Annex B: Background and Overview of Analyses

Gavi's Historical Decisions on TCV

In the 2008 VIS, the Board prioritised TCVs for Gavi's portfolio along with Rubella, HPV, and JE vaccines. Although no financial commitments were made at the time, the decision to prioritise TCVs was made under the assumption that an appropriate vaccine would obtain WHO PQ by 2011.

TCV has been included as part of Gavi's financial forecasts and was reviewed by the Audit and Finance committee in October 2017, which 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.

In 2011, following delays in the PQ timelines largely driven by the discontinued development of a lead vaccine candidate, the Board considered the temporary introduction of typhoid polysaccharide (Vi-PS) vaccine as a bridging strategy, but ultimately chose not to reconsider the 2008 decision and reaffirmed its preference for TCVs.

As part of the 2013 VIS process, it was agreed not to review TCVs as it was already prioritised and included in Gavi's financial forecast. At the Board meeting in November 2013, the Board was reminded that a support window would be opened for TCVs once a suitable vaccine obtained WHO PQ.

In the June 2017 meeting, the Board was informed that the Secretariat would refresh the original analyses and ask the Board to consider opening a funding window if TCVs were WHO recommended and received PQ by the end of 2017.

Typhoid Fever Overview

Typhoid fever is a systemic infection caused by the enteric pathogen *Salmonella* Typhi enterica serovar Typhi. The pathogen is generally spread through ingestion of fecally contaminated food or water. Although typhoid fever is largely considered an endemic disease, epidemics do occur.[2] Acute illness is characterised by prolonged fever, headache, and nausea, loss of appetite and constipation or sometimes diarrhoea. Serious complications occur in up to 10% of typhoid fever patients.[3] The symptoms of typhoid fever are difficult to differentiate from other febrile illnesses e.g. non-specific viral illness, malaria, dengue fever, or influenza.

New evidence indicates that major burden of severe disease exists in younger age groups - 27% of typhoid fever occurred in children under 5 years of age. While data sources likely reflect high typhoid incidence locations, they confirm that typhoid fever with severity sufficient for an outpatient visit or hospital admission is common in the under 5 year age group with a notable proportion of disease occurring between 6 months and 2 years of age.

[2] Typhoid vaccines: WHO Position paper. Weekly epidemiological record. 2008; 6:49-60.
[3] ibid

Improved living conditions and the introduction of antibiotics in the late 1940s resulted in a large reduction in typhoid fever mortality and morbidity in industrialised nations. Case fatality rates can be reduced to less than 1% with the appropriate antibiotic therapy whereas in pre-antibiotic era, the case fatality rate was as high as 20%.[4,5]

AMR has been called one of the biggest threats to global health. In 2015, the World Health Assembly endorsed a global action plan to tackle AMR[6]. Further, there was a meeting on AMR the UN General Assembly (UNGA)[7] in September 2016. This was only the fourth time in UNGA history that a specific health item was elevated to this level. The development and promotion of an effective typhoid vaccine and improvements in water quality, food safety, sanitation, and hygiene are important steps to prevent transmission of AMR strains.

Market Analysis

Vi-PS and oral live attenuated typhoid vaccines have been available since the early 1990s. However they are not licensed for use in children under two and six years of age, respectively, have a short duration of protection, and are programmatically difficult to deliver. TCVs currently in development are expected to have two major differences (i) TCV is immunogenic from infancy, which is important given the age distribution of burden and (ii) longer duration of protection. Although the duration of protection beyond 5 years is currently unknown, TCV induces immunological memory, which is critical for boostability and may be a key component of long term protection. Post-introduction studies will be needed to understand this better.

Bharat Typbar TCV was licensed in India in 2013 and is anticipated to obtain WHO PQ by the end of 2017. Efficacy data on Bharat's TCV candidate are not available yet but recent Phase 3 studies have shown 98% seroconversion after 42 days[8]. Further, a controlled human infection model of typhoid fever showed TCVs prevented up to 87% of typhoid infections[9]. There are five other TCVs in various stages of development with estimates for WHO PQ from 2019 to 2022. These manufacturers include Biological E (India), Incepta (Bangladesh), PT Biofarma (Indonesia) SK Chemicals (Republic of Korea), and Zydus Cadila (India).

From 2008-2013, TCV product development was further delayed due to prioritisation of other activities from the Alliance and subsequently of manufacturers. However following local licensure in 2013, the Alliance partners are actively engaging to support TCV with the focus on strengthening evidence generation to support policy decisions and advocacy efforts, improving

[4] Butler et al. Typhoid Fever Complicated by Intestinal Perforation: A Persisting Fatal Disease Requiring Surgical Management. Review of Infectious Disease 1985; 7(2):244-256.
[5] Typhoid vaccines: WHO Position paper. Weekly epidemiological record. 2008; 6:49-60.
[6] http://www.who.int/antimicrobial-resistance/global-action-plan/en/
[7] http://www.un.org/pga/71/event-latest/high-level-meeting-on-antimicrobial-resistance/
[8] Mohan VK et al. Safety and Immunogenicity of a Vi Polysaccharide–Tetanus Toxoid Conjugate Vaccine (Typbar-TCV) in Healthy Infants, Children, and Adults in Typhoid Endemic Areas: A Multicenter, 2-Cohort, Open-Label, Double-Blind, Randomized Controlled Phase 3 Study. Clin Infect Dis. 2015;61:393–402.
[9] Jin et al. Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of *Salmonella typhi*: a phase IIb observer-participant-blinded, randomised control trial. Submitted, Lancet; September 2017;

communication around country demand, and establishing product development partnerships supported by Alliance partner's funding.

As some pipeline manufacturers are Indian, priority may be given to the domestic market. Consideration of India's TCV introduction plans will be important to understand supply availability for Gavi-eligible countries. However, it is anticipated that India will focus on their current immunisation priorities before introducing TCV and thus it is not expected to disrupt supply required for Gavi countries during the forecast period.

From the perspective of the Alliance's healthy markets framework, the TCV market has low levels of market health given that inadequate supply is initially expected. The Alliance's first priority will be to support increased supply to meet country demand, particularly to satisfy the demand for catch-ups. As supply volume improves over time, the focus will shift to meeting country presentation preferences, with consideration for securing a certain level of buffer capacity, total systems effectiveness and pricing.

Demand Forecasting Methodology

A demand forecast for TCVs was prepared in August 2017 for the purpose of informing decision-making on the opening of a funding window. An updated and more detailed version of this forecast is planned to be completed and published by the end of 2017.

A projection of unconstrained demand was developed with inputs provided by the VI Typhoid sub-team. The forecast scope was the "Gavi 73" countries eligible for Gavi support as of 2011.[10] It was assumed that countries in the Asia Pacific region would have a better understanding of their typhoid burden and thus more likely to be early adopters of the vaccine. The vaccination schedule was assumed to be a single dose in routine immunisation and a single dose in one time catch-up. The target groups were modelled to be 9 month old infants for routine and 9 months to 15 year olds for catch-ups.[11]

A primary uncertainty is the extent which countries may pursue sub-national introductions; thus, three scenarios were developed:

1. **Scenario 1** (higher): all countries introduce national routine immunisation and catch-ups
2. **Scenario 2** (middle): all countries introduce national routine immunisation and subnational catch-ups
3. **Scenario 3** (lower): same as Scenario 2, but six large[12] population countries introduce sub-national routine

[10] For two of these countries, Ukraine and Moldova, no demand volumes were calculated

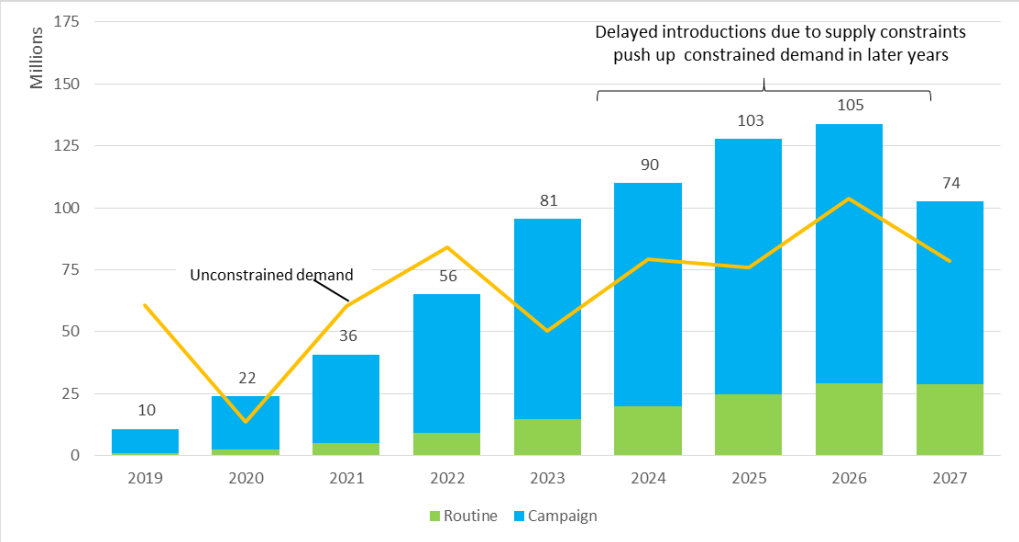
[11] Other key assumptions - Wastage assumptions: 15% routine, 10% campaign. Coverage assumptions: MCV1 for routine, 100% for catch – up campaigns.

[12] Large countries were chosen as countries with > 1m population of SI in Urban slums + Rural areas without access to clean water from : UN urban slum data and WHO/UNICEF Joint Monitoring Programme (JMP) for Water Supply and Sanitation, SDFv10 2014.

There is a range of potential demand across the scenarios and all scenarios exhibit high variability of demand on a year-to-year basis reflecting demand peaks from catch-ups. As the demand from Scenario 1 was the highest, it was compared with the supply projected to be available to the Gavi-eligible countries[13]. Due to the catch-up based demand, the initial period (2019-2022) is supply constrained. Post-2022 indicates that supply exceeds Gavi-eligible.

For this comparison it was assumed that India introduces TCV at the subnational level in high burden areas with catch-up over multiple years[14]. It is assumed that the India programme is independent of Gavi support. The corresponding supply requirements for India were also accounted for separately. For other countries that are not projected to be Gavi-eligible, it is assumed that these will introduce as and when adequate supply is available.[15]

To eliminate the supply deficits, a supply constrained demand forecast was developed by varying introduction assumptions and phasing catch-ups of large countries. The figure below provides estimates of constrained and unconstrained demand



Supply constraints	2019	2020	2021	2022	2023	2024	2025	2026	2027
Number of intros	1	1	1	3	2	6	10	7	4

While the introduction assumptions made in the current forecasts leverage the information readily available, an inherent degree of uncertainty remains as there is limited reliable information on country plans. This is compounded by the high

[13] There are 45 countries that are projected to be eligible for new vaccine support from Gavi at the time of the assumed introduction.
[14] India is assumed to introduce sub-nationally due to strong sub-national burden data, other vaccine implementation priorities and heavily constrained supply for national immunisation volumes
[15] Except Indonesia, which is assumed to introduce in 2022 but is dependent on adequate volumes available from a local manufacturer

volumes associated with catch-ups as these volumes can vary significantly based on small changes in country introduction assumptions.

This forecast represents the application of the current Board approved eligibility and transition policy. Changes or exceptions to this policy could vary demand significantly, particularly if this permitted large countries to apply for TCV support that have been excluded from the Gavi-eligible portion of this forecast.[16]

Impact Modelling

Two tools were used to estimate impact of introducing TCVs for Gavi-eligible countries. Both models indicate that an investment in TCVs is within Gavi's existing programmes based on the number deaths averted per fully vaccinated person and vaccine procurement costs per death averted.

The Integrated Portfolio Management (IPM) tool is a deterministic static model that can be used for various purposes including researching and developing pipeline analyses, measuring direct health impact, cost-effectiveness, and health system costs, and supporting policy decision making. IPM is also one of the tools being used to conduct 2018 VIS impact analyses. For the purposes of this analysis only direct vaccination impact was modelled. Per the IPM tool, Gavi supported introductions of TCV is forecasted to avert 0.3 deaths and 15 Disability Adjusted Life Years (DALYs) per every 1,000 fully vaccinated persons (FV) which is comparable to JE. TCV had a cost per death averted (Value for Money) of US$ 6,580 per future death averted (with a range of US$ 3,320 to US$ 10,420 based on varying cost estimates). This is within the range of Gavi's current investments and similar to JE and Rotavirus.

Yale School of Public Health developed a mathematical model describing transmission dynamics of typhoid fever, which accounts for essential features of typhoid epidemiology, including waning immunity to infection and the role of chronic carriers in transmission. This model has been previously used to describe typhoid transmission dynamics and impact of potential vaccination strategies, and is able to consider additional factors such as lifetime risk of typhoid, more realistic waning of protection, and indirect protection. Per the Yale model, Gavi supported introductions of TCV is forecasted to avert 0.7 deaths and 23 Disability Adjusted Life Years (DALYs) per every 1,000 FVP, which is comparable to Gavi's investment in Rotavirus. TCV had a cost per death averted (Value for Money) of US$ 4,190 per future death averted (with a range of US$ 2,110 to US$ 6,630 based on varying cost estimates). This is within the range of Gavi's current investments and similar to Pneumococcal Conjugate Vaccines.

[16] For example, Nigeria is currently excluded from this forecast given that it will not be eligible to supply for new vaccine support at the time an application window was launched.