per dose for the entire period, including vaccine procurement, VIGs and op costs support.

<sup>15</sup> In line with the Health System and Immunisation Strengthening Framework.

<sup>16</sup> *ibid*

- (c) Countries can consider sub-national introductions if sufficient data are available. Note sub-national introduction will change cost and impact estimates.
- 3.2. It is anticipated that countries, particularly those in Africa, will require targeted activities (e.g. generation of better disease burden data or cost effectiveness analyses) to make informed decisions regarding TCV introduction. The Alliance will coordinate with partners, in particular the Typhoid Vaccine Acceleration Consortium (TyVAC), which has the aim to accelerate evidence-based introduction of new TCVs.<sup>17</sup>
- 3.3. Those at highest risk of typhoid, generally represent the most disadvantaged groups within Gavi countries, thus linkages to Gavi's current investments in coverage and equity will be important. Unlike other vaccines supported by Gavi (except oral cholera vaccine (OCV)), the need for typhoid vaccination may decrease as countries work toward Strategic Development Goal 6 to improve access to safe water and sanitation<sup>18</sup>.
- 3.4. Typhoid outbreaks may occur in high burden countries, however data are limited. Therefore, the VI Typhoid sub-team currently recommends to focus on the integration into country's routine immunisation systems and to conduct preventative catch-ups in endemic countries, which will prevent outbreaks from occurring. The sub-team will be tasked to monitor the situation, implement processes to allow allocation of vaccines for outbreaks if needed, and report back to the PPC and Board.
- 3.5. Like other vaccines such as OCV or Japanese Encephalitis (JE), where a vaccine market did not exist, Gavi's investment in TCV will catalyse vaccine use and incentivise manufacturers. The Alliance should use this opportunity to answer scientific and programmatic questions, such as how to use TCVs sub-nationally, what is the impact of TCV on AMR, co-administration with other vaccines, integration with other interventions (e.g. WaSH) and help countries with decision making and prioritisation of TCVs by improving in-country surveillance and burden estimates. The Secretariat will provide regular updates to the PPC and Board as well as a formal report no later than two years after the first introduction.

#### **4. Overview of PPC Discussions**

- 4.1. The members of the PPC were supportive of opening the funding window, citing that the manufacturers have fulfilled the Alliance's request to develop a better vaccine that is safe and effective with an appropriate and sustainable price that can be used in younger ages with a longer duration of protection. The PPC also expressed that opening a funding window would

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<sup>17</sup> TyVAC, which is funded by Bill & Melinda Gates Foundation, is a partnership between the Center for Vaccine Development at the University of Maryland School of Medicine, Oxford Vaccine Group at the University of Oxford, and PATH, an international non-profit. TyVAC will focus on generating new evidence on typhoid disease burden, antimicrobial resistance, cost-effectiveness, health impact analyses, and regional data on TCVs. TyVAC will also conduct 2 comprehensive cost-effectiveness studies in Nepal and Malawi.

<sup>18</sup> <https://sustainabledevelopment.un.org/sdg6>

provide linkages to Gavi's mission and objectives, particularly focusing on vaccine uptake, health impact, coverage and equity, and market shaping.

- 4.2. Although the PPC recommended the opening of a funding window, the PPC requested that the Secretariat and partners work to address the existing knowledge gaps through the learning agenda. Gaps identified by the PPC included co-administration, responding to outbreaks with vaccination, and ensuring informed country decision making focused on improving in-country burden estimates as well as understanding the cost implications of adding TCVs to immunisation programmes.
- 4.3. The PPC also discussed what would be the potential implications of delaying the decision to 2018 VIS timelines, however given the negative repercussions of this delay on health impact, market shaping, and operational understanding, the PPC members agreed with taking a decision ahead of 2018 VIS timelines.

### **Section C: Actions requested of the Board**

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

- a) **Approve** the opening of a funding window for TCVs subject to the Secretariat receiving confirmation of WHO PQ of a vaccine such that in 2018, the Secretariat can invite country proposals for support from Gavi eligible countries.
- b) **Note** that the financial implications associated with the above approval for the period of 2019-2020 are expected to be approximately US\$ 85 million, which has been taken into account in the financial forecasts to be presented to the November 2017 Board for the 2016-2020 period.
- c) **Request** the Secretariat to develop a process to enable allocation of vaccines in Gavi-supported countries if needed in case of a typhoid outbreak and if requested by WHO.
- d) **Request** that, no later than two years from the first country introduction and in addition to regular updates, the Secretariat formally report back to the PPC and Board on lessons learned from initial country introductions and outbreak usage.

**Annexes**

**Annex A:** Implications/Anticipated Impact

**Annex B:** Background and Overview of Analyses

**Annex C:** Investment Framework

**Additional information available on BoardEffect**

**Appendix 1 (*in October 2017 PPC meeting book*):** Report to the Gavi Alliance Programme and Policy Committee: Typhoid Conjugate Vaccine

**Appendix 2:** Vaccine Implementation Typhoid Sub-team Terms of Reference