GLOBAL MARKET STUDY
TYPHOID VACCINES

Key Takeaways
- ViPS and Ty21a markets are largely focused on the private sector and travellers markets. Given the product characteristics of TCV, it is anticipated that demand for these markets will decrease and the manufacturers will exit the market in the mid- to long-term.
- Supply-demand balance is sufficient for ViPS and Ty21a for the foreseeable future.
- The demand for the TCV market is still evolving and currently there is significant uncertainty in defining local typhoid epidemiology, which affects the vaccination strategies chosen by countries.
- There is currently only one TCV manufacturer with WHO prequalification (2017), with another manufacturer anticipated to receive WHO prequalification (PQ) by the end of 2020. Four additional manufacturers are domestically marketed or in Phase III development and planning to apply for WHO PQ. If all anticipated manufacturers enter the market in the short- to medium-term and obtain WHO PQ, then the TCV supplier base will become more diverse and stable.
- Supply-demand balance is sufficient for TCV, assuming all anticipated manufacturers enter the market. There is a potential risk of oversupply in the long-term once all countries have conducted their one-time multi-age campaigns at the time of routine introduction.
- There is a significant level of uncertainty in whether demand will materialize and at what levels:
  - If demand materializes, there is a risk of imbalance due to large countries conducting multi-age campaigns in the mid-term. This risk can be mitigated with appropriate planning and communication from all stakeholders.
  - If demand does not materialize, then there is a significant risk of oversupply.

Disclaimer: This market study was completed before the impact of the SARS-CoV-2 pandemic could be fully ascertained. Demand projections are based on the assumption that any delay or disruption will be absorbed and resolved in 2021. Supply projections were based on the latest information provided by manufacturers in Q3 2020, which indicated limited supply disruptions. Uncertainty on the progression of the pandemic raises the risk of shifted priorities resulting in slower demand materialization and/or the reduction of supply availability beyond 2021. This will require an updated analysis of supply-demand balance of the typhoid vaccine market.

Context and Rationale

Typhoid vaccines consist of three types: typhoid conjugate vaccine (TCV), unconjugated Vi polysaccharide (ViPS), and live attenuated Ty21a vaccine (Ty21a). Although all three types of vaccines are deemed safe and efficacious, they have different vaccine characteristics, including different composition, dose schedules, presentation and recommended target age for vaccination. Figure 1 is an excerpt from the WHO position paper on typhoid vaccines, outlining the different vaccine characteristics.

Further, the different types of vaccines have different duration of protection. TCV is expected to confer protection beyond five years after primary immunization while ViPS protects for three years and Ty21a protects from one to seven years, with countries varying their timing of revaccination.¹

¹ WHO Typhoid vaccines position paper, March 2018: https://apps.who.int/iris/bitstream/handle/10665/272272/83913.pdf?ua=1
TABLE 1 CHARACTERISTICS OF DIFFERENT TYPHOID VACCINES

<table>
<thead>
<tr>
<th></th>
<th>Typhoid conjugate vaccine (Typbar-TCV&lt;sup&gt;®&lt;/sup&gt;)</th>
<th>Unconjugated Vi polysaccharide vaccine</th>
<th>Live attenuated Ty21a vaccine - Typhi</th>
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<tbody>
<tr>
<td>Composition</td>
<td>25 µg of purified Vi capsular polysaccharide conjugated to TT</td>
<td>25 µg of purified Vi capsular polysaccharide</td>
<td>2 to 6 x 10⁹ CFU of Ty21a (attenuated Ty2 strain of S. Typhi)</td>
</tr>
<tr>
<td>Route, dose</td>
<td>IM, 1 dose</td>
<td>IM/SC, 1 dose</td>
<td>Oral, 3 (in USA and Canada) doses every second (alternate) day</td>
</tr>
<tr>
<td>Presentation</td>
<td>Liquid</td>
<td>Liquid</td>
<td>Enteric-coated capsules</td>
</tr>
<tr>
<td>Recommended target age for vaccination</td>
<td>Adults and children ≥ 6 months to ≤ 45 years of age</td>
<td>Adults and children ≥ 2 years of age</td>
<td>Adults and children older than 6 years</td>
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</tbody>
</table>

WHO recommends programmatic use of typhoid vaccines for the control of typhoid fever; among the available typhoid vaccines, TCV is preferred at all ages given its improved immunological properties, suitability for use in younger children, and expected duration of protection.<sup>2</sup> Countries may also consider the routine use of ViPS in individuals 2 years or older and Ty21a in individuals 6 years or older. WHO recommends that countries consider the costs, programmatic issues and duration of protection when choosing a typhoid vaccine.

WHO also recommends that decisions regarding TCV administration, target population and delivery strategy (e.g., universal, risk-based or phased) should be based on the local epidemiology of typhoid fever, including an analysis of the disease burden and risk factors for transmission, availability and quality of surveillance data, cost-effectiveness, affordability and operational feasibility. In addition to the recommended dose schedule in Table 1, TCV catch-up vaccination of up to 15 years of age is recommended when feasible and supported by epidemiological data. Finally, WHO recommends vaccination in response to confirmed outbreaks of typhoid fever. Gavi opened a funding window for support of TCV routine introduction and one-time multi-age campaigns in November 2017.

Global Demand

TCV use in childhood vaccination programmes drives 96% of current global typhoid vaccine demand. The remaining 4% of demand, amounting to ~450,000 doses per year, is for ViPS and Ty21a vaccines arising for the traveller’s market, primarily in 20 HICs. As new TCV products become available, it is anticipated that demand will move to TCV and that ViPS and Ty21a demand will be minimal or nonexistent in the mid- to long-term. As of 2020, one country<sup>4</sup> has partially introduced TCV through a multi-age campaign of up to 15-year-olds and routine immunization of 9-month-olds as part of a phased national introduction.

The WHO position paper recommends that TCV vaccination strategy is driven by local epidemiological considerations. However, given typhoid’s nonspecific presentation and the lack of an appropriately sensitive point-of-care diagnostic, accurate typhoid epidemiology, including information on antimicrobial (AMR) resistance, remains a key programmatic challenge and drives substantial uncertainty in the selection of vaccination strategy (e.g., risk-based or national; campaign and/or routine) and the evolution of TCV demand. To capture the variability of the 2021-2030 TCV market, three estimates of TCV demand evolution were developed<sup>4</sup> and demand will be presented as a range of these estimates.

- **The higher estimate** anticipates a wide introduction scope<sup>5</sup> with more aggressive, national introduction strategies, including multi-age campaigns, assuming that many countries find accurate and concerning typhoid burden profiles as surveillance improves.
- **The lower estimate** assumes a sparse introduction scope<sup>6</sup> with fewer countries performing large, national multi-age campaigns, under the assumption that countries will have less interest or motivation to introduce TCV or will introduce in lower volume-requiring strategies (i.e. risk-based).
- **The moderate estimate** shows a moderate introduction scope<sup>7</sup> with strategies based on currently available burden data<sup>8</sup> and financial considerations of conducting a multi-age campaign.
Global mid-term demand for TCV is estimated to range from 43M to 163M doses per year (moderate estimate of 111M doses per year) and is expected to decrease in the long-term to 22M–96M doses per year (moderate estimate of 71M doses per year) once the one-time campaigns have been conducted.

Between 2022 and 2027, one-time campaigns could temporarily increase required volumes 2.5–2.8 times over routine demand, creating a need to coordinate the large campaigns and ensure sufficient timing of available supply.

Non-Gavi demand may be slow to materialize and modest in size, depending on currently available typhoid burden and typhoid AMR resistance data. There is also uncertainty related to which vaccination strategy non-Gavi countries would pursue given the availability of local financing (e.g. national or risk-based, routine only or with one-time campaigns). The lower and moderate estimates are based on available burden data, with four to eight non-Gavi MICs forecasted to introduce by 2030, accounting for 2M–6M doses in 2030 (7–9% of global demand). The higher estimate shows potential demand if improved surveillance discovers high typhoid burden and AMR, which will require more aggressive vaccination strategies resulting in an estimated 20M doses needed in 2030 (20% of global demand).

Gavi countries, excluding India, are likely to comprise the majority of global TCV demand. In the lower and higher estimates, which assume 13 to 48 countries introduce, mid-term demand is 16M–77M doses per year (moderate estimate: 85M doses per year). The demand decreases to 14M–51M doses per year in 2030 (moderate estimate of 41M doses per year) once the one-time campaigns are completed. India demand for TCV comprises the rest of global demand (moderate estimate of 24M doses in 2030).

FIGURE 2: TYPHOID VACCINE MANUFACTURERS (MARKETED AND IN DEVELOPMENT)
Global Supply

Currently, there are eight manufacturers for ViPS and one manufacturer for Ty21a. The ViPS and Ty21a vaccine products are currently being sold for use in travellers market to typhoid-endemic countries and target the private market; they are not used on a routine basis. Only one ViPS vaccine product, Typhim-Vi by Sanofi Pasteur, currently holds WHO prequalification. As these products have limited use, and given the product characteristics of TCV, it is anticipated that these manufacturers will exit once additional TCV manufacturers enter into the market. The current (2021) global available supply for commercialization (ASC) for ViPS and Ty21a is approximately 7M and is anticipated to decrease to minimal levels in the mid-term.

There is currently only one WHO prequalified TCV product, by Bharat Biotech International Limited (BBIL). The vaccine comes in both 1-dose and 5-dose vials, with 1-dose vials largely used in the private market and 5-dose vials mainly used by typhoid-endemic countries for routine and catch-up administration.

Biological E Limited (BioE), BioMed and Zydus currently have TCV products with local licensure in India, targeting the private market. BioE is expected to receive WHO prequalification by the end of 2020 and Zydus plans to apply for WHO prequalification. There are currently three products in Phase 3 development and all manufacturers are expected to apply for WHO prequalification. Some manufacturers have indicated minimal short-term delays and re-evaluation of their TCV development timelines due to the SARS-CoV-2 pandemic.

It is anticipated that all TCV products will be equivalent from both a technical and programmatic perspective; thus, the market will not fragment based on specific country preferences and supply availability. Although paratyphoid was out of the scope of this Market Study, its development and potential impact on the typhoid market should be monitored in the long-term.

For next year (2021), the global ASC for TCV is approximately 60M and is anticipated to increase by 200% in the short- to mid-term, driven by the number of new manufacturers entering the market. By the mid-term, at least three new manufacturers are forecasted to contribute more than 65% of global ASC, representing a significant diversification of manufacturers that will contribute to lower risk of shortages. The new entrants will improve the market health by creating a manufacturer base that is more stable, diverse and flexible.

The high scenario increases global ASC by over 70% from the base scenario in the short-term due to more optimistic assumptions on the timing of new manufacturer entry and the ability of existing manufacturers to reach their highest possible ASC. A low ASC scenario that is 60% lower than the base in the mid-term reflects more pessimistic timing of the new manufacturers and potential constraints or disruptions of existing manufacturers.

Demand and Supply Balance

For ViPS and Ty21a, the current and short-term base supply-demand balance is sufficient. It is anticipated that ViPS and Ty21a manufacturers will either exit the market or only supply very limited amounts in the future once additional TCV manufacturers enter the market in the mid- and long-term.

Base supply for TCV is meeting the moderate demand needs and no imbalance is anticipated in the short-, mid- or long-term. With the new manufacturers entering this market, it is unlikely that ASC will need to have a one-time surge to meet the demand of the one-time multi-age campaigns. This assumes transparent and open communications and sufficient planning and lead time, particularly surrounding the uncertainties of vaccination strategies implemented by countries (e.g., national versus subnational, one-time multi-age campaigns covering multiple cohorts, or large country introductions).

Given the amount of uncertainty around the level of TCV demand, the balances using base supply and higher and lower demand evolutions were also evaluated. If higher demand materializes, there is a risk of imbalance in the mid-term primarily driven by the one-time multi-age campaigns of Gavi countries. However, if demand does not materialize, then this market faces a risk of oversupply.

While it is important to ensure a diversification of the manufacturer base away from only one WHO prequalified manufacturer, this should be done sustainably, particularly considering that demand will decrease to a steady state covering one cohort once countries have conducted their one-time multi-age campaigns. Further, given the ongoing SARS-CoV-2 pandemic, it is essential to ensure that TCV development, WHO pre-qualification and its supply to countries remains a priority for these new manufacturers. If those manufacturers do not enter the market, then there will be significant supply constraints (low supply to moderate demand scenario).

### FIGURE 3: TYPHOID SUPPLY / DEMAND BALANCE

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<thead>
<tr>
<th></th>
<th>ViPS &amp; Ty21a</th>
<th>TCV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base</strong></td>
<td>Current</td>
<td>Current</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>Short-term</td>
<td>Short-term</td>
</tr>
<tr>
<td></td>
<td>Mid-term</td>
<td>Mid-term</td>
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<tr>
<td></td>
<td>Long-term</td>
<td>Long-term</td>
</tr>
<tr>
<td><strong>Base</strong></td>
<td>Current</td>
<td>Current</td>
</tr>
<tr>
<td><strong>Higher</strong></td>
<td>Short-term</td>
<td>Short-term</td>
</tr>
<tr>
<td></td>
<td>Mid-term</td>
<td>Mid-term</td>
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<tr>
<td></td>
<td>Long-term</td>
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10 Additional resource providing recommendations to ensure the quality, safety and efficacy of typhoid conjugate vaccines may be found at https://www.who.int/publications/m/item/tcv71-recommendations

11 All candidates are in early development stages.

12 Includes global ASC of both WHO prequalified products and non-prequalified products.

13 Where red represents insufficient ASC compared to demand, yellow represents low supply risk, green represents sufficient ASC compared to demand and dark green represents more than sufficient ASC compared to demand.
Pricing
Based on JRF reported data, ViPS median price per dose is US$ 8.02 and no prices were reported for Ty21a. The current TCV price for Gavi countries is US$ 1.50 per dose for a 5-dose vial. The current TCV private market price for India (single-dose vial or prefilled syringe) ranges from US$ 15 – US$ 30.14

The TCV price for non-Gavi countries is currently unknown and no countries have reported pricing information for TCV. Available data is expected to improve in the mid-term as non-Gavi countries introduce TCV.

As TCV is a relatively new market, it is not possible to assess if affordability will be an issue, particularly for MICs and if there is a need to complete multi-age campaigns. However, given the number of new manufacturers entering the market in the short- and mid-term, it is anticipated that TCV price will remain competitive.

Other Resources
WHO Typhoid vaccines position paper, March 2018:
https://apps.who.int/iris/bitstream/handle/10665/272272/WER9313.pdf?ua=1

Gavi Typhoid Conjugate Roadmap, July 2018:

Areas for Action
To enhance sustainable access to supply of TCV vaccines in coordination with immunization partners, WHO will concentrate on the following areas:

Short-term:
- Continue improving non-Gavi demand visibility by working with countries to develop their understanding of typhoid burden and typhoid antimicrobial resistance and assisting countries to make evidence-based decisions regarding introduction and vaccination strategies
- Engage in open dialogue with TCV manufacturers and monitor their development progress and prequalification plans to ensure a more balanced and healthier manufacturer base

Mid- to long-term:
- As non-Gavi demand visibility improves, discuss with non-Gavi countries any potential TCV access issues, particularly affordability issues, if there is interest in conducting one-time multi-age campaigns. Also, where possible, take any lessons learned from Gavi countries to inform the selection of vaccination strategy
- Regularly assess the development of paratyphoid vaccines, particularly bivalent typhoid and paratyphoid vaccines,15 which may significantly change product preferences and the market dynamics

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15 All candidates are in early development stages.