

Typhoid Conjugate Vaccine: Supply and Demand Update

UNICEF Supply Division

December 2022

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This update provides information on typhoid conjugate vaccine, including supply, demand, and country introductions. It highlights the uncertain pace of country introductions, and the challenges countries face to adopt the vaccine. This results in demand uncertainty and the need to improve forecast accuracy as well as concerns to ensure industry can plan supply availability.

1. Summary

- The typhoid conjugate vaccine (TCV) is the first typhoid vaccine to be developed suitable for children from six months up to 45 years of age. The World Health Organization (WHO) recommends TCV for use in routine immunization as a single dose in typhoid endemic areas, when feasible and supported by epidemiological data.
- UNICEF and Gavi, the Vaccine Alliance (Gavi), support countries to introduce TCV into their national immunization programmes. To date, only five countries globally have so far introduced TCV into their programmes, of which four countries introduced TCV with the support of Gavi through initial catch-up campaigns followed by routine programme immunization.
- To date, there are two manufacturers that currently produce WHO prequalified TCV vaccines, both of which have long-term arrangements (LTAs) with UNICEF.
- Overall, TCV is a product made to order and supply capacity is sufficient to meet country demand. However, any uncertainty in the uptake and introduction of the vaccine is due to countries not having sufficient accurate epidemiological data to make informed decisions on vaccine introduction and the need to make improvements in water and sanitation choosing TCV over competing vaccine priorities, and whether they are affected by an outbreak.
- Nevertheless, there are indications of increased future demand based on some recent National Immunization Technical Advisory Groups (NITAGs) recommendations to introduce the vaccine.¹
- UNICEF and Gavi are engaged with the industry to support countries to introduce TCV where appropriate, as well as to manage the inherent risks and expectations associated with uncertain anticipated demand.

2. Background

Typhoid is a serious bacterial infection caused by *Salmonella* Typhi. It spreads easily from person to person through contaminated food or water, especially in overcrowded populations living with inadequate safe water, sanitation, and hygiene. Its high prevalence mainly occurs in the regions of sub-Saharan Africa and South/South-East Asia (Figure 1, next page),² where poor communities, vulnerable groups, and children are at highest risk.³ It is the cause of an estimated 11-21 million infections a year, of which 128-161,000 people die annually. Children are disproportionately affected with the majority of cases known to occur between 5-15 years of age.⁴ Symptoms of typhoid infection can include fatigue, prolonged fever, headaches, rash, nausea, abdominal pain, constipation, and diarrhoea. Severe cases may lead to serious complications or even death.

These symptoms are often confused with a wide range of other common febrile illnesses prevalent in typhoid endemic regions, such as malaria, making clinical diagnosis difficult. Mistaken clinical diagnosis and poor surveillance data undermines a country's accurate understanding of typhoid fever prevalence and incidence. Disease diagnosis in most settings depends on confirmation by laboratory blood culture, which is not performed in the majority of cases in low-income countries (LICs), and lower middle-income countries (LMICs).⁵

While appropriate antibiotic treatment exists that can reduce the case fatality rates from typhoid to less than one per cent, there has been an alarming increase in antimicrobial resistance to typhoid, notably of *Salmonella* Typhi, in which drug-

¹ National Immunization Technical Advisory Groups (NITAGs) are multidisciplinary bodies of national experts that provide evidence-based recommendations to policymakers and immunization programme managers.

² Mogasale, Vittal, Brian Maskery, R Leon Ochiai, et al., [Burden of Typhoid Fever in Low-income and Middle-income Countries: A Systematic Literature-based Update with Risk-factor](#), The Lancet Global Health, Volume 2, Issue 10, Pages e570-e580, London, October 2014.

³ World Health Organization, [Typhoid Key Facts](#), WHO, Geneva, January 2018.

⁴ World Health Organization, [Typhoid Vaccines Position Paper](#), WHO, Geneva, November 2018 p. 154.

⁵ Ibid., p. 157.

resistance is spreading across Africa and Asia.⁶ The emergence of drug-resistance encourages countries to renew their focus on prevention. The use of TCVs in combination with increased access to clean water and improved sanitation can significantly reduce the spread and burden of the disease.⁷ A research study published in 2021 investigated the effectiveness of TCV among children in Pakistan. The study found that vaccine effectiveness was 55 per cent against suspected typhoid, 95 per cent against culture confirmed typhoid, and 97 per cent against extremely drug-resistant typhoid. The findings of this study reflect the strong effectiveness of TCV on typhoid disease among the most impacted group in Pakistan.⁸

The World Health Organization advises countries that are considering the adoption of the TCV for programmatic use as a means to control the disease in endemic regions to target the vaccination of high-risk groups and populations, especially against AMR.⁹ The World Health Organization also recommends the use of the vaccine for outbreak control, due to the epidemic potential of the disease, and the vaccine's effectiveness in interrupting transmission.¹⁰ The World Health Organization also suggests that international travellers get the vaccine for destinations that have a high risk of typhoid, especially if travelling for an extended period.

Until recently, countries only had two typhoid vaccines available to them to provide protection against typhoid fever. An injectable polysaccharide vaccine based on the purified antigen, and a live attenuated oral vaccine in capsule formulation. However, as manufacturers could not demonstrate the vaccine's efficacy in children under two years of age, the vaccines were only licensed for use in children over two years, and five years, respectively.

The TCV is the first typhoid vaccine that is suitable for children from six months of age. Based on published data,¹¹ WHO recommends TCV as the preferred typhoid vaccine of choice for all ages, due to its improved immunological properties, as well as for use in younger children and its longer duration of protection. Investigative studies for the duration of protection are ongoing. However, at present the available evidence from immunogenicity studies on Typhbar-TCV suggests that protection may persist for up to five years after primary immunization, and there is a lack of evidence concerning the need for booster vaccination.¹² The World Health Organization recommends the vaccine for routine administration as a

⁶ Marchello, Christian S, Samuel D. Carr, John A. Crump, [A Systematic Review on Antimicrobial Resistance among Salmonella Typhi Worldwide](#), PubMed, Bethesda, December 2020.

⁷ WHO, [Typhoid Key Facts](#).

⁸ Yousafzai, Tahir, Mohammad MPH, Karim Sultan MSc, Sonia Qureshi FCPS, et al., [Effectiveness of Typhoid Conjugate Vaccine against Culture-confirmed Salmonella enterica Serotype Typhi in an Extensively Drug-resistant Outbreak Setting of Hyderabad, Pakistan: a Cohort Study](#), The Lancet Global Health, Volume 9, Issue 8, London, August 1st 2021, p. 1154-1162.

⁹ Coalition Against Typhoid, [Drug Resistant Typhoid](#), Coalition Against Typhoid, Washington, 2018.

¹⁰ WHO, [Typhoid Vaccines Position Paper](#), p. 155.

¹¹ Ibid, p. 169.

¹² Ibid, p. 165.

single dose in children from six months of age and for adults up to 45 years of age living in endemic areas, as well as for use in catch-up vaccination campaigns for children up to 15 years, when feasible and supported by epidemiological data.

Typhoid conjugate vaccines are characterised by the Vi polysaccharide antigen, which is coupled to a carrier protein resulting in improved immunological properties that makes the vaccine suitable for use in younger children offering a longer duration of protection.¹³ The various carrier proteins used include tetanus toxoid (TT), diphtheria toxoid (DT), cross-reactive material 197 (CRM197), as well as a recombinant exoprotein A (rEPA).

The World Health Organization has prequalified two TCVs in four presentations from two suppliers in India. Both vaccines are offered in a one- and five-dose vial (Table 1).¹⁴ One is produced using a Vi-tetanus Toxoid (Vi-TT) conjugate vaccine from Bharat Biotech, and the other uses a Vi-cross reactive material (Vi-CRM197) from Biological E. Despite a difference in the conjugate protein, the two vaccines from BBIL and BioE are expected to have similar a performance.¹⁵

Table 1 World Health Organization Prequalified Typhoid Conjugate Vaccines

Manufacturer	Vaccine Type	Doses / Course	WHO PQ	Presentation	Form.	Shelf life	VVM	Cold Chain Vol / Dose	Storage
Bharat Biotech (India)	Conjugate	1 dose	2017	1-dose vial	Liquid	36 months	30	14.18 cm ³	2-8°C
	Conjugate	1 dose	2017	5-dose vial	Liquid	36 months	30	2.9 cm ³	2-8°C
Biological E (India)	Conjugate	1 dose	2020	1-dose vial	Liquid	24 months	30	14.7 cm ³	2-8°C
	Conjugate	1 dose	2020	5-dose vial	Liquid	24 months	30	2.9 cm ³	2-8°C

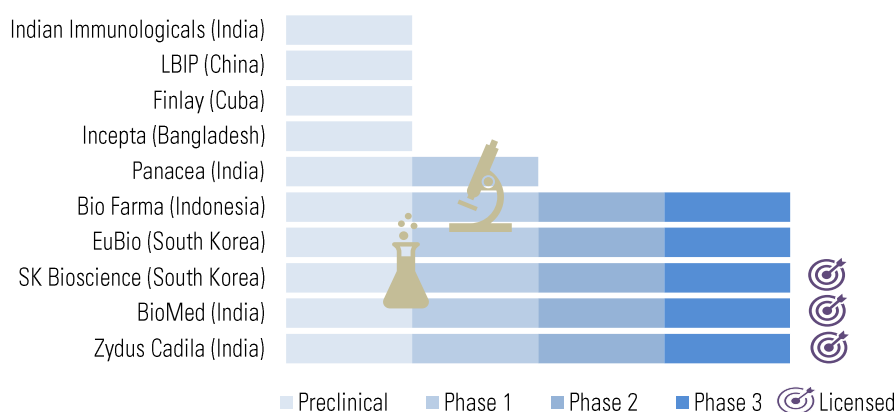
Source: World Health Organization

There are several other non-WHO prequalified TCVs on the market. Three TCVs are licensed of which two in India, and in one South Korea. India's vaccines are conjugated vaccines to tetanus toxoid of which BioMed's Vi-TT was licensed in 2008 for infants aged three months and older, and Zydus Cadila's Vi-TT was licensed in 2018 for children aged six months and older. The TCV from Bioscience in South Korea is conjugated with DT and was licensed in 2022 and has since been submitted to WHO for prequalification.

3. Innovation

Several manufacturers are developing TCVs that are in various stages of development, and which are conjugated with carrier proteins such as CRM197, DT, TT or rEPA (Figure 2).

Figure 2 Typhoid Conjugate Vaccine Product Development Pipeline



Source: UNICEF Supply Division

Other vaccines in preclinical stages not shown in Figure 1 include a trivalent typhoid/non-typhoidal *Salmonella* glycoconjugate vaccine for use in sub-Saharan Africa,¹⁶ and a multiple antigen presenting system (MAPS)-based typhoid and paratyphoid A vaccine, which is a promising alternative to traditional conjugation vaccines.¹⁷

¹³ Ibid, p. 160.

¹⁴ World Health Organization, [Prequalified Vaccines](#), WHO, Geneva, August 2022.

¹⁵ World Health Organization, [Comparison Table of WHO Prequalified Typhoid Conjugate Vaccines](#), WHO, Geneva, April 2021.

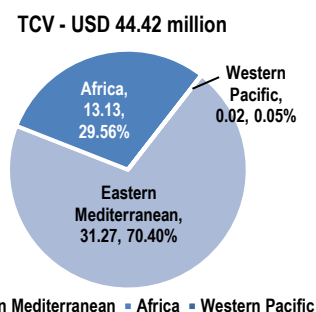
¹⁶ Coalition Against Typhoid, [11th International Conference on Typhoid and Other Invasive Salmonellosis](#), Coalition Against Typhoid, Hanoi, March 26th-28th, 2019, p.22.

¹⁷ Baliban, Scott M, Ying-Jie Lu, and Richard Malley, [Overview of the Nontyphoidal and Paratyphoidal Salmonella Vaccine Pipeline: Current Status and Future Prospects](#), PubMed, Bethesda, August 2020.

4. Current Market Situation

Independent market research estimates the size of the current typhoid vaccine market to reach an estimated USD 321 million and is anticipated to grow by an annual compound growth rate (ACGR) of 10 per cent to reach an estimated USD 719 billion by 2029.¹⁸ North America represents the largest typhoid vaccine market share and revenue reflecting rising healthcare expenditure. The Asia-Pacific market share is also expected to grow due to typhoid disease prevalence, the development of healthcare infrastructure, and rising government initiatives for immunization programmes. The growth is also driven by government initiatives in developing new products, as highlighted by the product development pipeline.

Figure 3 Typhoid Conjugate Vaccine Estimated USD Revenues and Market Share in MICs and LICs 2021

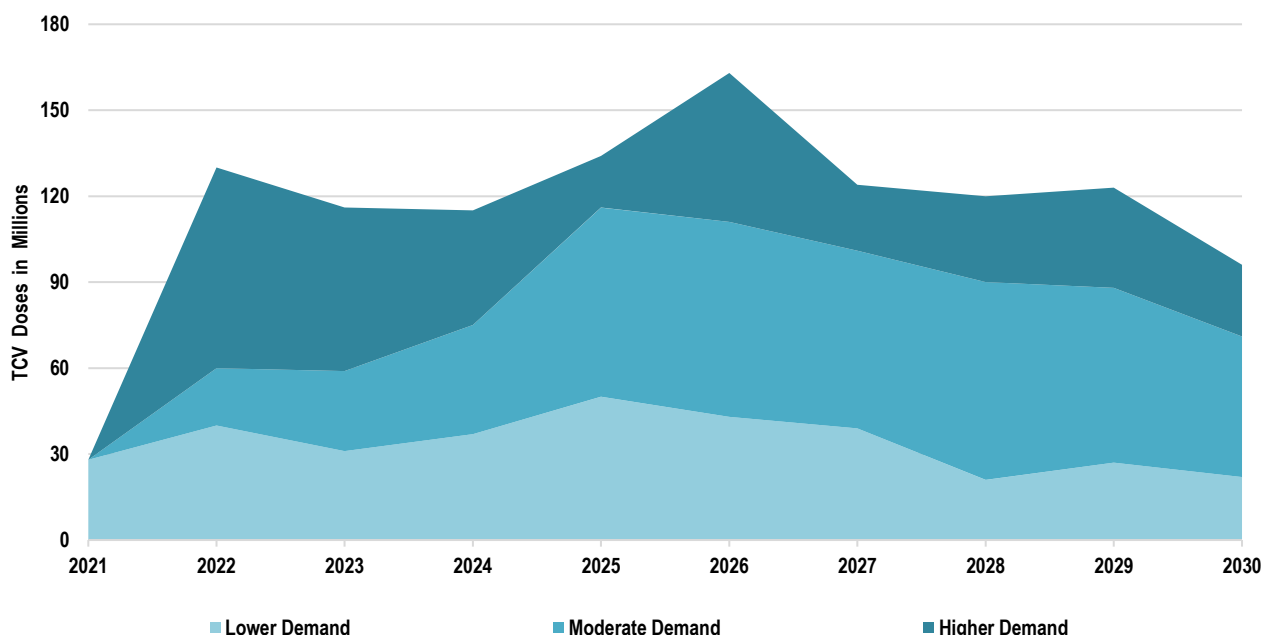


By contrast, the Global Vaccine Market Model (GVMM) estimates the total market revenues for TCV in middle-income countries (MICs) and LICs to have reached USD 44 million only, representing a market share of approximately 14 per cent, of which Africa accounts for 30 per cent and the eastern Mediterranean 70 per cent (Figure 3). The current global demand for TCV, aside from the volumes procured through UNICEF, has been limited for use in pilot projects, minimal uptake by India's private sector market, and the recent introduction in Samoa.

Source: GVMM

Despite the impact of COVID-19 on reduced routine immunization coverage rates globally, the global demand for TCV nevertheless remains highly uncertain and is still evolving. This is due to the significant uncertainty in defining local typhoid epidemiology, which hinders defining what vaccination strategy countries should adopt. The World Health Organization analysed the global demand estimate for 2021-2030 in accordance with its recommendations. The World Health Organization developed three scenarios based on their view of how TCV demand could evolve due to the lack of epidemiological data and uncertainty of countries vaccination strategy. Correspondingly, their high, moderate, and low scenarios reflect a wide, moderate, and sparse introduction landscape respectively (Figure 4).

Figure 4 Global Typhoid Conjugate Vaccine Demand Estimates 2021-2030



Source: World Health Organization

In terms of volume, WHO anticipates the global demand for TCV to peak in the medium term ranging from 43 to 163 million doses reflecting the demand driven by the campaigns in the countries eligible for support from Gavi.¹⁹ The World

¹⁸ Data Bridge Market Research, [Global Typhoid Vaccine Market - Industry Trends and Forecast to 2029](#), Data Bridge, Prune, May 2022.

¹⁹ Gavi, the Vaccine Alliance, [Eligibility](#), Gavi, Geneva, June 2022.

Health Organization expects the total demand from these countries eligible for Gavi support to account for the majority of global TCV demand. The demand outside of Gavi support may take longer to materialize and could account for seven to nine per cent of global demand by 2030 in terms of volume.²⁰

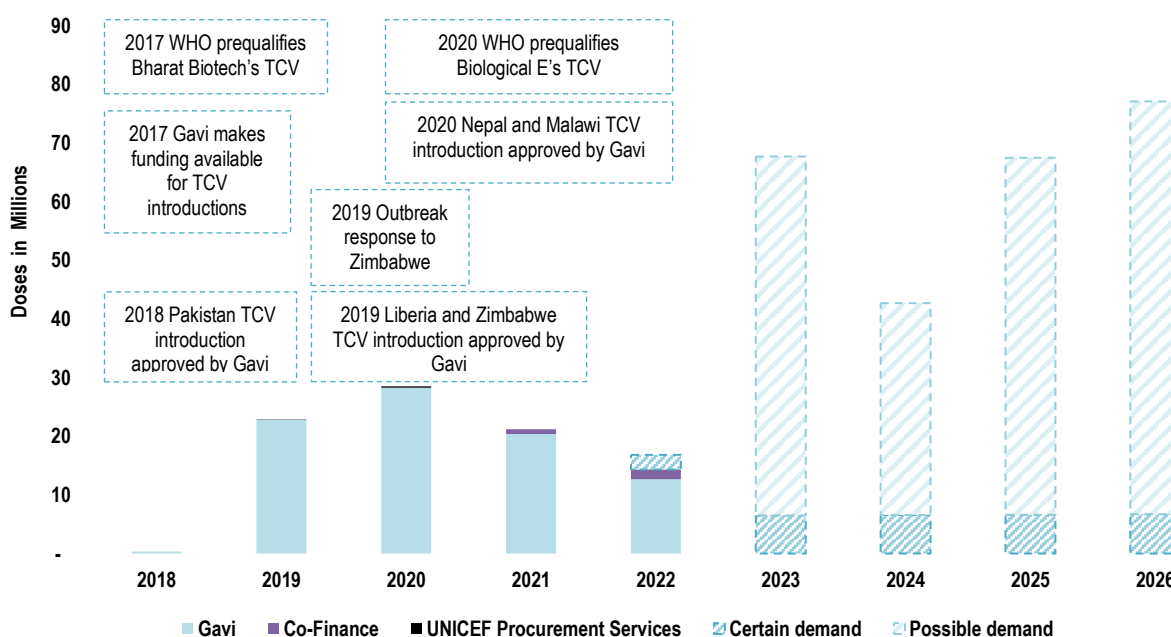
In November 2017, Gavi approved funding for countries to introduce TCV into their routine immunization programmes as well as for catch-up campaigns for children from 6 months to 15 years of age, including for outbreak response. Based on their epidemiological profile, countries may determine their immunization strategy (for example whether to adopt a phased or sub-national process, or variations of routine immunization and campaigns). From 2018 to date, only five countries have been approved by Gavi for routine immunization and catch-up campaigns, in addition to support having been provided for outbreak response in Zimbabwe in 2019.

UNICEF procures almost 100 per cent of the market share for LICs and LMICs. UNICEF anticipates this to continue until there is an uptake of the vaccine in upper middle-income countries (UMICs). However, as the disease burden is higher in sub-Saharan Africa, South and Southeast Asia, and these countries are mostly supported for TCV procurement by Gavi, UNICEF anticipates its procurement volume will increase as additional countries introduce the vaccine. UNICEF's share of TCV procurement may likely decrease slightly after 2030 when many MICs are projected to introduce the vaccine.

UNICEF supports the creation of supply security through its long engagement with governments on national immunization programming, from supply chain optimization to demand side investments to decisions on appropriate national vaccine schedules through NITAGs, as well as establishment of a diversified manufacturing base. UNICEF encourages existing and emerging manufacturers to diversify production in support of building regional capacity. Should clarity of epidemiology and impact peak demand for TCV to levels sufficient to prevent new cases, a clear case could be made for a regional supply base in Africa and Asia. UNICEF encourages manufacturers to proactively look and support market diversification of vaccine production, especially on the African continent.

4.1 Demand

Figure 5 UNICEF Typhoid Conjugate Vaccine Procurement and Demand Forecast through UNICEF 2018-2026



Source: UNICEF Supply Division

The TCV market is developing and as a result, there is uncertainty of the uptake and introduction of the vaccine. Factors contributing to the uncertainty include a lack of epidemiological data to support decision making for introduction and immunization strategies; potential improvements in water and sanitation; competing priorities with other vaccines and outbreaks. Though the uptake of TCV by countries has been slow, the NITAGs in some countries, such as Bangladesh, Burkina Faso, India, Kenya, and Zambia, have recommended the introduction of TCV, which is an indication of future demand. As of October 2022, five countries (Liberia, Malawi, Nepal, Pakistan, and Zimbabwe) have sought, and have

²⁰ World Health Organization, [Global Market Study: Typhoid Vaccines](#), WHO, Geneva, November 2020.

been approved for Gavi funding support to introduce the vaccine into their national routine immunization programme, including catch-up campaigns, as well as an outbreak response in Zimbabwe (2019). Samoa is the only country not eligible for Gavi support to have introduced the vaccine into its routine immunization.

UNICEF has been procuring TCV since 2018 (Figure 5, previous page), following WHO having prequalified the first TCV in 2017. The demand for TCV through UNICEF is mostly for the Gavi supported segment of the market, meaning countries that have chosen to introduce the vaccine, in addition to a few ad-hoc requests from countries outside of the Gavi segment. The demand from Gavi-supported countries is largely driven by the need for catch-up campaigns, which stabilises once the campaigns have been completed. The demand from MICs through UNICEF has been irregular and on an ad hoc basis, including some demand targeting the traveller market.

Since 2018 through to end 2022, UNICEF will have procured approximately 89 million doses. The procurement volume through UNICEF peaked at about 28 million doses in 2020 due to the requirements for catch-up campaigns in 2020. Even though the demand for TCV through UNICEF could range from between 42.7 million to 77.1 million over the course of 2023 and 2026, UNICEF is certain of the demand for 6.5 million doses per annum, which is the demand for the routine immunization in countries that have been approved by Gavi.

4.2 Supply

Current supply availability is sufficient to meet the demand through UNICEF, and globally, manufacturers have scaled up their production capacity in anticipation of the eventual roll-out of TCV in countries.

UNICEF launched its first tender for TCV in 2018 for the period 2019-2020. It was extended further by one year through to the end of 2021. The tender concluded with UNICEF signing an LTA with Bharat Biotech, the only manufacturer that had a WHO prequalified vaccine at that time. UNICEF launched another tender in 2021 for the period 2022-2024, and signed LTAs with both manufacturers having WHO prequalified TCV for those countries supported by Gavi and MICs. UNICEF awarded supply quantities covered by the demand from countries that have either introduced or been approved support by Gavi (Table 2). Given the high uncertainty of the demand forecast, a time-bound LTA was awarded for any quantities in support of MICs, which will be communicated as it becomes known.

Table 2: UNICEF Long-term Arrangement Awards for 2022-2024

Manufacturer	Vaccine	Market	Price per Dose	Schedule	Total Doses Awarded
Bharat Biotech (India)	Conjugate Vi-TT	Gavi	USD 1.50	1-dose	15,741,250
Biological E (India)	Conjugate Vi-CRM197	Gavi	USD 0.95	1-dose	23,524,130
		MICs	USD 1.50	1-dose	n/a
Total					39,265,380

Source: UNICEF Supply Division

As additional demand materializes, UNICEF will award additional doses to both manufacturers.

4.3 Pricing

UNICEF publishes the vaccine prices for each supplier holding LTAs with UNICEF, which may be referenced. UNICEF TCV prices can be viewed [here](#).^{21, 22}

5. Issues and Challenges

- Countries are slow to take up the vaccine as they have been prioritizing other requirements. They also have difficulty in being able to define the local epidemiology of typhoid, which makes it difficult for endemic countries to commit their engagement to controlling typhoid.
- The pace of generating demand is uncertain and is further exacerbated by the lack of information on any country introduction plans, vaccination strategy, whether these are at a national or sub-national targeted level. This is in addition to the inherent difficulties in being able to plan the needs for any outbreak response, as it is difficult to predict outbreaks given the nature of their occurrence.
- Manufacturers currently having been awarded UNICEF LTAs are concerned about the slow uptake of TCV and the lack of visibility on any planned country introduction schedule and timing. They have scaled up their production

²¹ UNICEF, [Pricing data](#), UNICEF, Copenhagen, November 2022.

²² UNICEF, [Typhoid Conjugate Vaccine \(TCV\) Price Data](#), UNICEF, Copenhagen, November 2021.

capacity to accommodate country requirements in anticipation of planned country introductions and need to manage and mitigate the supply and demand risk uncertainty.

6. Steps Forward

- UNICEF is engaging countries to obtain the information necessary to shape the generation of demand in the market and improve forecast accuracy in order to secure supply volumes. Gavi has made investments in Typhoid surveillance and diagnostics to assist country decision making in the introduction of TCV and targeting of catch-up campaigns.
- UNICEF will provide industry with updated country forecast data as new information becomes available.
- UNICEF and Gavi are engaging with industry to manage expectations around anticipated country demand and communicate plans for the timely generation of demand in the short- and medium-term. UNICEF and Gavi will seek to identify ways to ensure continued interest in this market.

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