White Paper

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Full Value of Vaccine Assessment of Microarray Patches for Typhoid Conjugate Vaccines

Contents

Cover image: The Global Fund/Vincent Becker

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Credit: Gavi/2024/Dominique Fofanah

Acronyms and abbreviations

AMR	Antimicrobial resistant
CE	Cost-effective
CEA	Cost-effectiveness analysis
COGS	Cost of goods sold
CS	Cost saving
DALY	Disability-adjusted life year
DCF	Discounted cashflow analysis
ECEA	Extended cost-effectiveness analysis
ECVP	Evidence considerations for vaccine policy
EPI	Expanded Programme on Immunisation
FVVA	Full Value of Vaccine Assessment
GDP	Gross domestic product
HCW	Healthcare worker
HCE	Highly cost-effective
HIC	High-income country
HPV	Human papillomavirus
HTR	Hard-to-reach
ICER	Incremental cost-effectiveness ratio
IVIR-AC	Immunization and Vaccine-related Implementation Research Advisory Committee
LMIC	Low- and middle-income countries
MAP	Microarray patch
MD	MAP developer
MDR	Multi-drug-resistant
MI4A	WHO's Market Information for Access to Vaccines
MIC	Middle-income country
MOV	Missed opportunities for vaccination
MR	Measles-rubella
MCV1	Measles-containing vaccine, first dose
MCV2	Measles-containing vaccine, second dose
NCE	Not cost-effective
NITAG	National Immunization Technical Advisory Group
NRA	National regulatory authority
NPV	Net present value
N&S	Needle and syringe
PDR	Programmatic doses required
PPC	Preferred product characteristics
PQ	WHO pre-qualification
S. Typhi	Salmonella Typhi
SIR	Susceptible-infected-recovered
TCV	Typhoid conjugate vaccine
UC	Use case
UMIC	Upper-middle-income country
VM	Vaccine manufacturer
VCE	Very cost-effective
WASH	Water, sanitation and hygiene
WQ	Wealth quintile
WTP	Willingness to pay
WUENIC	WHO/UNICEF estimates of national immunisation coverage
XDR	Extensively drug-resistant

Executive summary

Typhoid fever, caused by *Salmonella* Typhi (S. Typhi), is a significant global health concern in many low- and middle-income countries (LMICs). While recent estimates suggest the global **annual burden of typhoid is over 11 million cases and 128,000 deaths**, this is likely underestimated due to the **challenges in surveillance and diagnosis of the disease**. The emergence of **antimicrobial resistance and the impacts of climate change** suggest **typhoid prevention and management will continue to become more challenging.**

Typhoid conjugate vaccines (**TCVs**), which are recommended by WHO for use in endemic countries, **offer effective, long-lasting protection for children as young as 6 months of age**. It is a liquid vaccine and relatively thermostable, as demonstrated by the controlled temperature chain (CTC) qualification of one TCV. TCVs have been introduced in routine immunisation programmes in a few countries and have also been used effectively in epidemic response efforts. However, **TCV uptake so far has been slow** (only six countries have introduced it out of 44 high-incidence countries[1]) and therefore **barriers specific to typhoid immunisation are yet to be fully identified** as the programme ramps up. Some barriers are mostly linked to introduction decision-making (i.e. the burden is not well understood at the country level), while other barriers are linked to implementation feasibility and shared with other injectable vaccines, such as **challenges in vaccinating hard-to-reach populations, cold chain needs and high human resource demands**.

Typhoid conjugate vaccines microarray patches (TCV-MAPs) are a needle-free presentation that represents a promising innovation with the potential to overcome some implementation immunisation barriers. Vaccination by **MAP is expected to be easier than by injection, potentially enabling administration by lesser-trained health workers**, and could be **more thermostable than existing vaccines, simplifying logistics**. In addition, MAPs could provide an alternative to additional injections in the already crowded immunisation schedule for this target population. These potential advantages could **enable improvements in coverage in hard-to-reach populations and be more acceptable to patients**. As **TCV-MAPs are in pre-clinical development** and are expected to enter the clinic in the coming years, it remains to be seen how many of these potential benefits will materialise as product characteristics are not yet known. Assessing the **value of such an innovation to the extent possible at this early stage will help identify the critical product characteristics, guide potential future investments from a range of stakeholders** and inform if the **benefits could be commensurate with the expected price premium** compared to existing injectable TCV vaccines.

The **TCV-MAP Full Value of Vaccine Assessment** (**FVVA**) **aims to evaluate the value of TCV microarray patches and inform decision-making** on potential investment in and use of the technology by **funders, vaccine manufacturers** (**VMs**) **and MAP developers** (**MDs**) **and policy-makers at the country, regional and global levels**. This FVVA serves as a comprehensive framework for evaluating TCV-MAPs, analysing their health, economic and societal impact to assess their potential value alongside existing vaccines to optimise typhoid prevention and response efforts in LMICs. **The FVVA provides insights on the immunisation barriers that could be addressed, target populations that could be best served**, and the **potential demand for TCV-MAPs**. It also assesses the **potential impact of TCV-MAPs on disease transmission, delivery costs and cost-effectiveness as compared to needle and syringe** (**N&S**) **presentations** through a variety of TCV-MAPs introduction scenarios (national and subnational levels, broad or targeted to specific use cases, epidemic response) and **evaluates the impact on equity**. The FVVA also supports industry partners in **understanding the potential business cases and willingness-to-pay from countries** and allows **regulatory and policy-makers to identify the outstanding questions to clarify regulatory and policy pathways.**

Analysis of **public health impact** revealed that the **introduction of TCV-MAPs** presents an opportunity to reduce the global burden of typhoid fever, with the **potential to avert more than 5 million additional typhoid cases** (2%) **and 47,000 deaths** (3%) **over a span of 20 years compared to using the injectable TCV vaccine alone**. TCV-MAPs were also found to **positively impact equity in immunisation, by driving the greatest health impact to the poorest quintiles**. Greater protection within this segment would also have indirect health benefits to the broader population.

This impact could be achieved by reaching target populations that would benefit the most from TCV-MAP use. To identify these populations, **six priority use cases** were established and validated through expert

consultation. The identified use cases show that **TCV-MAPs could be used in fixed post, outreach and mobile settings to reach children less than 2 years old** (**target populations of routine immunisation**) **and 2–15 years across all settings** (**target populations of the catch-up campaigns recommended when TCV is introduced**). In addition, in **non-endemic high-income countries, the uptake of TCV among travellers and military personnel** could be facilitated using TCV-MAPs. As TCV recommendation is not universal, country archetypes have been developed to qualify the relevance of each use case to different country contexts.

The national introduction of TCV-MAPs could be cost-effective within the majority of the target population in the African region, particularly when TCV-MAPs are priced at or below US$ 3 per dose. However, **cost-effectiveness is unlikely in other regions**. The key drivers of cost-effectiveness are the TCV-MAP price and product attributes, particularly cold chain volume. These findings also hinge on the assumption that TCV-MAPs will help reach a proportion of the otherwise unreached populations. In instances **where national implementation of TCV-MAPs is unfavourable, a subnational deployment strategy could prove cost-effective**, especially **in areas with elevated typhoid mortality rates**. However, **when TCV-MAPs are used in response to outbreaks, limited health impact is expected**, and TCV-MAPs are unlikely to be cost-effective compared to TCV N&S. This is mainly driven by the relatively low observed mortality and costs of treatment of typhoid compared to the additional expense of deploying TCV-MAPs broadly. In contrast, for infectious diseases that have higher case fatality rates, result in long-term disability or lack effective or easily deployable N&S vaccine, MAPs could prove more beneficial in epidemic response.

MAPs could potentially represent a significant portion of the total TCV market, as shown by the demand sizing exercise, especially in outreach and mobile settings. Assuming that TCV-MAPs could become commercially available in 2033, **estimates of global demand for TCV-MAPs range from 14–33 million doses per year initially, increasing to 62–107 million doses annually by the tenth year.** This potential demand is mainly spread across LMICs and middle-income countries (MICs), with a minor segment comprising military personnel and travellers in high-income countries. The **broad range in potential demand is mostly due to uncertainties in the pace of TCV introduction and in the proportion of TCV doses switched to a MAP presentation**. These initial demand estimates do not include any price considerations. Given the observed limited willingness to pay, price sensitivity may restrict the extent to which these demand estimates may materialise. These estimates are based on the current TCV recommendations, and any potential future changes in the TCV schedule or dose regimen could impact these findings.

Through country consultations, **stakeholder perceptions** were found to favour **TCV-MAPs** as compared to N&S presentations, with respondents highlighting the **potential for increased thermostability as a key advantage**. However, **enthusiasm for TCV-MAPs does not necessarily translate into willingness to pay a price premium**. The willingness to pay analysis found that although all respondents were willing to pay the equivalent price, less than half (37%) were willing to pay a higher price for TCV-MAPs than injectable TCV. Increases or reductions in vaccine delivery costs had only a modest impact on willingness to pay for MAPs, indicating that **product costs are more important than changes in delivery costs. Price sensitivity may be lower in non-Gavi-eligible countries**. However, this trend warrants further analysis. Successful adoption of TCV-MAPs may hinge on strong uptake in high-income countries. Therefore, future exploration of willingness to pay among purchasers in these markets would be useful.

In conclusion, under the appropriate circumstances, TCV-MAPs could make a valuable addition to equitable and effective typhoid immunisation. These appropriate conditions span **parameters such as:**

- **geographies** (TCV-MAPs are most likely to be cost-effective in the African region);
- **introduction scenarios** (subnational introductions could be cost-effective in some countries where national introduction is unlikely to be);
- **product attributes** (driven by cold chain volume and thermostability profile);
- **price** (influencing the extent to which a TCV-MAP can be cost-effective, limiting countries' willingness to pay for TCV-MAPs); and
- **uptake in different target populations, including segments such as travellers and military in HICs,** which could drive the financial attractiveness of the business case.

Commercialising TCV-MAPs could be financially attractive, but this will be **contingent upon a substantial portion of the TCV market switching to a MAP presentation and uptake in high-income markets**. TCV could also be an interesting test case for MAPs, potentially opening the road to other vaccines to be put on a MAP, including future combination vaccines.

1 Full Value of Vaccine Assessment for TCV-MAPs

Key insights

- The TCV-MAP Full Value of Vaccine Assessment aims to evaluate the value of TCV microarray patches and inform potential investment and introduction decisions in the technology by multiple stakeholders, including funder, vaccine manufacturers and MAP developers and policy-makers at the country, regional and global levels.
- The FVVA assessed the potential value of TCV-MAPs through a methodology that explored the potential health and economic impact of the technology as well as the outstanding development and implementation questions.

1.1 Purpose and objectives

A Full Value of Vaccine Assessment (FVVA) framework seeks to thoroughly integrate evidence to evaluate the overall value of vaccines. It includes multiple analyses to assess public health needs, examines supply and demand considerations and considers the market and the vaccine's impact from health, financial and economic perspectives.[2] An FVVA considers the perspectives of a broad range of stakeholders, with the goal of communicating the direct and indirect benefits of a vaccine.[3]

This FVVA for typhoid conjugate vaccine microarray patches (TCV-MAPs) seeks to clarify the potential of this innovative technology to address unmet vaccine delivery needs, particularly in low- and middle-income countries (LMICs). The FVVA encompasses an evaluation of the socioeconomic and public health benefits that could be realised. It serves as a crucial tool to facilitate engagement and decision-making by stakeholders, including policy-makers, funders/procurers and countries, while also providing clarity for MAP developers (MDs) and vaccine manufacturers (VMs) on the potential demand for and preferred/critical characteristics of vaccine MAPs in LMICs. The FVVA provides insights about potential business cases, which could inform decision-making in advancing TCV-MAPs from funders, MDs and VMs.

The FVVA may also provide relevant information for country stakeholders in decision-making regarding the potential introduction of vaccine MAPs in their typhoid immunisation programmes. In LMIC markets, where affordability is a key consideration, understanding the full incremental value that an innovation can offer in terms of broader public health and socioeconomic gains is crucial. This assessment can help evaluate if a higher price point for the innovation is commensurate with its additional value, as well as inform demand and decision-making. Additionally, early willingness-to-pay estimates can inform global health partners on the required pathway to country uptake, funding needs and policy considerations. The FVVA will also support industry partners, regulators and policy-makers to identify the outstanding questions to clarify regulatory and policy pathways for the technology.

The first FVVA, for Group B streptococcus vaccine, was published in 2021,[4] and others have been published or are in development, including FVVAs for coronavirus vaccines,[5] tuberculosis vaccines[6] and measles-rubella microarray patches (MR-MAPs).[7] Unlike other vaccines for which FVVAs are in development, TCV-MAPs are currently in early-stage preclinical development. However, the development of TCV-MAPs has recently gained traction; typhoid vaccine manufacturer SK Bioscience and MAP developer Vaxxas entered into a joint agreement – with support from Wellcome – to develop a TCV-MAP, including preclinical studies followed by a phase one clinical trial.[8]

While being at an early stage of development leads to greater uncertainty in the product attributes and development and introduction timelines, understanding the potential impact and value proposition of the technology early in the development cycle can help inform investment decisions and may help shape the value proposition. As more information becomes available, updates to the FVVA may be required.

Credit: Gavi/2024/Jjumba Martin

1.2 Methodology to develop the FVVA

The TCV-MAP FVVA was developed between 2022 and 2023. It consisted of multiple workstreams designed to develop insights required to inform future decisions on TCV-MAP development and uptake (Figure 1). Several assessments were initially conducted to inform an understanding of typhoid immunisation barriers, product preferences and decision-making considerations for new vaccine introductions and presentations. These findings informed projections of the potential demand for TCV-MAPs. In addition, a production economics assessment was conducted to determine the potential costs of goods sold in TCV-MAP production. Results from these analyses were central to estimating the potential public health and socioeconomic impact of TCV-MAPs. The estimates of the potential public health and socioeconomic impact of TCV-MAPs were generated based on TCV-MAPs potential impact on disease transmission, delivery costs and cost-effectiveness compared to conventional injectable presentations. The production economics assessment and socioeconomic and public health impact analyses helped to inform the discounted cash flow analysis for TCV-MAPs, which assessed the potential financial viability of TCV-MAP development and commercialisation. Details of the methods for each assessment are available in the relevant sections and appendices of the FVVA.

All analyses, assessments and conclusions presented in this FVVA are TCV-product agnostic and do not focus on any specific TCV-MAP or TCV product. Rather, they represent a potential product based on characteristics and attributes of different MAP platforms in development and TCVs on the market.

Multiple stakeholder consultations were conducted to inform the FVVA, including a global stakeholder survey, focus group discussions to inform the TCV-MAP use cases, country consultations and consultations with industry leaders in TCV and MAP development.

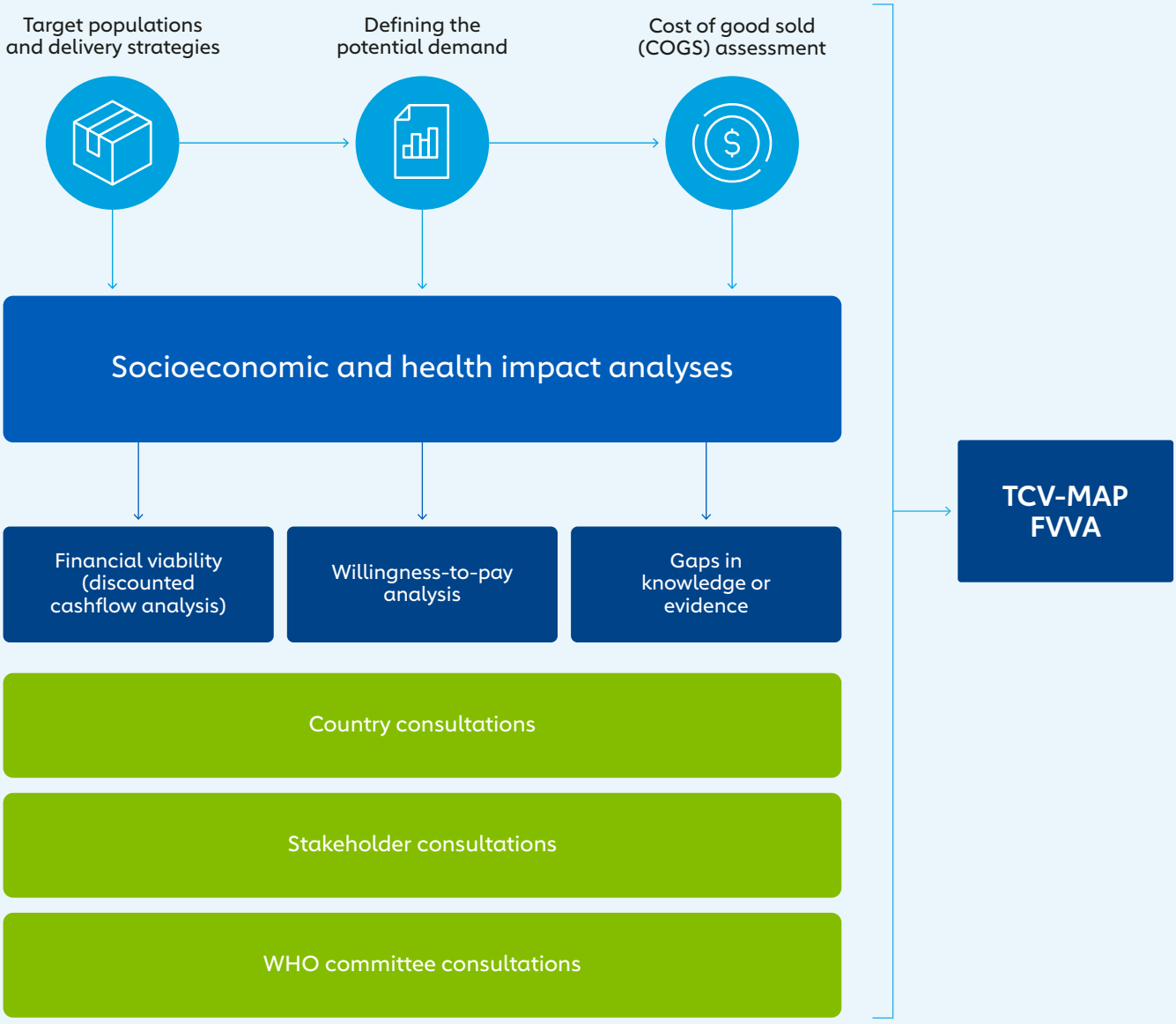
The country consultations were conducted in two rounds. The first round included consultations in eight typhoid-priority countries and was designed to provide feedback on:

1. key components considered for new vaccine presentation introduction decisions;
2. qualitative factors to be included in the quantitative socioeconomic and public health impact analyses;
3. decision-making considerations for products with an expected price premium (e.g. MAPs); and
4. feedback on the potential role of a TCV-MAP in country immunisation programmes, noting essential attributes for consideration.

The second round of consultations focused on willingness to pay and collected insights from stakeholders from 10 countries representing different levels of typhoid burden, TCV introduction status and Gavi-support status.

The FVVA and its development were guided by an expert group of advisers consisting of 14 experts in typhoid epidemiology, health economics, vaccine product development and programme implementation who informed key aspects of the methods and supported the analysis of the key findings of the FVVA. Additional validation of components of the socioeconomic and public health impact analyses was conducted through the WHO Immunization and Vaccines-related Implementation Research Advisory Committee (IVIR-AC).

Figure 1. **TCV-MAP FVVA project workstreams**



2 The global public health need for TCV vaccines and current implementation status

Key insights

- Typhoid continues to be a major cause of morbidity in many parts of the world, causing illness in 11-20 million people annually and resulting in over 128,000-161,000 deaths each year.
- Due to limitations in diagnosis and surveillance many cases of typhoid are not treated appropriately or in a timely manner which has contributed to the emergence of multidrug resistant typhoid.
- Effective vaccines against typhoid are available and TCV is beginning to be introduced in routine programmes in some endemic countries, but uptake so far has been slow.

2.1 Overview of typhoid epidemiology

Typhoid fever is a systemic illness caused by the bacterium *Salmonella enterica* serovar Typhimurium (S. Typhi), which affects millions of people worldwide, particularly those living in LMICs with inadequate access to safe water and sanitation. According to the WHO, typhoid fever causes illness in 11–20 million people annually, resulting in an estimated 128,000–161,000 deaths each year, with a mortality rate of 1–2% if untreated.[9] Symptoms of typhoid fever can range from mild to severe and include fever, headache, abdominal pain and diarrhoea. In severe cases, typhoid fever can lead to complications such as intestinal perforation or bloodstream infections, which can be life-threatening.[10]

Typhoid fever is primarily transmitted through the faecal-oral route, most commonly by consuming contaminated water or food handled by infected individuals.

Typhoid transmission occurs in many parts of the world where the disease is endemic, most notably in Asia and Sub-Saharan Africa. However, the disease can also be transmitted in an epidemic. Outbreaks of typhoid are increasingly common in areas with poor sanitation, and the disease can spread rapidly in high-density environments.[11]

As an enteric infection, typhoid fever has complicated epidemiology with interactions and associations with other enteric infections. Coinfection with other enteric pathogens, such as those causing diarrhoea or helminth infections, can affect the severity and clinical outcomes of typhoid fever. Moreover, interventions targeting enteric infections, such as improved water and sanitation infrastructure, can have indirect effects on the incidence and severity of typhoid fever.[12]

2.2 Current methods of typhoid prevention

Preventing typhoid fever requires a comprehensive approach that includes vaccination, improvements in water and sanitation infrastructure, and hygiene practices. Immunisation has long been a critical component of typhoid fever prevention through the use of either a two-dose injectable inactivated vaccine for people aged over 2 years or a four dose live attenuated oral vaccine in capsule formulation for people aged over 5 years. However, these vaccines do not provide long-lasting immunity and are not approved for use in children less than 2 years of age.

Typhoid conjugate vaccines, which have been recommended by WHO since December 2017, offer longer-lasting immunity and are approved for use in children from the age of 6 months.[13] There are currently three WHO prequalified TCVs – Typbar-TCV (Bharat Biotech), TYPHIBEV (Biological E.), and SKYTyphoid Multi Inj. (SK Bioscience) – which have a single dose schedule and have shown strong safety, efficacy and duration of protection.[14] These vaccines are liquid, and the Typbar vaccine has obtained the controlled temperature chain (CTC) qualification.[15] In addition, TCVs have also been shown to be cost-effective in high-burden countries.[16]

The WHO officially recommends incorporating TCVs into routine childhood immunisation schedules, while also conducting catch-up vaccination campaigns for children up to 15 years old. This recommendation particularly emphasises prioritising countries with a significant typhoid burden and/or cases of drug-resistant typhoid.

As of 2023, six countries have introduced TCV into their routine immunisation programmes including Liberia, Malawi, Nepal, Pakistan, Samoa and Zimbabwe.

Most countries that have introduced TCV thus far included nationwide catch-up campaigns for children up to age 15 years alongside introduction into routine immunisation schedules at 9 months of age. Routine introduction so far has been slow, as, based on conservative estimates of typhoid burden, 44 high-incidence countries could be in-scope for TCV introduction in their routine schedule.[17] In addition, although limited, TCVs have also been used in outbreak response campaigns in both Pakistan and Zimbabwe.

2.3 Typhoid diagnosis and surveillance

Surveillance and timely diagnosis of typhoid fever are crucial for effective control and prevention. Diagnosis of typhoid fever is typically made through blood culture. However, blood culture is not well suited in most endemic countries due to its limited availability at health facilities and low sensitivity, which is further reduced by pre-diagnosis antibiotic use.[18] Furthermore, access to laboratory services is often limited in resource-poor settings, and alternative diagnostic tests, such as rapid diagnostic tests, are being developed to improve access to timely diagnosis.[19]

In many LMICs, surveillance systems for enteric infections are limited or non-existent, making it difficult to accurately estimate the burden of disease and identify outbreaks. This is further complicated by typhoid fever's non-specific symptom profile, which shares clinical presentations that are common to other diseases occurring in typhoid-endemic areas.[20] Improved surveillance systems that incorporate laboratory confirmation and data sharing between healthcare facilities and public health authorities are essential to improving the early detection and response to typhoid fever outbreaks and to measure the impact of vaccination.

However, the lack of supportive surveillance infrastructure and reliable typhoid data should not hold countries back from vaccinating against typhoid and is not currently a barrier to receiving Gavi support for TCV introduction.[21] Decisions on vaccine introduction should be guided by all available information including population-based and modelling studies as well as outbreak reports.[22]

2.4 Typhoid treatment and antimicrobial resistance

Effective treatment for typhoid primarily relies on suitable antibiotics. Traditionally, chloramphenicol, ampicillin and cotrimoxazole have been the first-line antibiotics used to combat the disease. The overuse and misuse of antibiotics have led to the emergence of multi-drug-resistant (MDR) and extensively drug-resistant (XDR) strains of S. Typhi, making treatment more challenging and costly. A significant development occurred in late 2016 when Pakistan experienced the first outbreak of extensively drug-resistant typhoid. Since then, the emergence of antimicrobial resistance (AMR) has been identified as the major threat to treating typhoid fever. Between 2010–2018, approximately 35% of reported infections in Asia and 75% of those in Africa were multi-drug-resistant.[23]

Greater use of typhoid vaccines to prevent infection supports effective antimicrobial stewardship to preserve the efficacy of available antibiotics. "Vaccination against typhoid fever averts antimicrobial resistance both directly, by preventing transmission of resistant infections, and indirectly, by preventing cases of infection caused by antimicrobial-susceptible S. Typhi that would otherwise be treated with antibiotics and develop de novo resistance."[24] In modelling studies, immunisation with TCV was predicted to reduce the relative prevalence of antimicrobial-resistant typhoid fever by 16%.[25] Countries with a high burden of antimicrobial-resistant typhoid have been specifically prioritised for TCV introduction, including Pakistan, Nepal and Zimbabwe.[26,27]

2.5 Climate change

Climate change significantly increases susceptibility to typhoid outbreaks. The escalating frequency and severity of droughts and floods, exacerbated by climate change, pose substantial risks for typhoid transmission. Drought conditions compel communities to resort to potentially contaminated water sources, elevating the probability of typhoid infection. Conversely, floods inundate already strained sewage systems, leading to the widespread contamination of water sources with human waste, increasing the transmission of typhoid. Additionally, the displacement of populations resulting from natural disasters or conflicts increases the risk of typhoid exposure, as overcrowded living conditions in refugee camps or temporary shelters often lack adequate sanitation infrastructure and access to clean water. In such settings, close proximity among individuals heightens the risk of disease transmission. The convergence of these factors underscores the urgent need for comprehensive adaptation and mitigation measures to address the escalating threat of typhoid in the context of climate change.

3 Vaccine microarray patches for TCV

Key insights

- Vaccine MAPs are at an early stage in development, but the clinical evidence base continues to expand across multiple antigens, including with a first ever successful clinical phase one/two trial in infants for a vaccine-MAP (MR-MAPs).
- MAPs have the potential to address many barriers in vaccine delivery and uptake as compared to the N&S presentation. TCV-MAPs could improve coverage by expanding access to hard-to-reach populations, facilitated by key product benefits:
  - increased ease of use;
  - ability to be administered by lesser trained personnel;
  - improved safety as a sharps-free presentation; and
  - simplified waste disposal.

3.1 MAPs

Vaccine MAPs represent a truly transformative innovation in vaccine delivery that offer distinct advantages over N&S presentations and have the potential to address many of the barriers to immunisation identified by countries.[28]

MAPs consist of clusters of hundreds to thousands of micron-scale projections on a disc or other backing that can be applied to the skin directly or with an applicator.[29] The most common forms of MAPs currently in development are coated and dissolving MAPs. Coated MAPS feature projections that are covered with a dried vaccine formulation. Dissolving MAPs, on the other hand, have projections made from a blend of a polymer and a vaccine antigen, which are designed to dissolve into the skin after penetration[30] Further details on the MAP technology platform and key product attributes are described in Appendix 1.

Significant benefits of MAPs to vaccines broadly (i.e. product-agnostic benefits) include their potential to offer improved thermostability, reducing the need for cold chain infrastructure at the last mile, ease of use and deployment without the need for reconstitution, which further simplifies logistics and safety for vaccines requiring reconstitution. MAPs will likely be well suited for administration by community health workers, potentially by non-health workers and through self-administration. This will reduce the burden on trained healthcare personnel and extend the reach of immunisation programmes to remote and challenging settings.[31]
The minimally invasive nature of MAPs could provide an alternative to additional injections in the already crowded immunisation schedule for the target population for TCV. MAPs may also be perceived as less painful than an injection, increasing acceptance by individuals with

a fear of needles. As single-dose presentations, MAPs could also reduce missed opportunities for vaccination due to the reluctance to open preservative-free multi-dose vials.

MAPs could be used in any immunisation setting, including routine and supplemental immunisation activities and outbreak response. Based on the benefits highlighted above, MAPs also have the potential to improve equitable vaccine coverage and facilitate immunisation across the life course.

By simplifying vaccine delivery and administration, vaccine MAPs could potentially improve rapid immunisation response to epidemics or pandemics, where access to traditional vaccination methods may be disrupted or less effective.

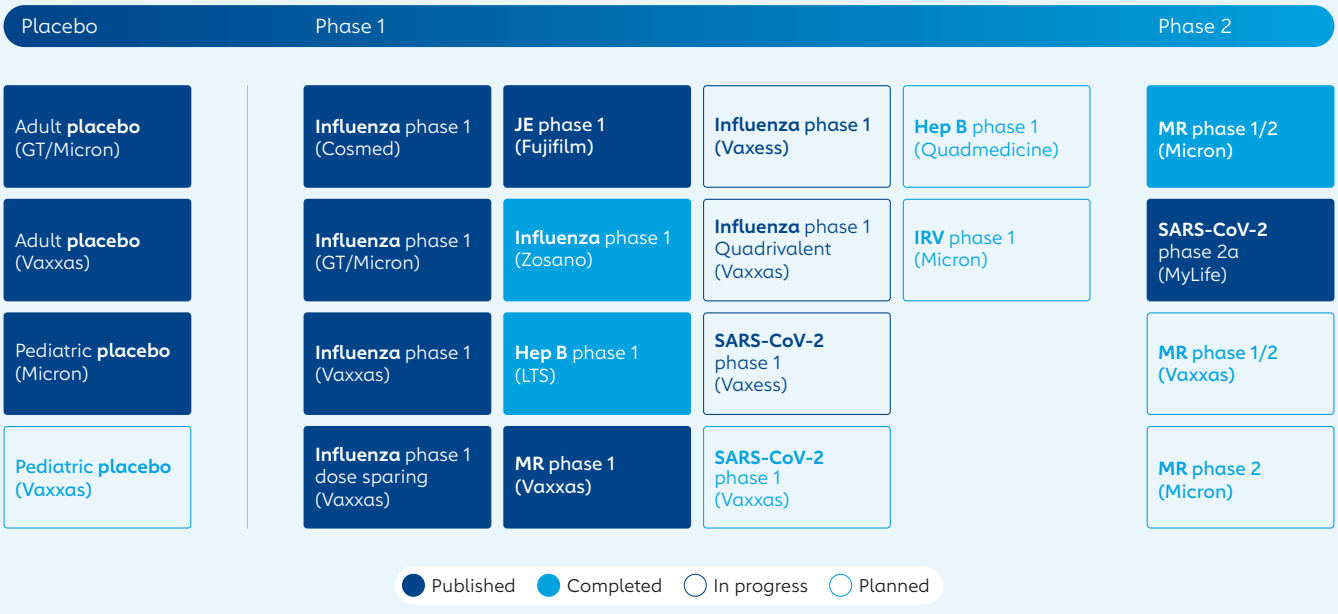
However, MAPs are likely to come at a price premium compared to currently available vaccine presentations. This complexity arises because the technology is groundbreaking and requires innovative manufacturing methods. Compared to traditional vaccine formats, MAPs involve extra components and more complex manufacturing processes, such as the inclusion of devices and applicators where necessary. Given their single-dose format, the MAP cold chain volume per dose will likely be larger than for multi-dose vials.

Credit: Gavi/2014/GMB Akash

3.2 Vaccine MAPs development status

Vaccine MAPs are being developed for several vaccines, including influenza, COVID-19,[32] Japanese encephalitis,[33] hepatitis B[34] and measles-rubella,[35] which have entered early-stage human clinical trials (Figure 2). A major milestone was reached in 2023 with the first-ever positive results of a phase 1/2 clinical trial in infants for MR-MAPs showing similar seroprotection rates for MR-MAP compared to the injectable MR vaccine.

Figure 2. **Clinical evidence base for vaccine MAPs in development**



GT: Georgia Institute of Technology; **LTS:** Lohmann Therapie-Systeme; **JE:** Japanese encephalitis; **Hep B:** Hepatitis B; **SARS-CoV-2:** Severe-acute-respiratory-syndrome-related coronavirus.

As clinical trials progress, further investigation is needed into additional aspects of the technology, including thermostability studies and assessments of the usability, acceptability and programmatic feasibility of MAPs (specifically focusing on challenges such as wear time and increased cold chain volume). Additionally, it will be essential to address technical challenges related to scalability and manufacturability and make significant investments in manufacturing lines or facilities to accelerate access to vaccine MAPs following market authorisation.[36] Lastly, guidance on key regulatory requirements for MAPs remains to be clarified, and a regulatory pathway to authorisation needs to be defined.

3.3 Potential MAPs benefits relevant to TCV

The value of MAPs will vary depending on the challenges faced by a specific immunisation programme, the attributes of MAPs, and the benefits they bring compared to injectable vaccines. Therefore, it is important to assess which potential benefits and challenges would apply to TCV-MAPs.

Key findings related to current TCV delivery challenges, product attributes, and MAPs perceptions were collected through country consultations and summarised in the following sections.

3.3.1 Current barriers/challenges with TCV delivery

TCV is one of the newest vaccines being introduced into Expanded Programme on Immunisation (EPI) in typhoid-endemic countries. Given the high uncertainty in the country-specific disease burden, among other factors, introduction has been slow.

As reported through country stakeholder surveys, key issues impacting a country's ability to reach its TCV-specific immunisation goals that may be addressed by TCV-MAPs include the following (not in ranked order):

- Hesitancy over multiple injections within a crowded vaccination schedule
- Pain from needle and syringe
- Cold chain continuity
- Waste management requirements
- Required skill level to deliver the vaccine
- Contamination due to multi-dose vials

Details of the country consultations conducted can be found in Appendix 8.

Credit: Gavi/2024/Arnauld Yalgwueogo

3.3.2 Key product attributes desired for TCV-MAPs

Due to the early stage of TCV-MAP development, product attributes are not yet known. In the absence of preferred product characteristics (PPCs), consultations and surveys conducted suggest that TCV-MAPs must have improved product characteristics and/or offer additional value compared to the N&S presentation to incentivise countries to switch from the current N&S presentation. Beyond safety and effectiveness, respondents most frequently reported thermostability, cold chain volume and the MAP application process as the most important MAPs attributes. Reasons cited for importance included:

- Thermostability: This could increase access among hard-to-reach (HTR) populations, address the heat sensitivity of current vaccines and reduce cold chain requirements, and facilitate controlled temperature chain (CTC) use.
- Cold chain volume: Stakeholders emphasised that current cold chain capacity is limited. The potential impact of the MAP cold chain volume on cold chain capacity will be an important factor when considering whether to introduce MAPs.
- Application process: A feature to prevent accidental reuse was noted as a key device attribute. The application process could improve ease of use.

TCVs that are currently WHO-prequalified are all liquid vaccines stored in 1- or 5-dose vials. All multi-dose vial TCV presentations can be stored in the cold chain for up to 28 days once opened, per the WHO's multidose vial policy.[37] One vaccine, Typbar-TCV, is licensed for use in a CTC for up to 3 days at 55°C and up to 7 days at 40°C.

Given the N&S TCV presentation is already quite thermostable and CTC qualified, the potential benefits of a TCV-MAP with an improved thermostability profile must be better understood and weighed against the increased MAP cold chain volume per dose compared to a multi-dose vial presentation.

Hence, based on the previously identified addressable attributes, the potential MAP benefits most relevant to TCV are likely to be:

- increased ease of use;
- ability to be administered by lesser-trained personnel;
- improved safety as a sharps-free presentation; and
- simplified waste disposal.

These benefits could allow TCV-MAPs to improve coverage by facilitating expanding access to hard-to-reach populations.

3.3.3 Country interest and perceptions of TCV-MAPs

In a series of consultations and surveys conducted to assess the potential benefits and challenges of TCV-MAP introduction, stakeholders reported positive perceptions of MAPs. A total of 79% of respondents perceived MAPs as a preferred alternative to N&S vaccine presentations. The remaining 21% found the presentations to be similar based on the expected attributes (Appendix 1). Additionally, 75% of participants considered that MAPs could be very useful or quite useful for immunisation, broadly citing the following reasons:

- "More convenient application, preparation and overall vaccine delivery process";
- "Ease of injection pressures on children";
- "Potential to be given by community health volunteers"; and
- "Useful for mass campaigns and HTR areas".

Details of the country consultations conducted, including countries, participants and profiles, can be found in Appendix 8.

Credit: Gavi/2024/Jemimah Eitokpah

4 Target populations and delivery strategies

Key insights

- TCV-MAP use cases were defined according to three dimensions of:
  a. delivery location: where TCV-MAPs are administered;
  b. target population: who is receiving TCV-MAPs; and
  c. provider: who is administering TCV-MAPs.
- Decisions related to how countries introduce typhoid vaccination are largely influenced by their typhoid burden and level of typhoid AMR and if there is potential use of typhoid vaccination in the private market.
- There are important country-dependent factors that impact how TCV-MAPs would likely be used in countries, including the level of typhoid and AMR burden, country income level and private vaccine market presence. These factors were used to define country archetypes.

4.1 Methods

Use cases (UCs) define a specific situation in which a product or a service could potentially be used to accomplish a defined goal and can assist in strategic decision-making. With the aim of better understanding the optimal strategy for using MAPs in national immunisation programmes, TCV-MAP UCs were developed and validated through a literature review, as well as expert and country consultations.

To develop the use cases and country archetypes for TCV-MAPs, published and unpublished literature and data to understand the characteristics of TCVs, the TCV market, and typhoid epidemiology, including the burden of disease, target populations, affected countries and programmatic barriers were assessed.

TCV-MAP UCs were defined by assessing the key factors that influence TCV-MAP use. Country archetypes for TCV-MAPs were defined considering income levels, regional market characteristics, typhoid incidence and level of AMR, level of typhoid surveillance, level of access to clean water and sanitation, availability of policy on typhoid vaccination, and historical use of typhoid vaccines.

Validation of the UCs and country archetypes was conducted by obtaining feedback via an online survey and virtual consultations from typhoid experts and countries that have either introduced TCV or were interested in introducing TCV.

4.2 Outcomes

4.2.1 Identified use cases

The TCV-MAPs use cases were defined along three dimensions to better understand the potential for their use in different circumstances:

a. delivery location;

b. target population; and

c. vaccine administrator.

The delivery location dimension was selected as, given the assumed product characteristics of the MAP presentation (e.g. ease of administration, lighter weight and volume, and potential CTC characteristics), it could be more impactful to use a MAP presentation in outreach or mobile settings.

The target population dimension was selected due to the heterogeneous disease burden and the non-universal recommendations for using TCV per the WHO position paper (introduction at less than 2 years of age with catch-up up

to 15 years of age).[38] The WHO position paper also identifies potential special populations that could require typhoid vaccination, such as food handlers, laboratory workers and travellers from non-endemic to endemic countries.

Finally, the third dimension selected was the vaccine administrator. Like delivery location, this largely relates to the assumed product characteristics of a MAP and the assumed ease of administration that could potentially expand the workforce administering TCV-MAPs.

- Additional factors specific to TCV-MAPs that influenced the use case development included:
- TCV is indicated from 6 months up to 45 years of age.
- Typhoid has a long incubation period and outbreaks can last years.
- Peak typhoid incidence occurs in children aged 5–15 years of age. Thus, school delivery may be an important strategy to reach those that carry the highest burden.
- Other interventions can be used for typhoid control.
- The private market for typhoid vaccination is significant in some countries.

This analysis resulted in six prioritised UCs for TCV-MAPs (detailed further below and in Figure 3).[39]

Additionally, expert consultation indicated that vaccination of military personnel has historically represented a major consumer of typhoid vaccines. For the US alone, the military vaccinates approximately 150,000 service members per year with typhoid Vi polysaccharide vaccine, as compared to the global polysaccharide vaccine demand of 450,000 doses per year.[40,41] While data is limited on this group, vaccination of military personnel deploying into typhoid-endemic areas was included in the use cases as it is likely compulsory and has potential applicability across a broad spectrum of countries.

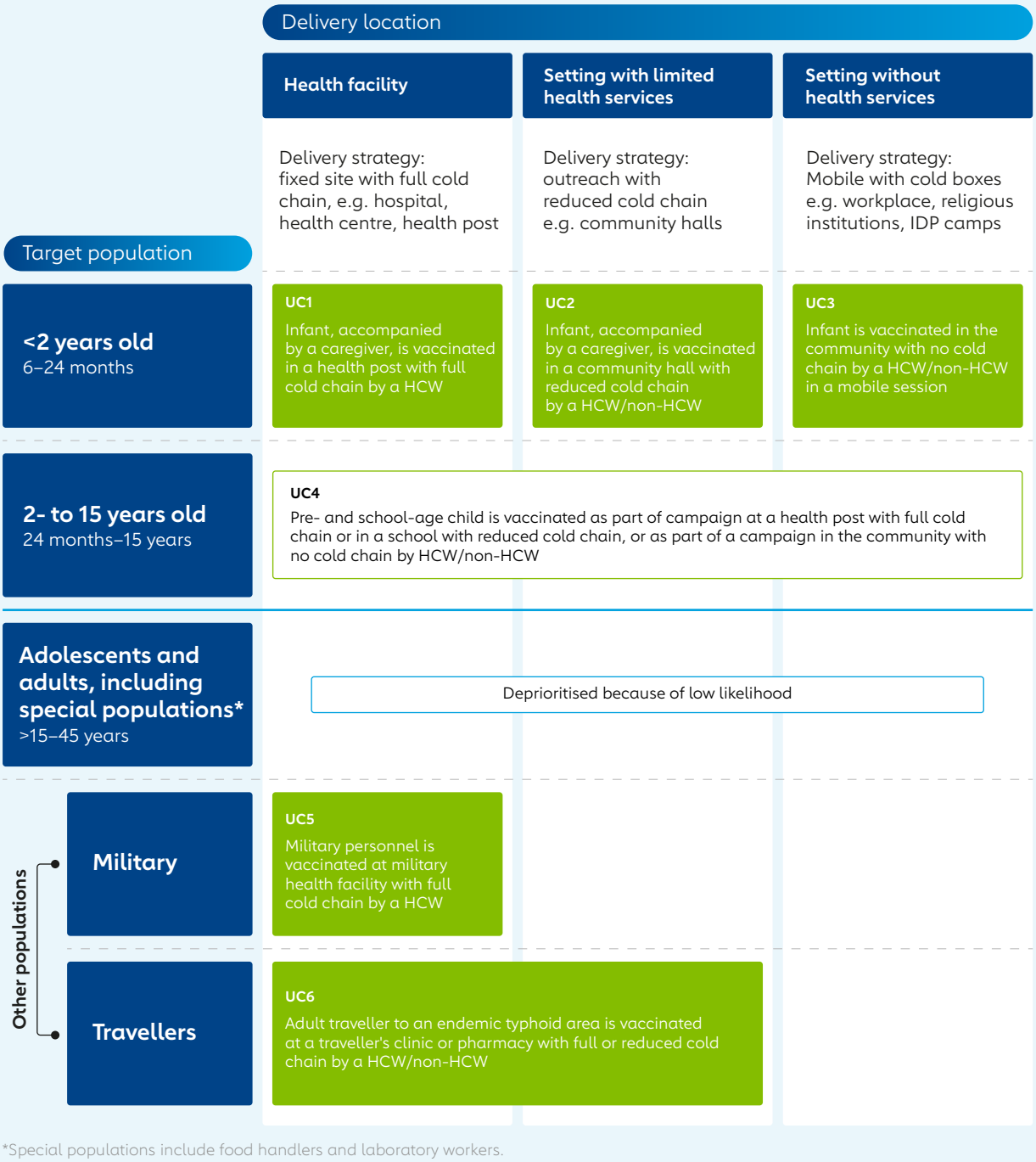
Lastly, despite typhoid fever being rare in high-income countries, it forms an important health risk for international travellers, and new vaccine presentations such as TCV-MAPs may also bring benefits to high-resource settings.[42] Due to increasing global travel, typhoid cases have been on the rise in non-endemic settings, and multi-drug-resistant and extensively-drug-resistant typhoid cases are imported every year.[43] However, only 5% of travellers who become infected with typhoid fever have received a vaccination before travel.[44] TCV-MAPs have the potential to increase vaccine uptake among travellers due to higher patient acceptance, ease of administration and improved convenience. This is particularly the case if the vaccine is approved for self-administration, e.g. the oral Ty21a vaccine.

The final prioritised UCs are described in Table 1 and Figure 3.

Table 1 **TCV-MAP UCs**

Use case	Description
UC 1	Delivery to a child less than 2 years of age in a health facility that has full cold chain capabilities by a healthcare worker (HCW) or non-HCW.
UC 2	Delivery to a child less than 2 years of age in a setting with limited health services and reduced cold chain capabilities by an HCW or non-HCW.
UC 3	Delivery to a child less than 2 years of age in a setting with no health services and no cold chain capabilities (e.g. mobile with cold boxes) by an HCW or non-HCW.
UC 4	Delivery to a child older than 2 but younger than 15 in any delivery location (full cold chain, reduced cold chain or no cold chain) by an HCW or non-HCW.
UC 5	Delivery to military personnel in a health facility with full cold chain capabilities by an HCW.
UC 6	Delivery to an adult traveller either in a health facility (e.g. travellers' clinic) or setting with a reduced cold chain (e.g. pharmacy) by an HCW or non-HCW.

Figure 3. **Prioritised UCs for TCV-MAPs**



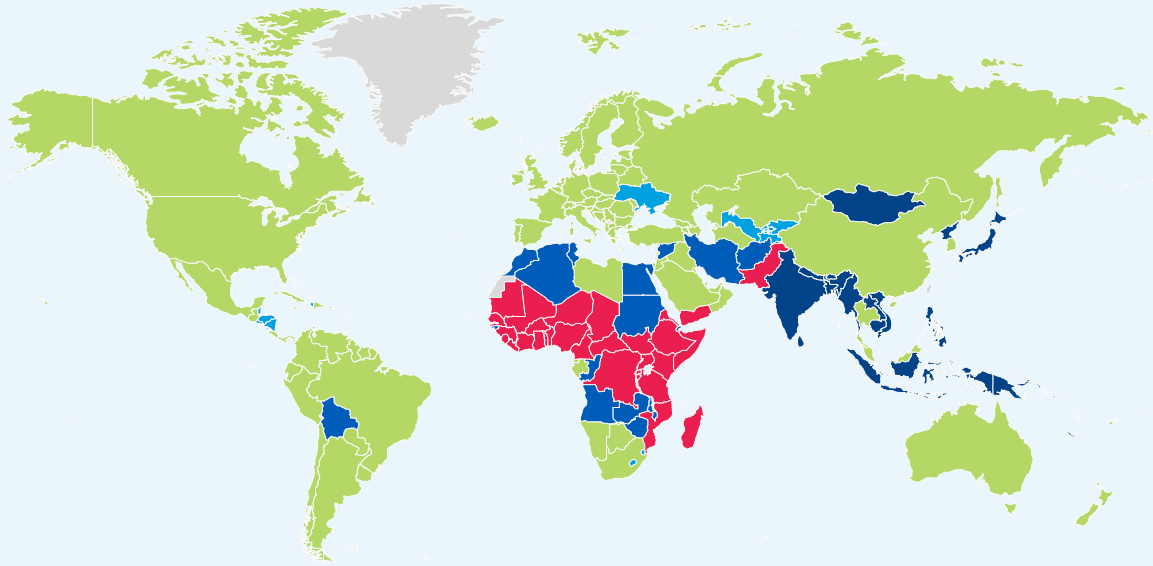
*Special populations include food handlers and laboratory workers.

HCW: Healthcare worker; **IDP:** Internallu displaced person; TCV-MAPs can be administered by either a HCW (e.g. doctor, nurse, midwife, pharmacist, CHW, etc) or a non-HCW (e.g. teacher, community leader, self- or caregiver-administered).

4.2.2 Application of the TCV-MAP country archetypes to the UCs

Typhoid vaccination is not universally recommended to all countries, and it is likely that different subgroups of countries may use TCV-MAPs in a different manner. To capture potential differences, countries were grouped by country archetype, and the likelihood and relevance of each UC were assessed in each of the country archetypes. The likelihood assessment was based on the country archetype's level of typhoid burden, potential vaccination policies, potential private market and historical typhoid vaccine use. Figure 4 provides an overview of the country archetypes and countries by archetype group. Further details on the country archetypes can be found in Appendix 3.

Figure 4. **Map of TCV-MAP country archetypes**



Country archetypes are based on similar income classification, typhoid disease burden and private health service use.

A	· HIC/UMIC · **Low** typhoid incidence and/or AMR
B	· LMIC/LIC · **High** typhoid incidence and/or AMR
C	· LMIC/LIC · **Medium** typhoid incidence and/or AMR
D	· LMIC/LIC · **Low** typhoid incidence and/or AMR
E	· LMIC/LIC with significant private market (Asia and Western Pacific regions) · **Medium-high** typhoid incidence and/or AMR

Country archetype	Number of countries
A	111
B	31
C	19
D	11
E	20

Credit: Gavi/2022/Isaac Griberg

5 Defining the potential demand for TCV-MAPs

Key insights

- As the full demand for TCV-N&S has yet to materialise due to limited country introductions to date, potential demand for TCV-MAPS remains uncertain.
- However, due to TCV-MAPs potential to more easily reach HTR populations, as well as the prioritised use cases for TCV-MAPs showing potential for broad use across different healthcare settings, TCV-MAPs could represent a sizeable portion of the TCV demand, up to 107 million doses per year once demand is fully ramped up.
- TCV-MAP demand estimates range from 62–107 million doses per year 10 years after commercialisation.
- However, there is high uncertainty in potential demand, mostly driven by the market penetration of TCV-MAPs, and by country uptake for TCV.
- Market penetration will be driven by TCV-MAPs technical attributes and price point.

5.1 Methods

Based on the defined UCs, the potential demand for TCV-MAPs was estimated to assess the programmatic doses required (PDR) over the first decade of introduction (2033–2042) following an estimated marketing authorisation in 2033. This analysis leveraged the methodology of the WHO's Market Information for Access to Vaccines (MI4A) *Global Market Study Typhoid Vaccines* to estimate the steady state TCV PDR until 2042.[45] MI4A's market studies provide a global perspective on vaccine market dynamics across various vaccines, including TCV. Demand is estimated using a population-based methodology that has been used in prior vaccine MAP demand forecasts and validated by the MI4A Advisory Group.

The 10-year demand forecast for TCV-MAPs was conducted for 183 countries (WHO Member States), accounting for variability in each country's expected TCV introduction year, target population and anticipated coverage. As defined in the use cases for TCV-MAPs, the target populations for TCV-MAPs include three age groups: <2 years, 2–15 years and 16–45 years. For the 16–45-year-old adult population, proportional segmentation was applied to estimate the number of individuals who were either military personnel or private travellers.

5.2 Key inputs

Two key variables were used in defining the dose split between TCV-N&S and TCV-MAP presentations: TCV-MAP adoption year and TCV-MAP market penetration.

TCV-MAP adoption years were forecasted using a predictive framework considering three criteria: 1) historical introduction timing of recent new vaccines, 2) forecasted Gavi eligibility, and 3) typhoid burden and AMR estimates.

A market penetration percentage was defined for each of the target populations and country archetypes to capture the percentage of TCV-N&S PDR that would "switch" to a TCV-MAP. For the base scenario, the market penetration was set at 80% for all target populations except the military personnel, which was set at 50% given the lower likelihood that MAPs may be used in this population due to adherence concerns. Given limited data, these assumptions were based on expert input collected during the consultations and considered input from the TCV-MAP expert group. They are also aligned with the assumptions made for the MR-MAP initial FVVA (iFVVA).[46] The 80% market penetration aims to set a theoretical maximum potential of the demand while accounting for the fact that not all countries are likely to switch to a MAP presentation. It is aligned with countries' general preference for a MAP presentation

over N&S but does not account for price sensitivity. Accounting for the demand uncertainties, in addition to the base case, further market penetration scenarios were also analysed.

Given the anticipated product characteristics of TCV-MAPs, it is assumed that TCV-MAPs can reach more of the HTR population and reduce missed opportunities for vaccination (MOV) populations compared to the N&S presentation. This additional reach was modelled via two vaccination strategies:

a. annual routine vaccination of HTR and MOV populations less than 2 years old; and

b. a one-time catch-up of 2–15-year-olds when TCV-MAPs are first adopted.

The HTR population was defined considering three key populations: 1) urban slums, 2) remote rural, and 3) security compromised. The MOV population was estimated to be 2% of the less than 2-year-old population based on guidance from experts leading the MOV strategy at WHO. The size of this population was held flat for the entire forecasting period. However, as a MAP presentation is not expected to address all the barriers to reaching HTR populations and reducing MOV and in view of the limited evidence available on the coverage achievable by MAPs in these populations, an assumption of 20% coverage for routine vaccination of less than 2-year-olds and 10% for 2–15-year-olds otherwise unreached by TCV-N&S was applied.[47]

Additionally, this analysis assumes that no programmatic, supply or demand constraints are present. The steady state TCV PDR starting point is assumed to be as forecasted by the MI4A *Global Market Study Typhoid Vaccines* (e.g. all countries that are interested in TCV will have introduced TCV by 2030). Where possible, country-specific data were obtained from standardised sources. Where data were missing or of low quality, extrapolation from country archetype data was conducted.

Given the level of uncertainty in the various assumptions and, consequently, on the overall demand and PDR for TCV-N&S as well as TCV-MAPs, additional scenarios were developed to measure the impact of those factors. Eleven different scenarios were simulated to assess the level of uncertainty inherent in the assumptions across different variables in TCV-MAP demand (Appendix 4).

Figure 7 provides an overview of the results of three key scenarios compared to the base case, demonstrating the impact of the most informative demand dynamics.

- **Base case scenario**: 26 Gavi-eligible and 8 non-Gavi-eligible countries would introduce TCV. National routine introduction for all introducing countries. TCV-MAPs account for 80% of PDR.

- **Low-demand scenario**: In this scenario, 13 Gavi-eligible countries and 4 non-Gavi-eligible countries are modelled to introduce TCV by 2042, and fewer national multi-age campaigns occur. Based on the *Global Market Study Typhoid Vaccines* MI4A projections low case.

- **High-demand scenario**: 100% TCV-MAPs penetration. In this scenario, it was assumed that MAPs would replace the entire TCV-N&S market share, compared to 80% in the base case scenario.

- **Targeted TCV-MAP introduction scenario**: Country-specific assumptions were made on the delivery split between TCV-MAPs and TCV-N&S for UC 1, 2 and 3 in each country based on the proportion of vaccines that are delivered at fixed-post settings as compared to mobile and outreach.

5.3 Outcomes

In the base scenario, TCV-MAPs are expected to gradually ramp up as country introductions occur and account for approximately 26% of total global PDR in 2033 and reach 80% by 2042. Figure 5 provides an overview of the evolution of TCV-MAP adoption compared to TCV-N&S. TCV-MAP PDR begins at around 25 million doses in 2033 and increases to around 95 million doses by 2042. From a use case perspective, the greatest share of the PDR was attributed to UC 1, followed by UC 2 and UC 3. Figure 6 provides an overview of the TCV-MAP PDR by UC.

Figure 5. **Percentage of TCV PDR by presentation (base case demand)**

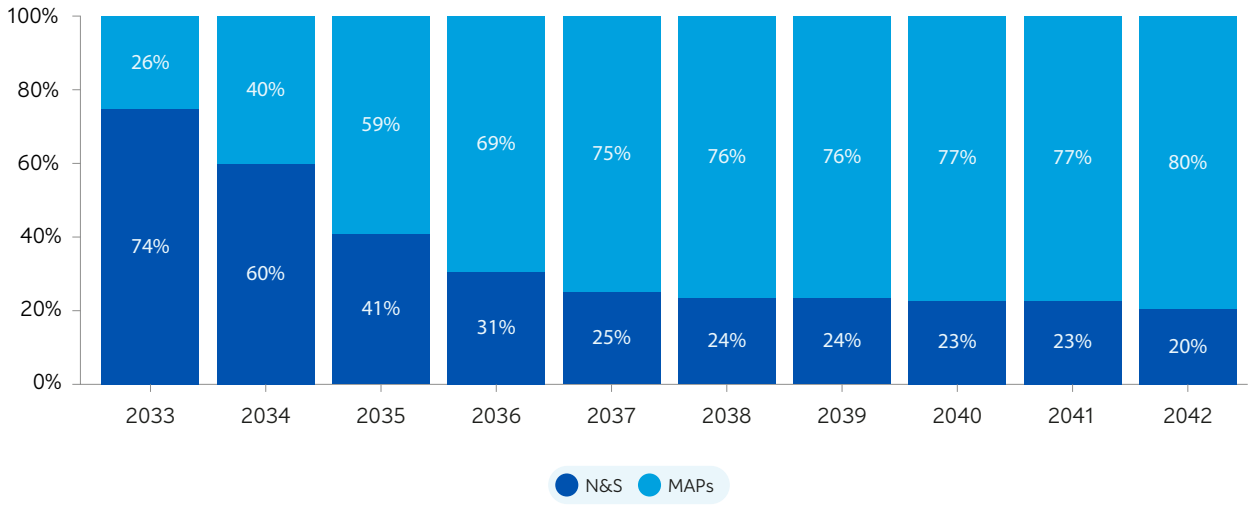


Figure 6. **Percentage of TCV-MAP PDR by use case (base case demand)**

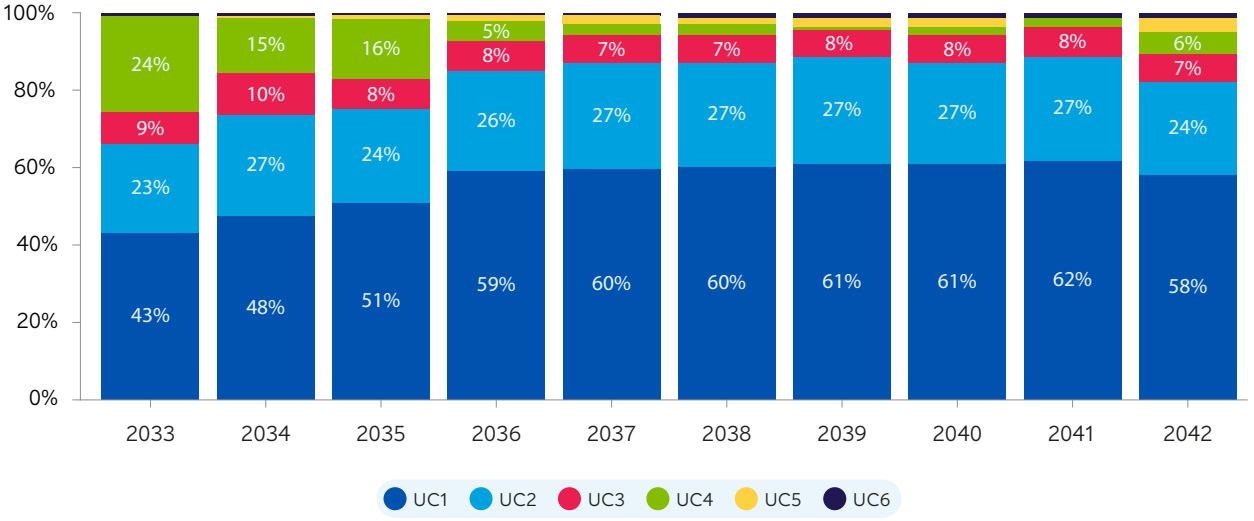
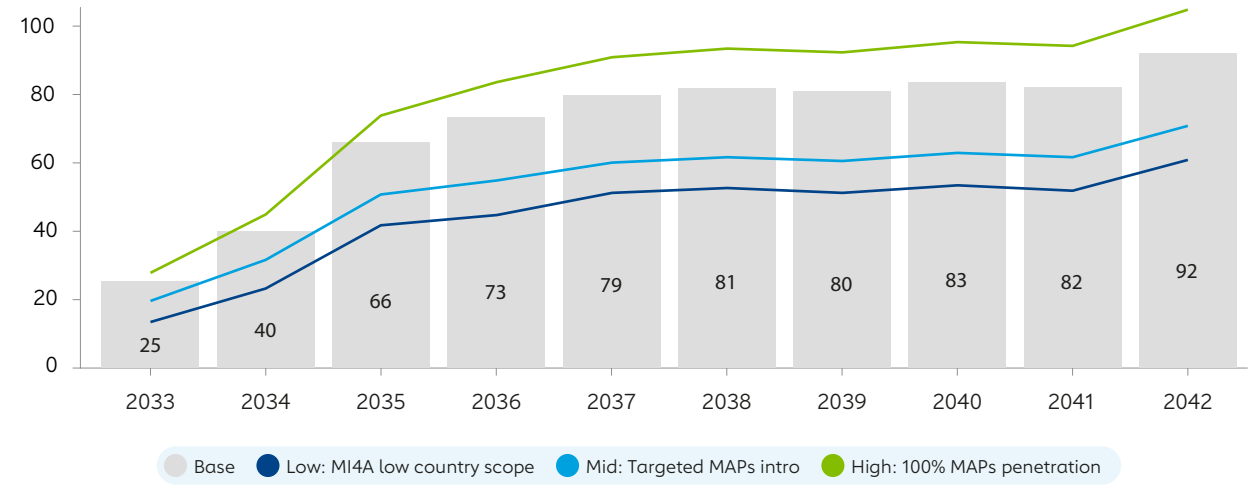


Figure 7. **TCV-MAP demand projections 2033-2042, key scenarios (in millions)**



In 2033, the first year of expected introductions, the PDR of TCV-MAP is estimated to be between 14 and 33 million doses in the low-demand and high-demand scenarios, respectively. By 2042, PDR is estimated to be between 62 and 107 million doses in the low-demand and high-demand scenarios, respectively. The highest projected use of TCV-MAPs is in less than 2-year-olds in health facilities, almost 80% of which is accounted for by low-income countries (LICs)/LMICs with high typhoid burden and/or AMR.

As TCV is a new immunisation programme, there remains significant uncertainty in uptake, subsequently impacting the scale and timeline of introductions of TCV-MAPs in all scenarios, a key driver of the demand forecast uncertainty. The assumptions of country adoption of TCV-MAPs have implications for the target population size and delivery strategies. The introduction strategy of TCV-MAPs is particularly important for two countries, India and Nigeria, which currently account for approximately one-third of the total TCV-MAP PDR. As both countries begin their introduction of TCV, understanding whether they would potentially adopt TCV-MAPs nationally or sub-nationally, targeting specific populations or vaccination strategies, would help to refine the demand estimates.

6 Socioeconomic and health impact of TCV-MAPs in endemic settings

Key insights

- TCV-MAPs are expected to have differing impacts on sub-groups of the population compared to TCV-N&S based on socioeconomic indicators and disease-specific risk factors. An equity analysis seeks to quantify this impact.
- Over 5 million typhoid cases and 47,000 deaths could be averted by introducing TCV-MAPs over 20 years.
- Through national introduction in routine settings, TCV-MAPs can be a cost-effective tool for improving coverage among the lowest wealth quintiles and in priority countries where mortality is high.
- TCV-MAPs are likely to be cost-effective for most of the target population in the African region, at or below a price of US$ 3 per dose. However, they are unlikely to be cost-effective in other regions.
- The potential value of introducing TCV-MAPs at a subnational level depends on whether they are cost-effective at the national level. Where national introduction is not likely to be cost-effective, a subnational implementation strategy may offer value for money. In the five countries evaluated, subnational implementation can avert 3–15% of cases at <1–3% of the cost compared to national rollout.

6.1 Methods

To assess the potential socioeconomic and public health impact of TCV-MAPs and to identify determinants of their value proposition compared to TCV N&S, an extended cost-effectiveness analysis (ECEA) was performed.

The ECEA for TCV-MAPs aimed to address key gaps in knowledge on the value of innovation. Existing models and tools for assessing typhoid vaccines are limited because they only consider direct costs and impacts, focusing on factors like efficacy, protection duration, and vaccination schedule. These models do not provide a comprehensive view of the broader public health benefits and value of such innovations. New components to be included in the ECEA were determined by developing a qualitative framework (Appendix 2), which assessed all components that would be valuable for a broad economic analysis of innovative vaccine presentations. Unlike most existing analyses, this ECEA compares a new vaccine presentation to an existing one instead of comparing a new vaccine to no intervention. Two key considerations were used to evaluate the inclusion of components into the framework: the existence of an established methodology for quantifying the component and expected differences in model inputs between vaccine presentations.

Aligning factors for inclusion in the framework was achieved through in-depth country consultations where participants shared insights on key factors that inform vaccine introduction or presentation switch decisions, including factors with a potential difference between presentations (MAP vs N&S). Through the development of the framework, three components are considered in the ECEA outside of the standard cost-effectiveness analysis considerations:

1. Carbon footprint/environmental impact
2. Ease of use of the new presentation for vaccinators
3. Equity in coverage among the target population

While established methods to quantify the carbon footprint of different vaccine delivery presentations are limited, environmental impact based on waste generated through immunisation activities was accounted for in assessing delivery costs associated with TCV-MAP delivery.

The ease of use of TCV-MAPs by vaccinators was also accounted for in the delivery cost assessment of TCV-MAPs through the differentiated human resource costs associated with the potential of lesser-trained health workers administering TCV-MAPs.

Equity impact was assessed through the ECEA, which included segmentation of the target population for vaccination by wealth quintile within each country to understand differential coverage, risk exposure and access to healthcare.

6.1.1 Analysis overview

The ECEA for typhoid uses a simulation-based approach that combines a dynamic susceptible-infected-recovered (SIR) model of typhoid transmission with a disease outcome model. This SIR model categorises transmission data by age and wealth quintile. Given the anticipated differential impact of TCV-MAPs and TCV-N&S on population subgroups based on socioeconomic indicators such as wealth and disease-specific risk factors, an equity analysis was conducted to quantify this impact across wealth quintiles.

The transmission model projects the spread of typhoid, while the disease outcome model estimates the incidence and mortality when vaccination is conducted using the TCV N&S presentation or a TCV-MAP. By integrating the health and economic impact between the two presentations, incremental cost-effectiveness ratios (ICERs) were estimated, which infer a relative value for TCV-MAPs.

Global analysis:

To evaluate the socioeconomic and public health impact of TCV-MAPs and to identify the factors impacting the value proposition, national implementation of TCV-MAPs through routine vaccination was modelled in 133 LICs, LMICs and MICs. This analysis included variations in coverage and impact by wealth quantiles across the target populations.

High-income country analysis:

In 15 HICs, selected based on their relatively high typhoid incidence (more than 50 cases per year), a cost-effectiveness analysis was performed from a societal perspective. Unlike the global and subnational analyses, a transmission model was not implemented because it was assumed that the vaccine's impact on transmission is negligible in high-income countries. The target population for these countries differs from that of LMICs and is primarily restricted to adult travellers, often visiting friends and family, returning from highly endemic countries.

Subnational analysis:

To evaluate the potential cost-effectiveness of TCV-MAPs when delivered using a geographically targeted approach, a subnational analysis was conducted in five countries – Malawi, Nepal, India, Kenya and Burkina Faso. Each analysis used differential distributions of typhoid risk factors and vaccine coverage by wealth quintile.

The analyses identified the thresholds at which TCV-MAPs could be cost-effective given trade-offs in product attributes, delivery cost and product price.

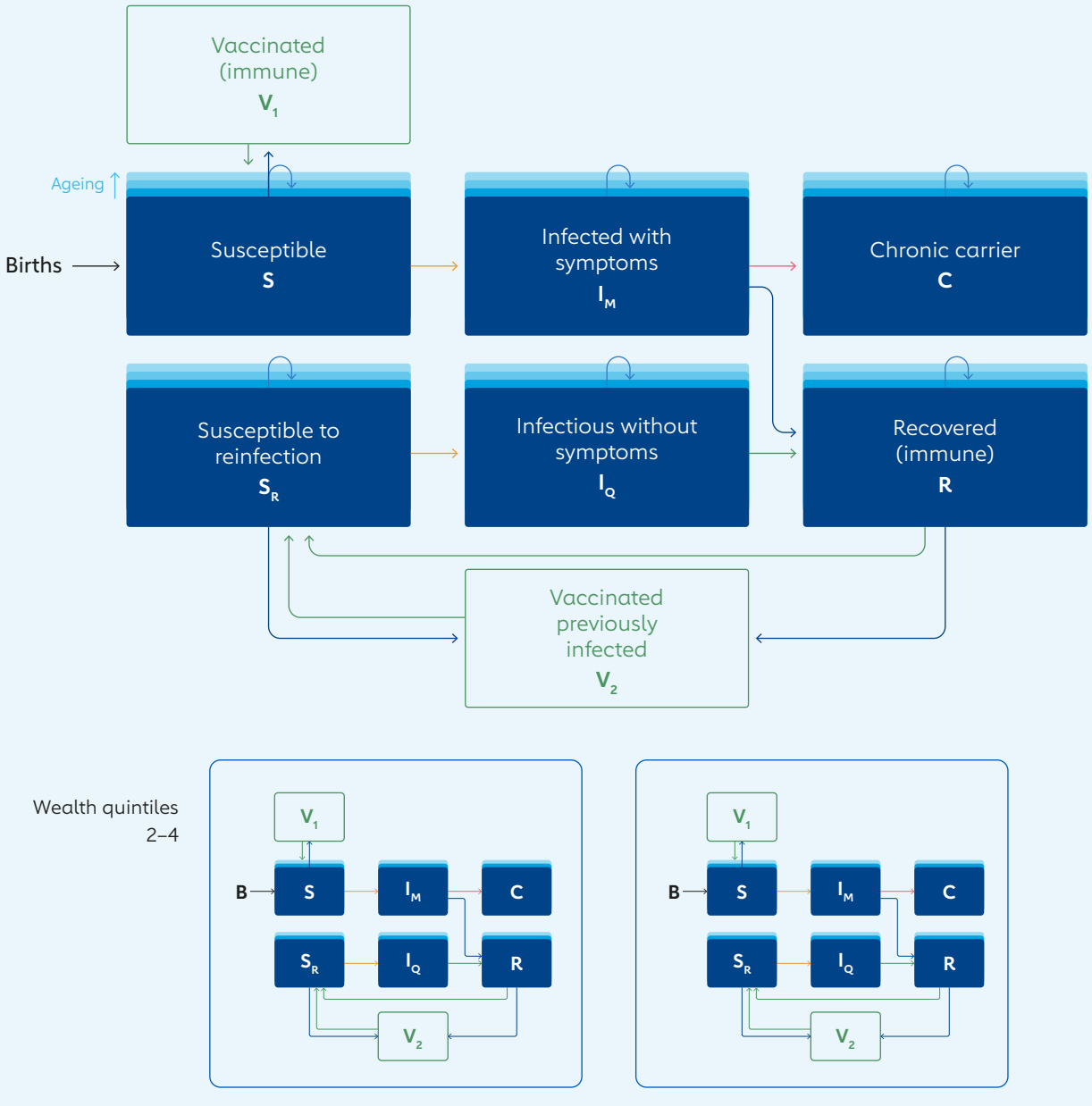
6.1.2 Transmission and treatment model

To simulate the impact of expanded vaccine coverage driven by TCV-MAPs and compare outcomes to TCV N&S, an existing age-stratified model of typhoid transmission was expanded to include an additional stratum: wealth.[48] This allowed for the assignment of transmission rates according to the exposure to unsafe sanitation and the assignment of vaccination coverage deemed appropriate for each wealth quintile. Typhoid incidence estimates by age group were derived from a previous burden model and burden estimates from the Institute for Health Metrics and Evaluation. The incidence for each wealth quintile was then re-estimated based on the degree of exposure to unsafe sanitation and the odds ratio for typhoid for those who have been exposed and do not have safe sanitation. The burden estimates were then used to estimate the effective transmission rate.[49]

Vaccination is simulated using a transmission model that has reached endemic equilibrium (a stable incidence) due to a lack of data to project changes over the time horizon. Vaccination is applied to the age group of interest (i.e. routine vaccination at 9 months). Protection from vaccines is due to two mechanisms: direct protection due to vaccination and indirect protection or herd immunity due to reduced transmission in the community. The final outcomes of disease, recovery or death, are determined by a set of conditional probabilities of the disease. The risk factor for typhoid incidence (lack of improved sanitation) and its prevalence across wealth quintiles allowed for the determination of the relative risk of typhoid in each quintile of the population (Figure 8).

The output of the transmission model is typhoid cases. In order to calculate costs, disability-adjusted life-years (DALYs), and deaths, a probability tree model of outcomes is applied to the cases with parameters specific to each country, where possible. The model includes stratification by antimicrobial sensitivity or resistance, which impacts the probability of disease severity, care seeking in outpatient or inpatient settings, complications and deaths. The model also takes into account the existent immunity in the population, which depends on the population's exposure to typhoid, as well as the immunity gained through the preceding deployment of TCV N&S.

Figure 8. **Disease transmission model stratified by age and wealth quintile**



6.2 Key inputs

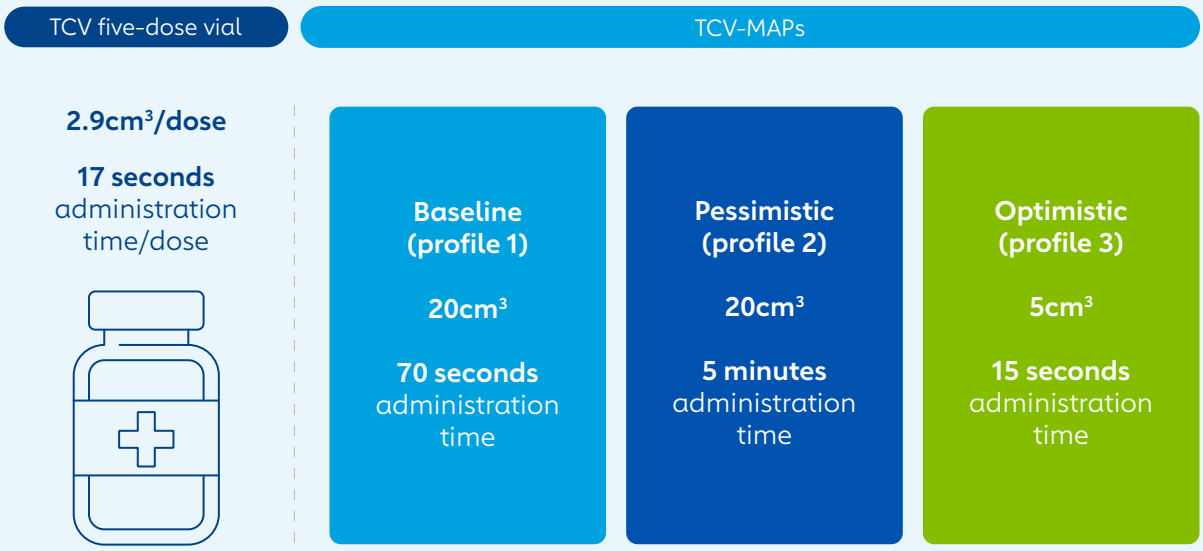
This ECEA presents the differential impact, costs and cost-effectiveness of adding TCV-MAPs following TCV N&S introduction over a time horizon of 20 years (2033-2052) from the health system perspective.

The TCV-MAP profiles (Figure 9) used in the analysis differ based on two attributes, storage (cold chain) volume and administration time, which are impacted by the MAP wear time as the vaccinators are assumed to monitor the vaccine over the MAP wear time. Administration time is a conservative assumption and does not necessarily reflect how TCV-MAPs could be implemented programmatically.

- **Baseline TCV-MAP profile** has a volume of 20 cm^3 and requires 70 seconds administration time.
- **Pessimistic TCV-MAP profile** has a volume of 20 cm^3 and requires 5 minutes administration time.
- **Optimistic TCV-MAP profile** has a volume of 5 cm^3 and requires 15 seconds administration time.

The TCV-MAP profiles are based on the target product profiles for other vaccine MAPs (HPV,[50] MR[51] and rabies[52]), publicly available information from MAP developers and characteristics of prequalified typhoid conjugate vaccines. These three TCV-MAP profiles are evaluated against the TCV N&S 5-dose vial presentation, which has a volume of 2.9 cm^3 and requires administration time of 17 seconds.

Figure 9. **Different TCV-MAP profiles and their attributes**

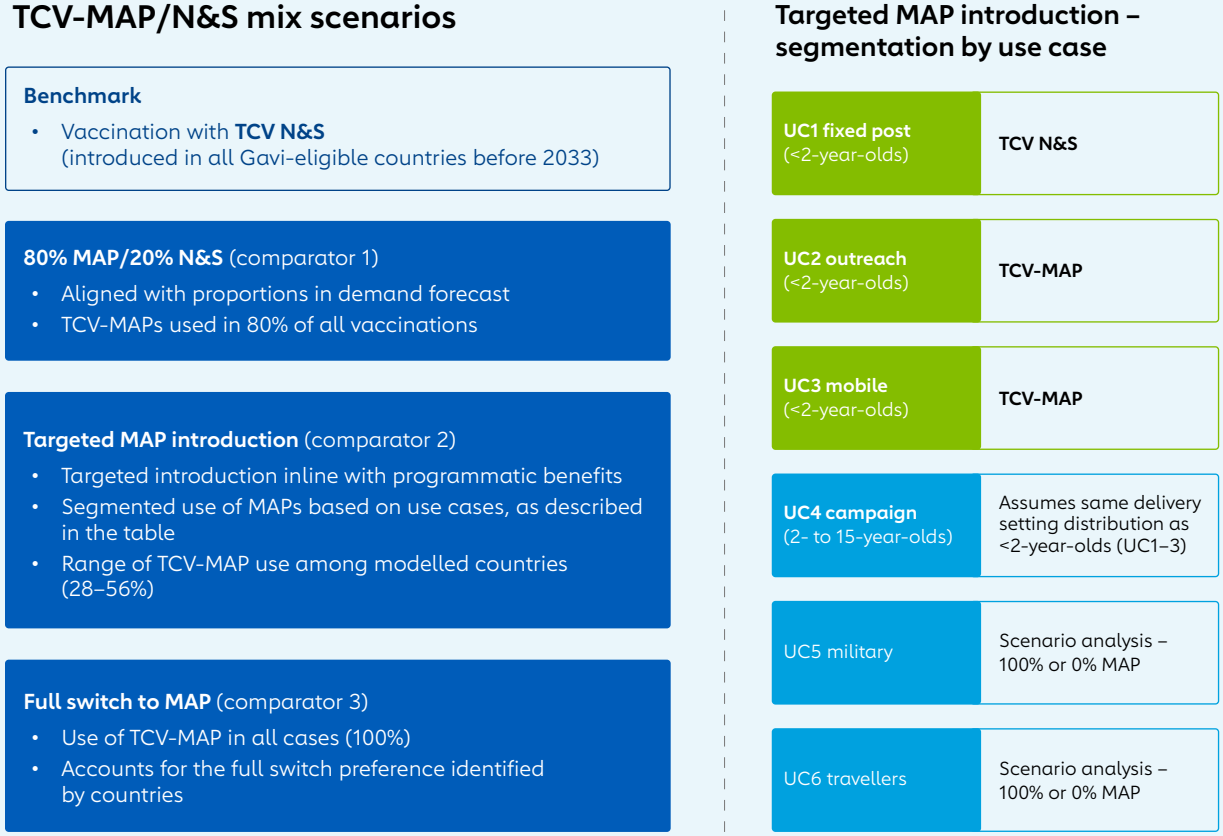


Thermostability is assumed to be the same for all MAP profiles and equivalent to TCV 5-dose N&S presentation: storage at +2°C to +8°C or in controlled temperature chain (CTC): 7 days at 40°C | 3 days at 55°C

Three different presentation mix scenarios for the market penetration and associated UCs of TCV-MAP as compared to TCV-N&S were assessed in line with key scenarios outlined in the demand forecast (Section 5). It is assumed that TCV N&S will be introduced in all Gavi-eligible countries before 2033, preceding the introduction of TCV-MAP in 2033.

- **Base case** (comparator 1) assumes that TCV-MAPs will be used in 80% of all routine vaccinations, with TCV-N&S used in the remaining 20%.
- **Targeted MAP introduction** (comparator 2) assumes TCV-N&S is used in fixed post-vaccination (UC 1), and TCV-MAPs are used in outreach and mobile strategies (UC 2 and 3).
- **Full switch to MAP** (comparator 3) assumes a complete switch to TCV-MAPs in all use cases.

Figure 10. **TCV-MAP presentation mix scenarios**



The key input parameters relevant to the vaccine product used for the global and subnational analyses are presented in Appendix 7. Different price scenarios were explored, including the baseline price point for TCV-MAPs of US$ 3.00, as well as alternative price points of US$ 2.00, US$ 2.25 and US$ 4.50.

Coverage of the first dose of measles-containing vaccine (MCV1) has been used as a proxy for TCV coverage, given the limited data on TCV and similarities between the two vaccine target populations and routine administration schedules. The coverage rate for TCV-N&S has also been held steady at the latest available rate for the 20-year time horizon of this analysis. It is assumed that TCV N&S has been introduced in routine vaccination programmes and multi-age cohorts, and catch-up campaigns with TCV-N&S have been conducted (as has been the case in the first six countries to introduce TCV) prior to TCV-MAP introduction.

MAP-specific assumptions include that the proportion of the population reached by each delivery setting (fixed post vs outreach vs mobile) remains unchanged following the introduction of TCV-MAPs. However, it is assumed that there will be an increase in coverage after introducing the TCV-MAP to the total population. A coverage increase of 20% per year in the population that is otherwise unreached by N&S presentation is assumed, as MAPs can potentially address some programmatic barriers associated with HTR and MOV populations. This is based on estimates of zero-dose children outside of conflict settings who are potentially reachable by addressing some programmatic barriers associated with N&S delivery. All the additional coverage gained by MAPs is attributed to the two lowest wealth quintiles in the population to account for the greater likelihood of those previously unreached in the poorer groups. This assumption is important when considering the equity implications of TCV-MAP introduction.

Lastly, it is also assumed that there are no external improvements outside of the immunisation programme over the time horizon. This includes improvements to development, infrastructure or water, sanitation and hygiene.

Estimates of TCV N&S and TCV-MAP adoption timelines, as well as populations that will also be reached by TCV-MAPs, are aligned with the demand forecasts (Section 5).

6.2.1 HIC analysis-specific inputs

Given the expected price premium for TCV-MAPs and wide variation among private market vaccines in HICs, a TCV-MAP price equivalent to twice the price of the polysaccharide Typhim Vi vaccine (currently the most common vaccine in HICs) was applied in this analysis. Among the 15 HICs, the median price of a single dose vial of Typhim Vi was US$ 28 and ranged from US$ 13 to US$ 155, depending on the country. In addition, differences between typhoid polysaccharide and TCV were taken into account in this analysis, including improved vaccine efficacy.

6.2.2 Thresholds for determining cost-effectiveness across all the ECEA analyses

The interpretation of the results of any cost-effectiveness analysis is very dependent on the thresholds of cost that would make an intervention worth the additional investment. There are different thresholds that are commonly used in cost-effectiveness analysis in global health, and they differ in their approach to quantifying **health opportunity costs**.[53] Throughout the cost-effectiveness analyses performed, results are presented to provide insights on cost-effectiveness under different thresholds. TCV-MAPs are considered cost-saving if they avert more DALYs and cost less than the TCV N&S presentation.

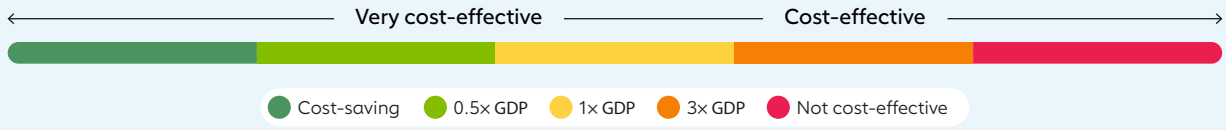
Where TCV-MAPs cost more but provide greater health impact (DALYs averted) than TCV N&S, various thresholds based on comparing the computed ICERs to the per capita gross domestic product (GDP) to evaluate cost-effectiveness are used.

Cost-effectiveness thresholds:

- **Cost-saving** if the ICER is below 0 (the intervention has greater impact and less cost)
- **Highly cost-effective** if the ICER is less than 0.5X per capita GDP.
- **Very cost-effective** if the ICER is greater than 0.5 and below 1X the per capita GDP.
- **Cost-effective** if the ICER is greater than 1 and below 3X the per capita GDP.
- **Not cost-effective** if the ICER is greater than 3X the per capita GDP.

Credit: Gavi/2022/Asad Zaidi

Figure 11. **Cost-effectiveness thresholds**

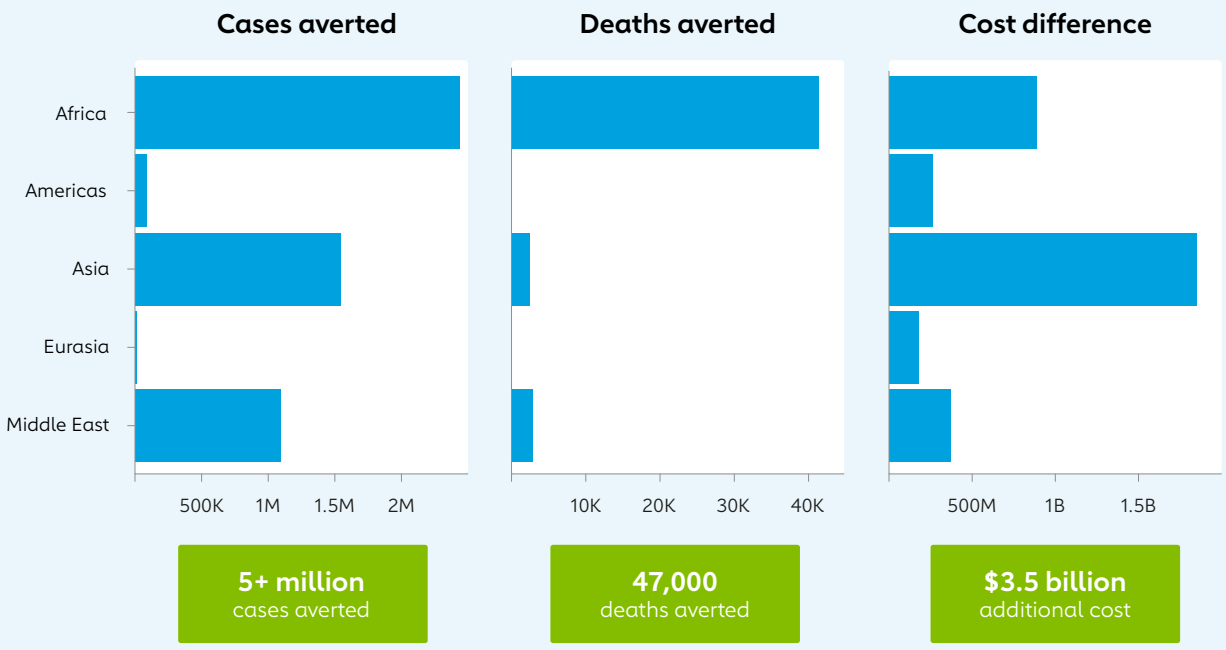


6.3 Outcomes

6.3.1 Global analysis

If TCV-MAPs are introduced in all LMICs that are likely to use TCV in routine settings, an additional 5.2 million cases (2%), 47,000 deaths (3%) and 2.4 million DALYs (3%) could be averted as compared to TCV N&S over 20 years. The majority of the averted burden would come from the African region. Factors contributing to this trend include typically higher case fatality rates and lower starting vaccine coverage than other regions. The use of TCV-MAPs to achieve these improved health outcomes will come at a cost of US$ 3.5 billion over 20 years. The greatest share of the estimated additional cost will be required for vaccinating the target population in Asia due to the larger population, lower incidence and lower case-fatality rate of typhoid (Figure 12).

Figure 12. **Additional Impact of TCV-MAP introduction by region**

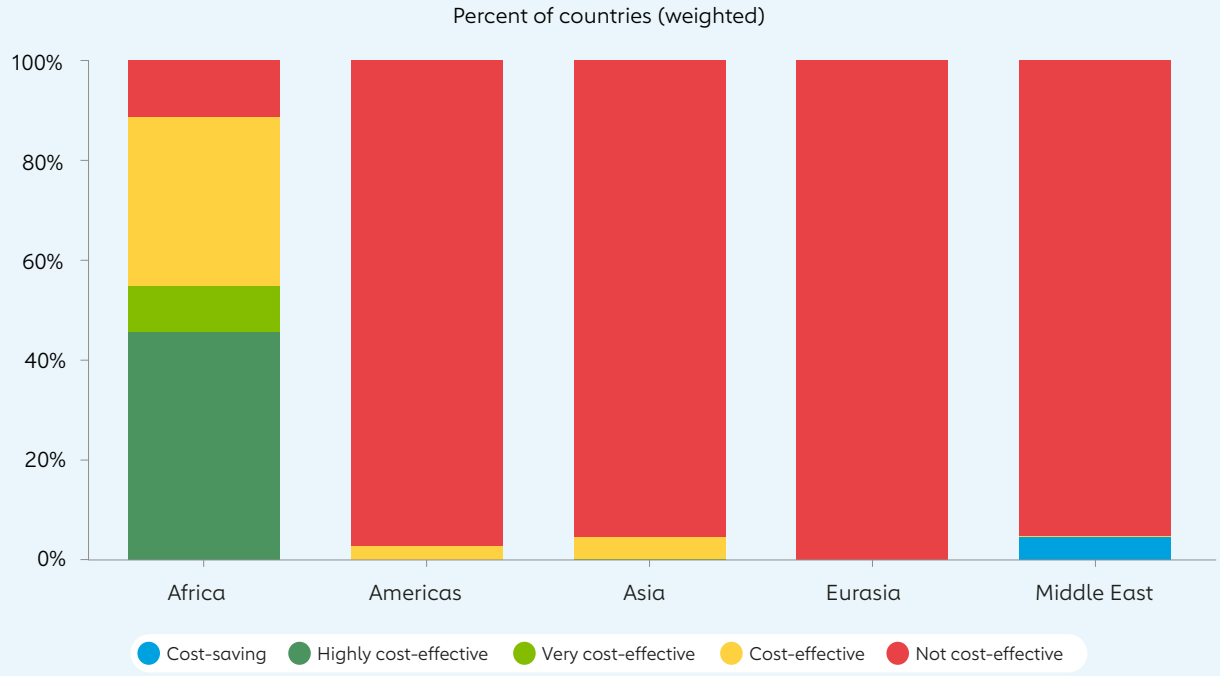


The baseline cost-effectiveness analysis, assuming a MAP price of US$ 3 and an 80% switch to TCV-MAPs found that MAPs could be cost-effective or cost-saving compared to N&S in approximately 44 (33%) of the 133 countries included in the global analysis, or 14.5% of the population considered.

6.3.1.1 Cost-effectiveness by regions

TCV-MAPs could be cost-effective in 78% of countries in Africa, representing about 89% of the population in this region (Figure 12). In all other regions, TCV-MAPs are not cost-effective for many countries and populations. TCV-MAPs are likely to be cost-effective for approximately half of Gavi-eligible countries.

Figure 13. **Cost-effectiveness of TCV-MAPs by region**



6.3.1.2 Cost-effectiveness by MAPs price and product profile

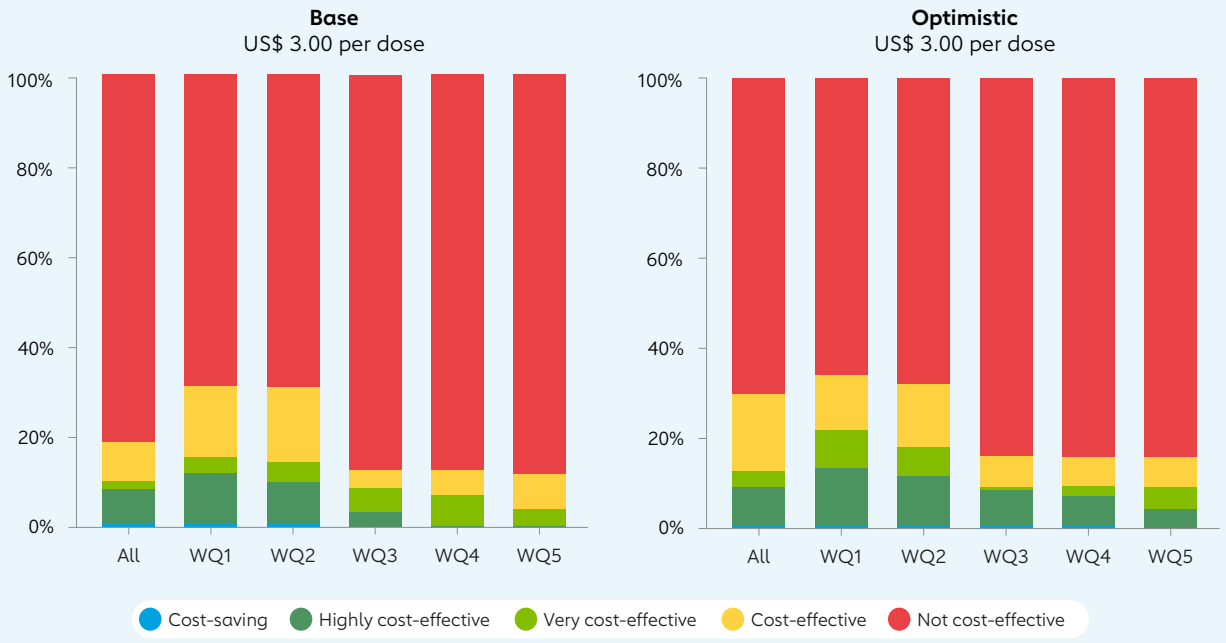
The cost-effectiveness of TCV-MAPs will likely be driven by the MAP price and product characteristics such as cold chain volume and thermostability. At a price point of US$ 3, TCV-MAPs are likely to be cost-effective for approximately 20% of the global target population for all the MAPS/ N&S mix scenarios.

6.3.1.3 Cost-effectiveness by wealth quintiles

Across all countries, TCV-MAP use will drive the greatest health impact to the lowest wealth quintiles, which will have indirect benefits on other populations. Those who are previously unreached are more likely to be in these wealth quintiles, contributing to the reduction of inequities in immunisation. The majority of cases, deaths and DALYs are averted in the lowest two wealth quintiles within a country due to this assumption, while costs are more evenly distributed across wealth quintiles. The positive impact of reduced burden for the upper wealth quintiles is entirely due to indirect effects. The concentration of burden averted in the lower two quintiles is a function of the strategy's design targeting individuals in those quintiles.

Credit: Gavi/2024/Dominique Fofanah

Figure 14. **Cost-effectiveness of TCV-MAPs by MAP profile and wealth quintile**

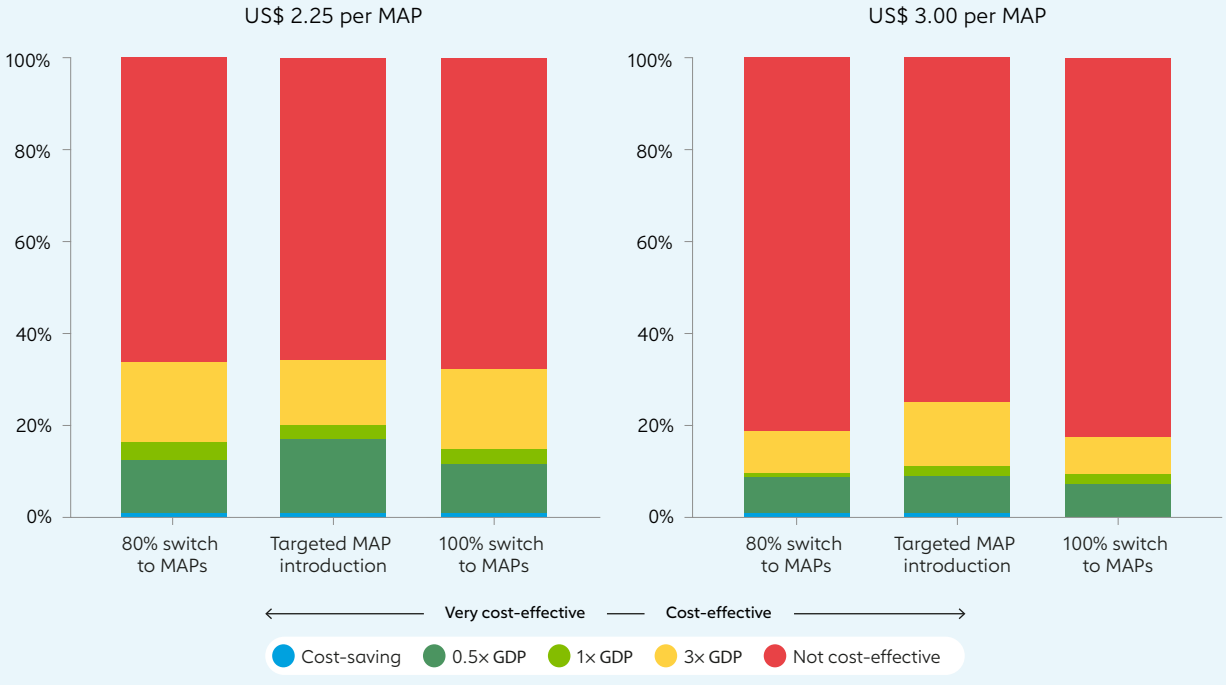


WQ: Weath quintile

6.3.1.4 Cost-effectiveness by MAPs introduction scenario

Whether a targeted approach to introduction (TCV-MAPs only used in mobile and outreach settings) is cost-effective largely varies from country to country and is less likely to be cost-effective in those countries with higher cost of vaccine delivery through outreach and mobile activities.

Figure 15. **Cost-effectiveness of TCV-MAPs by MAP price and MAPs/N&S mix scenarios**



6.3.2 High-income country analysis

In the countries evaluated, TCV-MAPs could be cost-effective in 10 of the 15 HICs, representing up to 26% of travellers from HICs, mainly among high-incidence countries, including Gulf countries. Baseline uptake of typhoid vaccines among travellers is low (5%). Therefore, no substantial change in traveller coverage is expected with TCV-MAPs, but preference for MAP may develop due to improved convenience. TCV-MAPs are unlikely to be cost-effective in countries such as the US and Japan, which are the countries with larger traveller populations, due to anticipated high price points and very low or no typhoid-related mortality in this population. Decision-making in HICs may not be influenced by societal cost-effectiveness, as typhoid vaccination decisions are made by the individual.

6.3.3 Subnational analysis

The potential impact of TCV-MAP introduction in terms of the potential typhoid cases and deaths averted are fairly localised in some of the countries assessed, and by using TCV-MAPs in high-impact districts, countries could see substantial public health gains for a much lower cost. Table 2 and Figure 16 provide an overview of the cost-effectiveness of TCV-MAPs if introduced nationally as compared to TCV-MAP introduction only in districts where TCV-MAPs would be cost-effective.

The potential for a subnational introduction of TCV-MAPs to be a valuable strategy is dependent on the cost-effectiveness at the national level. Where national introduction is not likely to be cost-effective, a subnational implementation strategy that target regions within a country with elevated typhoid risk may have value for money if typhoid mortality is high and there is heterogeneity between subnational regions in sanitation and vaccine coverage. In three of the evaluated countries, where subnational implementation can bring value – Burkina Faso, India and Malawi – this strategy has the potential to avert 3–15% of the typhoid cases at <1–3% of the cost compared to national rollout under the base case assumptions. When national introduction is cost-effective, such as in Kenya, there is no improved value proposition for TCV-MAPs with a subnational implementation. In Nepal, the value of a subnational strategy for MAPs is limited even when deploying a subnational strategy due to the low case fatality rates observed in the country.

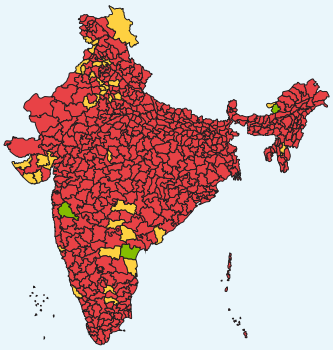
Table 2 **Overview of the results of the subnational analysis in five assessed countries**

	Burkina Faso	India	Kenya	Malawi	Nepal
National introduction	NCE	NCE	CE	NCE	NCE
Subnational introduction	VCE	CE	CE	CE	NCE
Percentage of districts where subnational strategy could be cost-effective	8%	9%	81%	6%	0%

CS = Cost-saving, HCE= Highly cost-effective, VCE= Very cost-effective, CE = Cost-effective, NCE = Not cost-effective

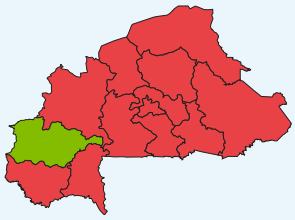
Figure 16. **Comparative impact of National and subnational TCV-MAP introduction in India, Burkina Faso, Kenya, Malawi and Nepal**

India



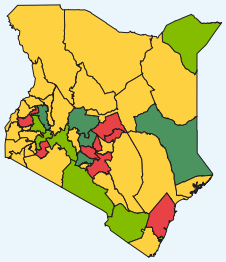
Base profile, US$ 3	National intro.	CE + districts
Cases averted	**571,400**	**86,864**
Deaths averted	782	118
Cost	**$662M**	**$10.4M**
ICER/GDP	15.5	1.62
# districts	707	63

Burkina Faso



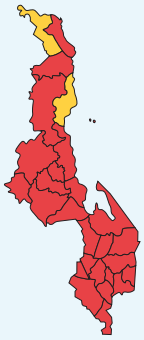
Base profile, US$ 3 per dose	National intro.	CE districts
Cases averted	19,743	3,194
Deaths averted	171	28
Cost	14.2M	434,948
ICER/GDP	5.06	0.95
# districts	13	1

Kenya



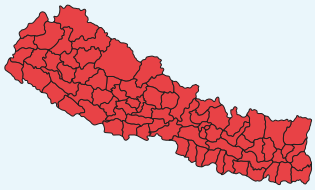
Base profile, US$ 3 per dose	National intro.	CE + VCE districts
Cases averted	37,690	35,766
Deaths averted	878	833
Cost	45.8M	36.6M
ICER/GDP	1.26	1.05
# districts	47	37

Malawi



Base profile, US$ 3	National intro.	CE + VCE districts
Cases averted	6,941	178
Deaths averted	181	5
Cost	14.5M	100,628
ICER/GDP	6.35	1.80
# districts	32	2

Nepal



Base profile, US$ 3	National intro.	CE + VCE districts
Cases averted	9,393	0
Deaths averted	13	0
Cost	16.4M	0
ICER/GDP	42.9	0
# districts	77	0

Cost-saving · 0.5× GDP · 1× GDP · 3× GDP · Not cost-effective

CE: Cost-effective; VCE: Very cost-effective

7 Socioeconomic and health impact of TCV-MAPs in epidemic settings

Key insights

- TCV-MAPs do not have a sizeable health impact when used in response to an outbreak, as compared to TCV-N&S.
- When used in response to multi-year outbreaks commonly associated with AMR (MDR and XDR), TCV-MAPs are unlikely to be cost-effective.

7.1 Methods

To evaluate the impact of TCV-MAPs compared to TCV N&S for use in a reactive campaign in response to a typhoid outbreak, an epidemic analysis was conducted using transmission patterns from past multi-year epidemics of typhoid in Malawi and Nepal.

Although typically endemic, outbreaks and epidemics of typhoid occur, usually marked by a temporary increase in the incidence. There are two kinds of typhoid outbreaks: 1) short-lived outbreaks typically associated with the contamination of a water source or the breakdown in sanitation services,[54,55] or 2) multi-year epidemics following the establishment of a new clade of typhoid.[56]

TCVs have now been used to address outbreaks of MDR typhoid in Zimbabwe and outbreaks of XDR typhoid in Pakistan.[57] Similar outbreaks of AMR typhoid are likely to continue to occur. The speed of deployment and uptake of vaccines are important factors in their success in stemming the tide of outbreaks.[58]

The potential value of employing MAPs for outbreak response stems from their ease of use, enabling delivery by lesser-trained staff. These characteristics could potentially enable a faster response and extend the reach and coverage of MAPs compared to the N&S presentation.

Using extensive mathematical epidemiology work on a typhoid transmission model fit to real-world data in Malawi and Nepal, the impact of TCV N&S compared to a potential TCV-MAP is simulated.

7.2 Key inputs

As previously established, vaccination may modify the outbreak of a new clade. To glean transferable insights from these two case studies, alternative scenarios assuming no routine vaccination before the epidemic, routine vaccination with relatively low coverage (50%) and routine vaccination with relatively high coverage (90%) are assessed. Outcomes if routine vaccination is established only after the initial reactive vaccine with either N&S or MAPs are also assessed.

Table 3 presents the modelled strategies, which include variation in vaccine delivery (campaign vs routine) and the presence of routine immunisation before and after an outbreak. Routine vaccination is deployed using TCV N&S at varying levels of coverage.

The analysis compares a reactive vaccination campaign using TCV N&S at 70% coverage, at a price of US$ 1.50 per dose to TCV-MAPs at 76%, 84% and 92% coverage, and a price of US$ 2.25, US$ 3.00 and US$ 4.50 per dose. Additionally, the initiation of the reactive campaign with MAPs is simulated to take place one month after detection of the outbreak and a reactive campaign with TCV N&S takes place six months after detection of the outbreak.

In scenarios that include routine vaccination prior to an outbreak, this is modelled to have been implemented five years prior to the outbreak.

Table 3 **Vaccination strategies assessed in epidemic analysis**

Scenario		Vaccination strategy	Existing routine TCV coverage	Campaign coverage	Price
No routine TCV	**1**	Reactive campaign only, no routine vaccination	None	**N&S** 70% **MAPS** 76% 84% 92%	**N&S** US$ 1.50 **MAPS** US$ 2.25 US$ 3 US$ 4.5
Routine TCV after outbreak	**2**	Reactive campaign Followed by routine vaccination at low coverage (50%)	None		
	3	Reactive campaign Followed by routine vaccination at high coverage (95%)	None		
Routine TCV before outbreak	**4**	Reactive campaign Existing routine vaccination at low coverage (50%)	50%		
	5	Reactive campaign Existing routine vaccination at high coverage (95%)	95%		

Box 1 **Epidemic analysis key assumptions**

- Response time following outbreak detection:
  - MAPs: 1 month
  - TCV N&S: 6 months
- A single four-week reactive vaccination campaign is conducted following outbreak detection
- Age groups targeted: 9 months–15 years old
- Reactive strategies use only TCV-MAPs or only TCV N&S, depending on the vaccination strategy
- TCV-N&S is used for all routine vaccinations
- In scenarios with existing routine vaccination, introduction occurs five years prior to the outbreak
- Baseline TCV-MAP profile used in all scenarios

7.3 Outcomes

In both settings where the analysis was conducted (Malawi and Nepal), the assumed faster outbreak response and higher coverage that could be achieved by TCV-MAPs in an epidemic situation would result in marginal improvements in health impact compared to TCV-N&S. TCV-MAPs would only avert an additional 6–10% of cases and almost no additional deaths (Figure 17 and Table 4).

Additional scenarios that assessed the impact of TCV-MAPs in the presence of differing levels of routine vaccination against typhoid before or following an outbreak further supported that TCV-MAPs have little additional impact on the magnitude of an outbreak compared to TCV-N&S. Results of the analysis, which varied coverage rates for TCV-MAPs, suggest that the majority of additional cases averted arise from the faster deployment that is assumed for MAPs, rather than the incremental gains in coverage. This suggests the potential value in alternative measures for typhoid outbreak preparedness and that faster deployment of TCV may be of value.

Figure 17. **Impact of TCV-MAP and TCV N&S on incidence in response to outbreak – Malawi**

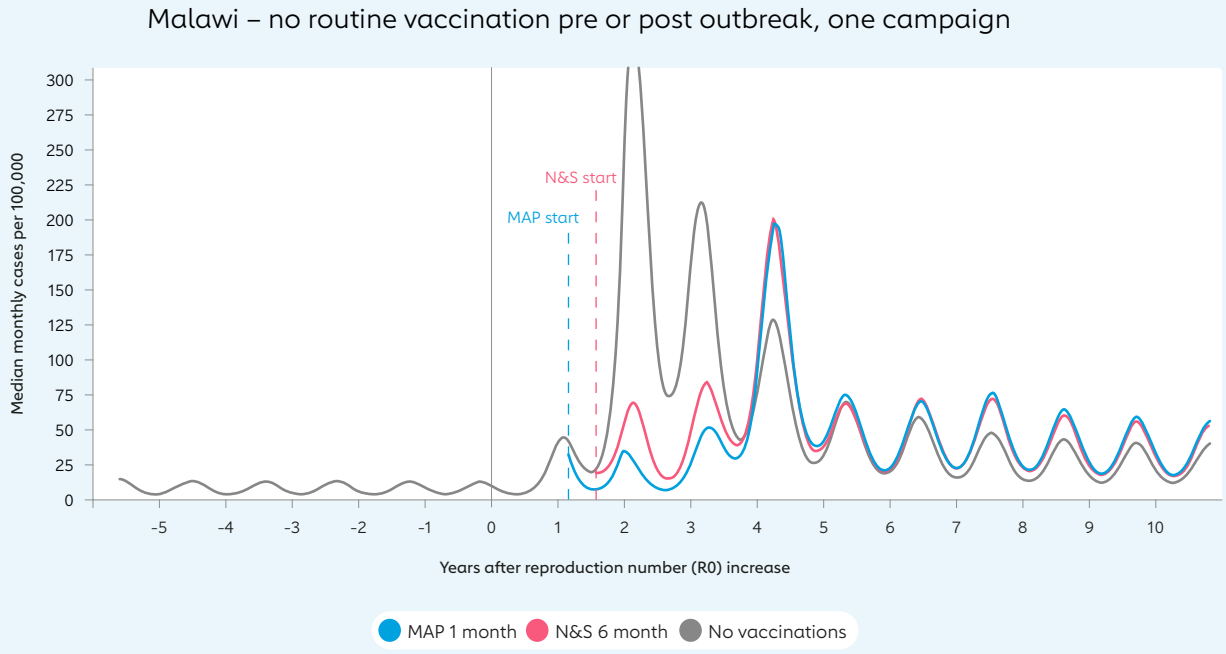


Table 4 **Health impact of vaccination strategies in outbreak response – Malawi**

			Total typhoid cases					
Strategy	**Coverage**	**Response time**	No vaccination	Reactive campaign only	Reactive campaign 50% routine coverage post-outbreak	Reactive campaign + 95% routine post-outbreak	Reactive campaign 50% routine coverage pre- and post-outbreak	Reactive campaign 95% routine coverage pre- and post-outbreak
No vaccination			**7,574**					
TCV-N&S	70%	6 months		5,731	5,010	4,352	4,117	3,138
TCV-MAPs	76%	1 month		5,402	4,628	3,931	3,833	2,870
TCV-MAPs	92%	1 month		5,383	4,615	3,913	3,828	2,867

The limited impact of TCV-MAPs in response to an outbreak is insufficient to generate cost-effectiveness compared to TCV N&S. The lack of cost-effectiveness was driven by both the low mortality of typhoid and the low cumulative costs of treatment compared to the additional expense of deploying a TCV-MAP compared to an N&S.

For infectious diseases that have higher case fatality rates (e.g. Cholera, Ebola) or that cause long-term disability, averting as few cases as in the current analysis could prove cost-effective if the cases lead to a higher disease burden. Moreover, typhoid fever is predominantly treated on an outpatient basis for a short duration, however, a disease with more complicated treatment or long-term healthcare needs (such as those that may arise because of rising levels of AMR) may lead to greater value from a MAP presentation, even at a price premium, over the N&S presentation. Other factors that could affect the potential cost-effectiveness of MAPs are the form and cost of alternative interventions, and whether MAPs can reach key populations.

8 Financial viability and willingness-to-pay analysis

Key insights

- Under the base case scenario of the discounted cashflow analysis, TCV-MAPs present a marginally positive return on investment of around US$ 12 million over the first 10 years following commercialisation.
- Increasing uptake in HICs will improve the financial attractiveness of TCV-MAPs.
- Under a high-demand scenario, the potential return on investment may be US$ 280 million over the first 10 years.
- The greatest risk to achieving a positive net present value is TCV-MAP demand. In a low-demand scenario, losses could represent approximately US$ 137 million over the first 10 years.
- MAP price is the most influential driver of financial viability.
- Price sensitivity is high among stakeholders; willingness to pay a higher price for a TCV-MAP compared to TCV-N&S was relatively low (37%) for both self-procuring and Gavi-eligible countries.

8.1 Discounted cashflow analysis

8.1.1 Methods

To assess the potential financial viability of manufacturing and commercialising a TCV-MAP product from the perspective of the producer, a discounted cash flow (DCF) analysis was conducted. The analysis used estimates of demand, price, investments in development and manufacturing setup to calculate the net present value (NPV) of TCV-MAPs.

The variables with the highest level of uncertainty that are critical to a positive financial return are:

- demand for the product, particularly in the HIC travellers' segment;
- TCV-MAP price and unit cost of goods sold (COGS); and
- initial financial investments required to establish the manufacturing facility and perform the pivotal clinical trials.

Demand, price, COGS and initial investment in pivotal clinical studies and manufacturing are the critical factors driving the financial performance of TCV-MAPs. The TCV-MAPs business case also shows very specific aspects that should be considered when determining the realistic pathway towards product marketing authorisation. The business case also includes considerations about the initiative's risk profile and the potential interventions that may be required from global health partners to mitigate those risks.

Credit: Dwi Prasetya

8.1.2 Key inputs

8.1.2.1 Demand

Demand for TCV-MAPs is expected to be split into three main segments: HIC travellers, Gavi-supported countries and self-procuring MICs. MAP adoption across all three segments is critical to the success of the business case. The travellers segment, while minimal from a volume standpoint (approximately 2%), commands higher sales prices and accounts for almost 17% of the estimated revenues in the base case. This contribution is required to allow for the economies of scale necessary to achieve the lowest COGS levels and ensure a reasonable price for each segment.

In this DCF analysis, it is assumed that 100% of the estimated demand (see section 5: Defining the potential demand for TCV-MAPs) is captured by the commercialising entity. This refers to both country adoptions as well as the share of the market gained. In this analysis, it is assumed that 100% of the estimated demand of TCV-MAPs is captured by one commercialising entity. Any change to this assumption will reduce the estimated financial return.

8.1.2.2 Price and COGS

Potential prices for TCV-MAPs are likely to be significantly higher than the current prices for existing N&S presentations. TCV-MAP prices for Gavi-supported countries have been assumed to be between 1.5 and 3 times the current UNICEF procurement prices for TCV (US$ 3–4.5 per TCV-MAP). Prices for HICs are also expected to be higher than the current travellers market benchmarks in HICs (US$ 36–72 per TCV-MAP) (Table 5).

Uncertainty in the potential COGS of producing TCV-MAPs remains high. COGS can define the lowest potential level for the sale price of a product. From the limited information on the MAP manufacturing process available, the estimation of COGS for the DCF analysis used public and semi-public information. These estimates are dependent on the assumptions taken on the manufacturing plant use and the assumptions on the cost of the vaccine "bulk product" estimated based on UNICEF procurement prices for TCV. These "outside-in" COGS estimates were compared to results obtained through a different methodology using a modelling approach of the manufacturing process, and this comparison resulted in a COGS range used to sense-check the benchmarked prices mentioned above. While both methodologies used to estimate COGS focus mostly on TCV-MAP dedicated plants, opportunities exist for efficiency gains linked to the production of multiple MAP products in the same facility, from manufacturing process optimisation and from economies of scale. However, their order of magnitude remains uncertain.

Table 5 **Discounted cashflow analysis scenario parameters**

Scenario	Price per dose	COGS per dose	Clinical trial US$	Manufacturing US$	Production capacity available
Base	US$ 3–36 Gavi US$ 3 LMIC US$ 4 UMIC US$ 4.2 HIC US$ 36	US$ 3 <80% production (80 million doses) US$ 2.30 >80% production (80 million doses)	Phase 1–2: Paid by grantee Phase 3: 3,000 subjects, $13.8 million	Initial: US$ 30 million Expansion: US$ 30 million	Year 1–4: 10 million doses Year 5 onwards: up to 100 million doses
Low	US$ 3–25.7 Gavi US$ 3 LMIC US$ 4 UMIC US$ 4.2 HIC US$ 25.7	US$ 3.50 <80% production (80 million doses) US$ 2.70 >80% production (80 million doses)	Phase 1–2: Paid by manufacturer, US$ 16.8 million Phase 3: 9,000 subjects, US$ 41.5 million	Initial: US$ 80 million	100 million doses capacity from year 0
Mid (targeted TCV-MAP introduction)	Same as base				
High	US$ 4.50–72 Gavi: US$ 4.50 LMIC US$ 6 UMIC US$ 8.3 HIC US$ 72	Same as base		Initial: US$ 80 million	100 million doses capacity from year 0

UMIC= Upper-middle-income country

8.1.2.3 Financial investment

Lastly, the level of financial investment for clinical trials and the establishment of manufacturing facilities depends on many unknown variables. For clinical trials, a fully defined regulatory strategy identifying the national regulatory authorities of reference, the trial design, size, and sites have yet to be determined, and the cost could be between US$ 13.8 million and US$ 41.5 million.[59] Many uncertainties remain regarding the potential design, capacity and throughput/yields of manufacturing facilities for vaccine-MAPs, which impact the size of the required upfront financial investment. For the DCF analysis, a total investment of US$ 60-80 million has been assumed.[60]

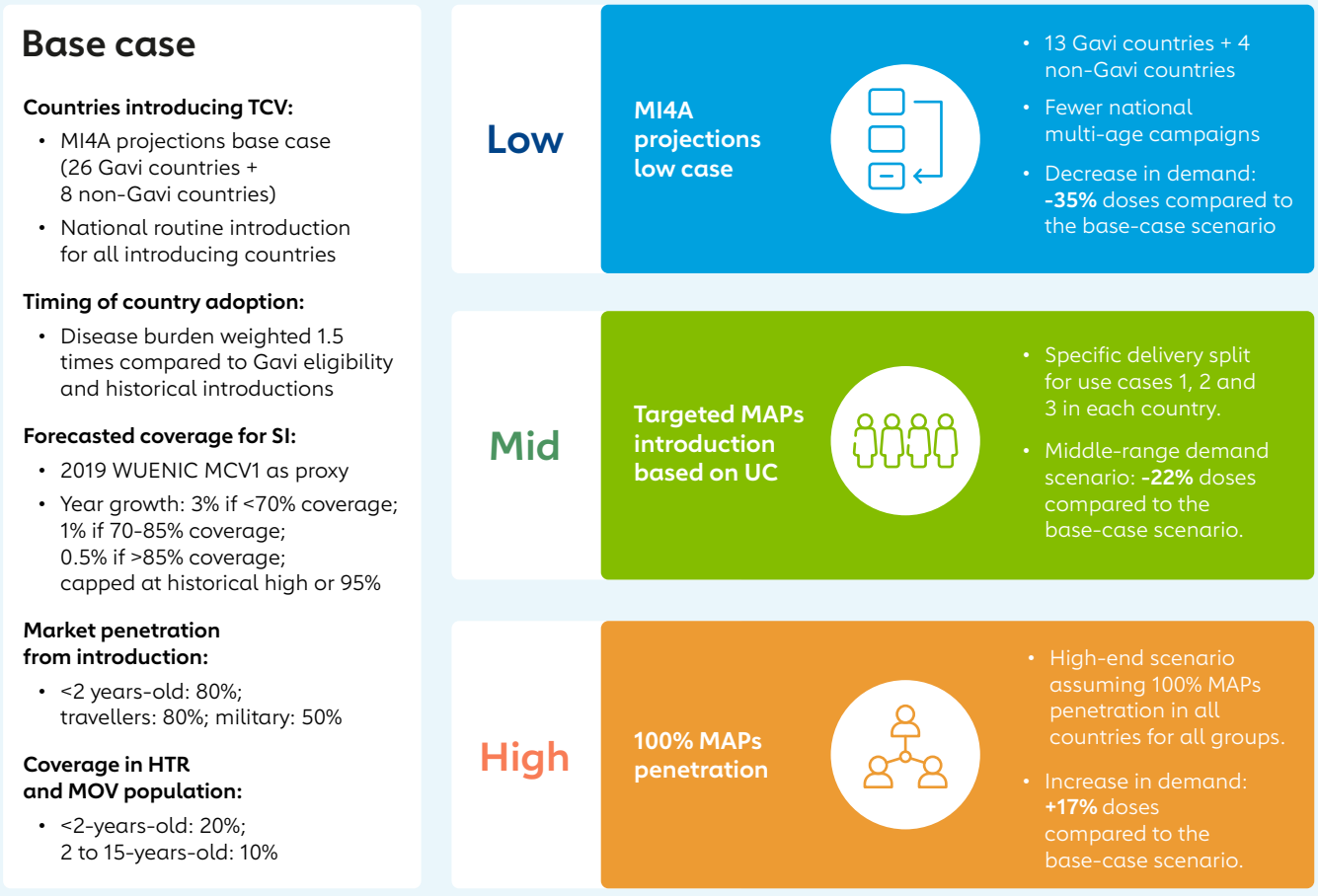
The existence of uncertainties across all these three key factors influencing the project's financial return raises the risk profile of the initiative. This has implications for the targeted expected return that a commercial entity would set when considering the development and commercialisation of a TCV-MAP product.

8.1.3 Outcomes

A positive financial return of US$ 12.2 million is estimated over the first 10 years of commercialisation, assuming that a lower level of financial return on investment is accepted (10.5%), generally associated with higher-risk investments as in innovations.

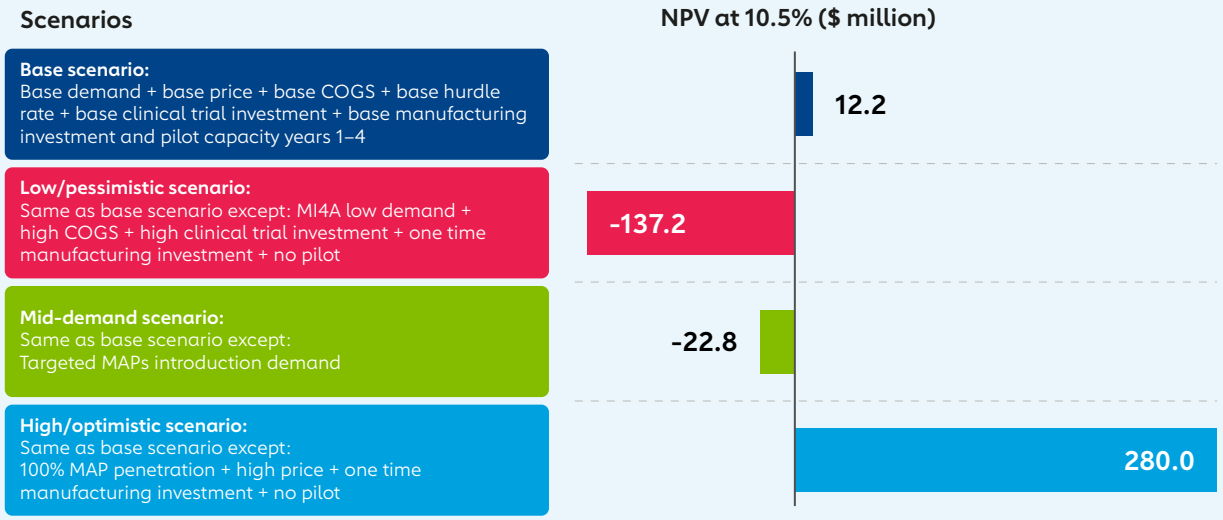
Additional scenario analysis was conducted to capture the impact of the full range of price, investment, production and demand dynamics (Figure 18 and Table 5). Under a high-demand scenario, the potential NPV may be US$ 280 million over 10 years. In a low-demand scenario, losses could represent around US$ 137 million over 10 years (Figure 19). The analysis identified the greatest risk to achieving a positive NPV is TCV-MAP demand and that uptake in HICs will be key to improving the financial attractiveness of investing in TCV-MAP development.

Figure 18. **Demand scenarios assessed in DCF analysis**



SI: Surviving infants
HTR: Hard-to-reach
MOV: Missed opportunities for vaccination

Figure 19. **Net present value of TCV-MAP development and commercialisation (10 years)**



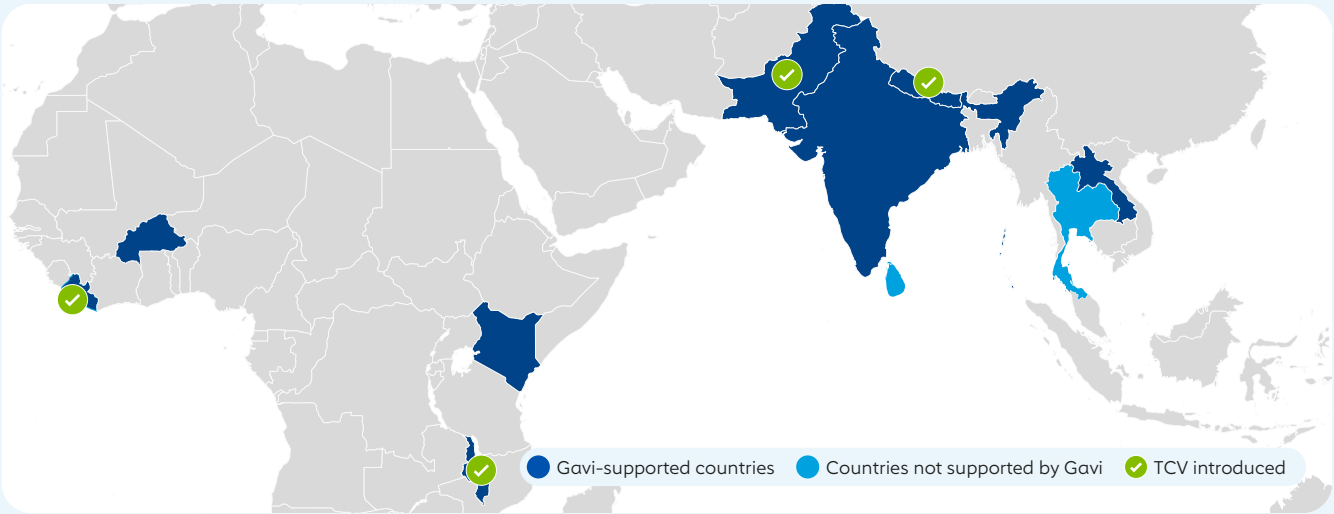
One key outcome from the DCF analysis is that while the potential return on investment is uncertain at this stage, TCV could be an interesting test case for MAP as a vaccine platform, potentially paving the way for other vaccines to be put on MAPs, including future combination vaccines.

8.2 Willingness-to-pay analysis

8.2.1 Methods

To inform the value proposition of TCV-MAPs, a willingness-to-pay (WTP) analysis was conducted through country consultations with stakeholders from 10 countries representing different typhoid burdens, TCV introduction statuses and Gavi-support statuses (Figure 20). Stakeholders interviewed had expertise in vaccine implementation, health financing, health economics and vaccine decision-making (n=29). Organisations represented include national ministries of health, National Immunization Technical Advisory Groups (NITAGs), multilateral global health organisations and academic institutions.

Figure 20. **Countries included in willingness-to-pay analysis**



The WTP questionnaire was designed based on the Gabor-Granger pricing methodology, which determines a participant's willingness to buy a product at a given price point by determining the price of a current product and probing on an increased price for an alternative until the highest acceptable price is reached. Since MAPs are expected to have a price premium, price points lower than the current TCV N&S presentation were not assessed. To determine a participant's maximum willingness to pay, price premiums from 50 to ≥150% were assessed. The impact of changes in delivery costs (increases or decreases) on willingness to pay was also assessed.

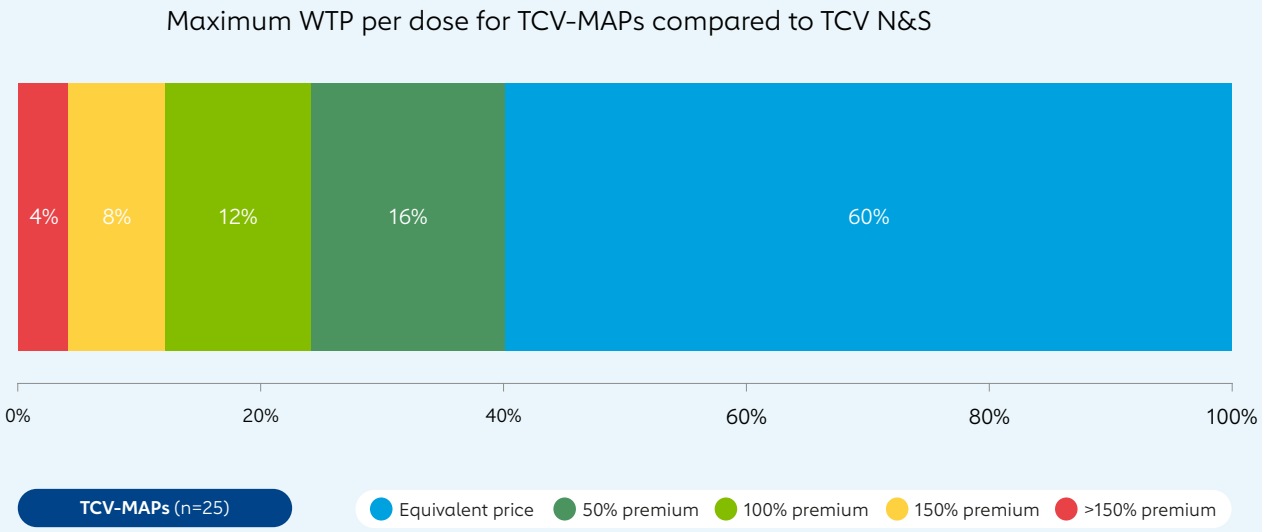
8.2.2 Key inputs

To assess TCV-MAP WTP, it was assumed that TCV N&S presentation was US$ 1.50 based on UNICEF standard prices (equivalent TCV-MAP price point) and delivery costs were assumed to range from US$ 0.12–1.07 TCV-MAPs, compared to a range of US$ 0.34–0.73 for TCV N&S. For stakeholders from Gavi-supported countries, participants were instructed to assume that the TCV-MAP price premium at introduction would be covered by donor funding with the long-term goal for the programme to be sustained and fully funded by the country in the long term.

8.2.3 Outcomes

Given the proposed product attributes of TCV-MAPs (Appendix 1), most participants (79%) perceived MAPs as better than conventional vaccine presentations. Despite favourable impressions of MAPs, less than half (40%) were willing to pay a higher price for TCV-MAPs (Figure 21). In addition, the analysis showed that respondents from Gavi-supported countries were more price-sensitive and commented on future sustainability more frequently than their counterparts from non-Gavi-supported countries. No differences in willingness to pay were observed based on the TCV introduction status of countries.

Figure 21. **Country WTP for TCV-MAPs as compared to TCV-N&S**



Vaccine price was highlighted as the most important cost component as potential reductions in delivery cost enabled by a MAP presentation had little impact on willingness to pay for TCV-MAPs. However, some respondents noted that they might consider paying a higher price for MAPs if they were used to target specific populations or geographic areas with low coverage.

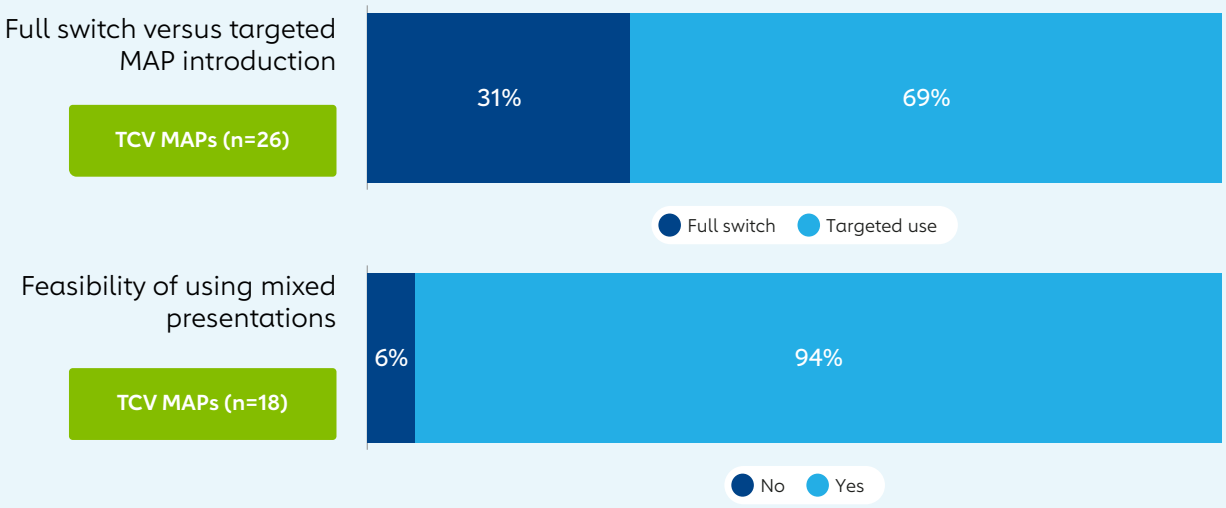
Although stakeholders had positive perceptions of TCV-MAP product attributes, the findings from the WTP analysis reinforce the assumption that price sensitivity is high in many typhoid-endemic countries. To achieve and maintain sustainable demand and ensure access to TCV-MAPs, both manufacturers and funding/procuring entities will need to ensure that affordability is achievable for these countries.

It should, however, be noted that the results may be limited by the sample size of participants (29) and countries represented (10) and the uncertainty of the final TCV-MAP price. As a result, future changes in TCV-MAP product attributes and final TCV-MAP price may shift WTP responses.

8.2.4 TCV-MAP introduction strategies

As part of the WTP analysis, stakeholders were also asked about their preferred introduction strategy for TCV-MAPs. Approximately 70% of respondents preferred a targeted MAP introduction compared to a full switch, and more than 90% of respondents indicated that using mixed presentations (both TCV N&S and TCV-MAP simultaneously) would be feasible in their country's context (Figure 22).

Figure 22. **Country preferences of MAP introduction strategy**



Compared to a full switch, a targeted approach could enable immunisation programmes to maintain injectable vaccine coverage in regions with robust immunisation rates while directing TCV-MAPs towards HTR areas with lower coverage rates. Moreover, a targeted approach would reduce the total number of TCV-MAPs procured and associated additional costs compared to what would be needed for a complete switch to TCV-MAPs. Some respondents also acknowledged the logistical challenges that may be associated with using mixed presentations, citing the need for careful segmentation of areas to prevent confusion among healthcare workers and caregivers.

Credit: Gavi/2023/Khasar Sandag

9 Key gaps in knowledge or research evidence

Key insights

- The understanding of the potential impact of TCV-MAPs remains incomplete due to the early stage of development and limited real-world evidence for vaccine MAPs.
- Addressing evidence gaps surrounding TCV-MAPs can inform their development and strategies to effectively facilitate implementation.
- Recommendations for further investigation include implementation research and acceptability studies to clarify the adoption likelihood and potential penetration of MAPs in different country contexts.

Given the early stages of TCV-N&S introduction, TCV-MAP development and limited real-world evidence generated on vaccine MAPs to date, many gaps remain in understanding the potential impact of TCV-MAPs. This is compounded by the slow rate of TCV introductions to date, which has limited the identification of challenges and opportunities related to reaching TCV coverage targets and the expected disease burden when a TCV-MAP could come to market. Key areas of uncertainty include future typhoid epidemiology, TCV-MAP development and product characteristics, TCV-MAP price, potential demand and programmatic implementation.

While numerous expert and stakeholder consultations have been conducted to gather information and validate conclusions of the FVVA, key questions and opportunities for refinement remain. Reduction of these uncertainties can contribute to increasing the robustness of the conclusions drawn in the analyses within the FVVA and provide greater clarity to decision-makers on future TCV-MAP implementation. This section outlines the key research areas and evidence to be generated to address the remaining gaps in knowledge.

Typhoid epidemiology

- Typhoid AMR is already a significant threat in some countries. The potential impact of AMR proliferation in other countries can be better understood through modelling studies of transmission and impact.
- Further epidemiological studies aimed at understanding the evolving endemicity of typhoid considering the impact of climate change will be required.

TCV-MAP development and product characteristics

- Analyses will need to be refined once more accurate product-specific data on TCV-MAP attributes (e.g. cold chain volume, wear time, length of storage in CTC, etc.) are available.
- Additional expert assessment of the manufacturing process at scale could help ascertain the likely cost of goods under different scenarios (e.g. different production yields, potential shared process between various MAPs) until real data can be gathered once manufacturing is operational.

TCV-MAP price

- Further WTP studies will be required to understand price thresholds for different countries and the potential need for co-financing schemes.
- Once more up-to-date information on the commercialisation strategy and manufacturing setup from front-runner vaccine manufacturers and MAP developers is available, a refined price benchmarking analysis will be necessary.
- An updated ECEA should be carried out when new model input assumptions for variables driving the cost-effectiveness results are available. This includes key cost-effectiveness drivers such as TCV-MAP price and cold chain volume.

Additional evidence may also be needed to inform regulators, policy-makers, funders, procurers and countries to support policy and introduction decisions for TCV-MAPs and MAPs more broadly. These gaps in evidence can be generated through implementation research in the domains of demand and adoption of TCV-MAPs as well as their delivery and administration. A review of existing assessments and published research was conducted to identify potential gaps in evidence required for future policy and introduction decisions on TCV-MAPs. From the gaps identified, implementation research questions were developed based on considerations for policy and introduction decisions aligned to the WHO Evidence Considerations for Vaccine Policy Development (ECVP).[61] Research questions for investigation and activities that may support the required evidence generation are outlined in Table 6 and Figure 23

Demand and adoption of TCV-MAPs

- Implementation research and acceptability studies could be needed in order to clarify the likelihood of TCV-MAP adoption and the potential for MAP penetration vs N&S in the different use cases and country archetypes.

TCV-MAP delivery and administration

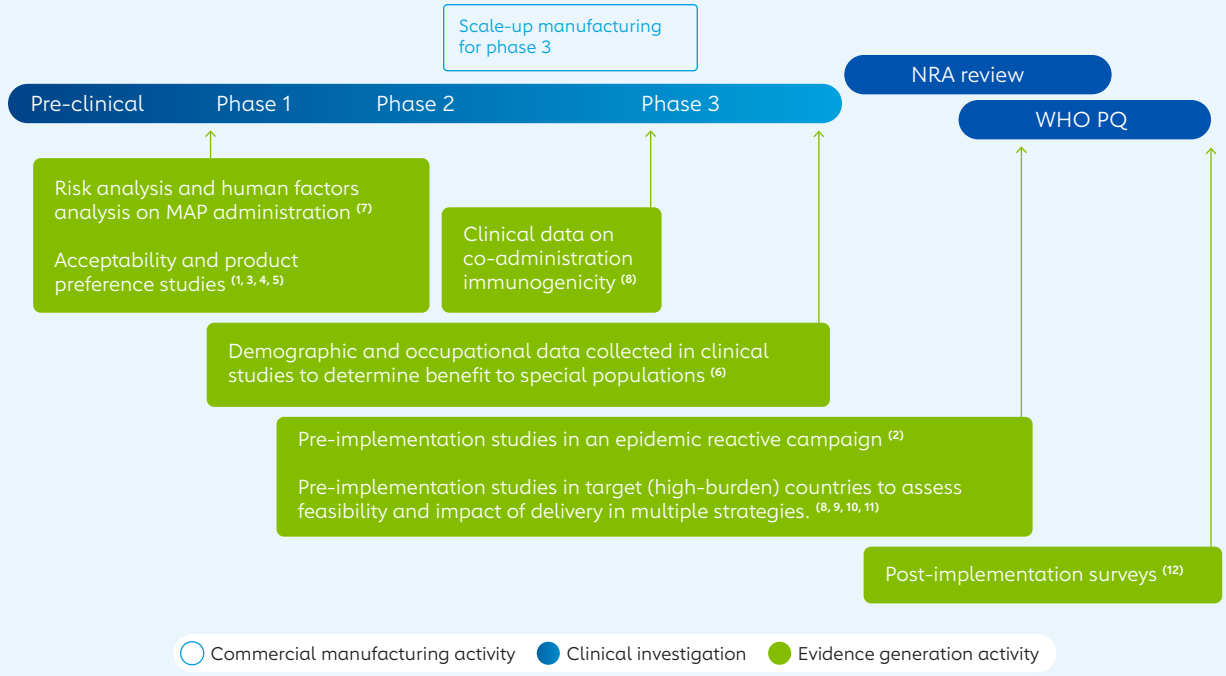
- Implementation research studies could be necessary to improve understanding of the optimal delivery strategies taking into account priority populations, caregiver and administrator preferences, cohesion with existing vaccination programmes and product attributes.

Credit: Gavi/2022/Asad Zaidi

Table 6 **Outstanding implementation research questions identified to support evidence generation**

	Potential implementation research question	Supportive evidence required
Demand and adoption of TCV-MAPs	**1.** Will the impact of TCV-MAPs in reducing the number of injections be meaningful to the caregiver and/or the vaccinator?	Acceptability and product preference studies (may be assessed alongside clinical study or independently)
	2. In an epidemic context: • Could a TCV-MAP presentation accelerate deployment of reactive vaccination campaigns? • Could a TCV-MAP expand vaccine coverage? • Under what scenarios (e.g. self-administration and home delivery of vaccines, delivery in immunisation centres, door to door vaccination)?	Pre-implementation study in an epidemic reactive campaign
	3. Will the option for self-administration of TCV-MAPs in adults improve uptake? • In which populations and scenarios? • What are the key implementation challenges? **4.** What will the impact be on compliance, safety and reporting?	Acceptability and product preference studies Policy requirements for self-administration
	5. Will the availability of TCV-MAPs increase uptake in typhoid vaccines by travellers?	Acceptability and product preference studies
	6. Will TCV-MAPs provide additional benefit to those in occupations at high risk of infection and disease transmission including food handlers and health workers?	Demographic and occupational data can be collected in clinical studies to determine benefit to special populations recruited in the studies (if sample size is sufficient)
TCV-MAP delivery and administration	**7.** How likely are TCV-MAPs to be administered incorrectly in programmatic settings? • What is the likelihood of incorrect application technique? • What is the likelihood of incorrect wear time? • What training and oversight is needed to minimise MAP use errors?	Risk analysis and human factors analysis on TCV-MAP administration
	8. Is the administration of TCV-MAPs alongside other vaccines feasible? • Are there any additional challenges or opportunities presented? • What impact will countries' TCV schedules have on the ability to co-administer given the 6-month, 9-month and 15-month routine schedules under consideration?	Pre-implementation studies in target (high burden) countries to assess feasibility and impact of delivery in multiple strategies Clinical data on co-administration immunogenicity Stakeholder interviews on how multiple presentations would be handled
	9. Can TCV-MAPs be used alongside TCV-N&S in routine programmes? • How should the presentation be segmented? • To what extent will segmentation be possible at a subnational level?	Pre-implementation studies in target (high burden) countries to assess feasibility and impact of delivery in multiple strategies
	10. What is the optimal design of mass immunisation sessions with TCV-MAPs? • Is simultaneous observation of patients feasible?	Pre-implementation studies in target (high burden) countries to assess feasibility and impact of delivery in multiple strategies.
	11. Can TCV-MAPs be delivered effectively by community health workers (CHWs)? • What policy changes may be required to enable delivery by community health workers?	Pre-implementation studies in target (high burden) countries to assess feasibility and impact of delivery in multiple strategies
	12. How will TCV-MAPs impact vaccine hesitancy? • In parents and caregivers to infants and children vaccinated? • To vaccinators? • To adults?	Post-implementation survey
	13. What are the optimal communication strategies for introducing MAPs?	

Figure 23. **Illustrative timeline of evidence generation activities required**



NRA: National regulatory authority; **PQ:** Pre-qualification

(x) Related implementation questions as per Table 6

10 Principal findings and conclusion

10.1 Key inputs

The research summarised in this FVVA shows the following:

Impact

- Over 5 million typhoid cases and 47,000 deaths could be averted through the introduction of TCV-MAPs over 20 years to replace traditional vaccines for identified use cases. Improving the response to typhoid burden is critical in the context of evolving endemicity impacted by increasing anti-microbial resistance and climate change.
- TCV-MAPs could be used to reach the infant (<2) target population in all delivery settings (fixed post, outreach or mobile). Whether they are delivered by an HCW or CHW does not seem to play a differentiating role in UCs as opposed to what has been observed for other MAPs.
- In terms of the potential to improve equity, TCV-MAP use will drive the greatest health impact to the lowest wealth quintiles, which will have indirect benefits on other populations.

Cost-effectiveness

- TCV-MAPs are likely to be cost-effective for the majority of the population in the African region, at or below a price of US$ 3 per dose. MAP price and product characteristics (driven by cold chain volume) are key drivers of cost-effectiveness. However, TCV-MAPs are not likely to be cost-effective for other regions due to low disease incidence and mortality.
- Where national introduction is not likely to be cost-effective, and there is heterogeneity between subnational regions, subnational implementation could be cost-effective if typhoid mortality is high.
- TCV-MAPs do not have a sizeable health impact when used for outbreak response and are unlikely to be cost-effective compared to TCV multi-dose vial presentation.

Demand

- Potential demand for TCV-MAPs spans a broad range driven by the uncertainty of demand for TCV in the currently available presentations due to limited and delayed country introductions to date.
- Demand ranges from 14–33 million doses per year in year one up to 62–107 million doses per year in year 10. Mainly distributed across LMICs and MICs, with a small military and travellers market in HICs.
- TCV-MAPs could represent a sizeable proportion of the TCV market, even under targeted use (e.g. outreach or mobile UCs only).
- However, price point and product attributes (driven by cold chain volume) will determine how much of the TCV demand would switch to a MAP presentation.

Perceptions and price

- Most respondents interviewed during country consultations prefer TCV-MAPs over N&S presentations.
- Willingness to pay a price premium for TCV-MAPs is limited in both self-procuring and Gavi-supported countries.
- The potential for delivery-cost savings through a MAP does not have a significant impact on WTP.
- Price sensitivity may be lower in non-Gavi-eligible countries. Further investigation is required as the business case for TCV-MAPs could hinge on high uptake in HICs.

Commercialisation

- Development and commercialisation of TCV-MAPs could potentially be financially attractive. However, this will depend on sufficient demand for TCV-MAPs, including uptake in high-income markets.
- The development of TCV-MAPs could support MAPs as a platform for other vaccines, including potential future combination vaccines.
- Commercialising multiple vaccine MAPs could have positive implications for savings in manufacturing and development costs.

10.2 Conclusion and limitations

Under the right conditions, TCV-MAPs could be a valuable addition to typhoid immunisation. These conditions hinge on parameters such as:

- **Priority geographies**: TCV-MAPs are most likely to be cost-effective in the African region.
- **Targeted introductions**: Subnational introductions could be cost-effective in some countries where national introductions are unlikely to be as effective.
- **Compelling product attributes**: Driven by cold chain volume and thermostability profile.
- **Attractive price**: Influencing the extent to which TCV-MAPs can be cost-effective and influencing countries' and donors' willingness to pay for TCV-MAPs.
- **Uptake in different target populations**: This includes segments such as travellers and military in HICs, which could drive the financial attractiveness of the business case.

However, these conclusions need to be qualified, as the results from the FVVA analyses are based on the currently available information on MAPs and typhoid, which is limited in some respects. Beyond the limitations in the availability and quality of typhoid surveillance data to assess the true burden of the disease, the slower-than-expected ramp-up of injectable TCV in endemic countries has led to uncertainties in the future demand for TCV and subsequently to a broad range of demand scenarios for TCV-MAPs.

In addition, the most advanced vaccine MAPs are only about to enter late-stage clinical trials. Therefore, assessing key MAP benefits, such as additional coverage within HTR or otherwise unvaccinated populations, is largely based on expert judgement at this stage. Targeted implementation research can help inform and improve the assessment, but only the deployment of vaccine MAPs in the field will tell how much the expected benefits will materialise. As TCV-MAPs are in the pre-clinical stage, uncertainties about their final attributes, costs of production and price are still high, and these factors may impact many of the key parameters defining the right conditions under which TCV-MAPs could be a valuable addition to typhoid prevention.

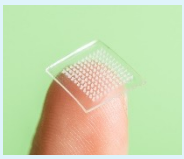
Appendices

Appendix 1

Microarray patches (MAPs) concept card

What are MAPs?

Prototype microarray patch. The microarray comes inside an applicator component that makes a click sound to confirm delivery.

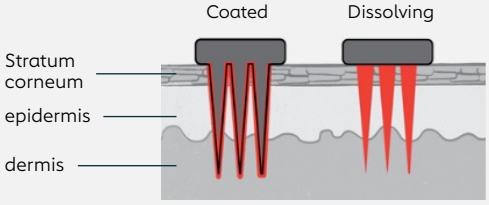


Points on a microarray that contain vaccine.

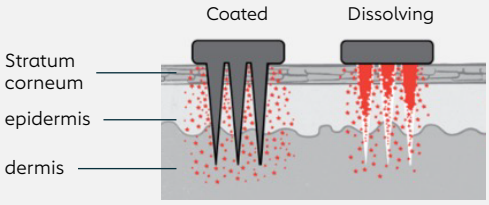
- Patches that consist of **hundreds or thousands of tiny projections.**
- The projections can be **coated with or composed of a vaccine** (dry formulation).
- **Applied to the skin and pressed down** so that the points penetrate the top of the skin. After a few minutes, the vaccine in or on the points dissolves in the skin and the patch can be removed.
- The projections only **penetrate the top layers of the skin** to deliver the vaccine.
- Typically perceived as **less painful than an injection.**
- Application may result in a small red or darkened area on the skin at the site of application lasting up to days or weeks, or other minor local adverse events.
- MAP **cold chain volume** per dose is around 20 cm3 compared to 2–3 cm^3 for a typical vaccine in a multidose vial. However, since syringes are not required (about 43 cm^3), the overall storage volume would be less.
- **Under development for delivery of several vaccines** including influenza, measles-rubella (MR) and typhoid conjugate vaccine (TCV).

Mode of action

1 Patch is applied



2 Vaccine is released



3 Vaccine goes from the skin to the rest of the body

MAP may offer many potential benefits for vaccine delivery

- Increased ease of use and ability to be administered by lesser trained personnel
- Improved safety due to elimination of reconstitution and associated errors and risks as no needle
- Simplified non-sharps waste disposal
- Potential for improved thermostability
- Single-dose presentation, which can reduce wastage and missed opportunities for vaccination due to the reluctance to open preservative-free multidose vials

Vaccine MAPs may be used in various immunisation delivery settings (e.g. routine, supplemental, house-to-house, outbreak response, pandemic preparedness) depending on the vaccine of interest and could enable alternative delivery scenarios.

MAPs may increase equitable coverage of vaccines and address immunisation barriers that country stakeholders have identified with current vaccine presentations (e.g. storage in multidose vial and administered via needle and syringe). For instance, MAPs may increase coverage rates by 10–30% in hard-to-reach populations.

The MAP delivery platform is an innovation of high interest to the Vaccine Innovation Prioritization Strategy (VIPS) Alliance – an initiative led by Gavi, the Vaccine Alliance; the World Health Organization; the Bill & Melinda Gates Foundation; UNICEF; and PATH, who are exploring vaccine candidates that could benefit from it.

Generic MAP product profile

There are different types of MAPs currently under development. MAPs for vaccines are at an early stage of development, it may be a decade or more before a vaccine MAP could be introduced in your country. Below is a description of product attributes that may be feasible for the different products in development.

Table 7 **TCV-MAPs attributes**

Attribute	Description
Application	A MAP has a built-in component that makes a click sound to let you know that you've pressed hard enough to deliver the vaccine. It cannot be clicked again, preventing accidental reuse.
Cold chain volume per dose	MAP cold chain volume per dose is approximately 20 cm^3 compared to 2–3 cm^3 for a typical vaccine in a multidose vial. However, since syringes are not required (approximately 43 cm^3), the overall storage volume would be less.
Disposal	Non-sharps waste disposal.
Doses per container	Each MAP would hold a single dose of the vaccine.
Preparation	Reconstitution of the vaccine with a diluent is not required. MAPs would be ready for administration as soon as the packaging is open.
Thermostability	MAPs have the potential for storage in a controlled temperature chain (CTC). • A CTC-qualified vaccine can be stored and transported at ambient temperatures (for example, not exceeding 40°C) for a specific number of days just before administration. • Different MAP presentations can be used in a CTC for different durations (e.g. 3–7 days). Temperature exposure must be monitored during the time in CTC using the vaccine vial monitor (VVM) plus a threshold indicator (a card with a sticker that changes colour), and any unused doses should be discarded after the specified number of days has passed.
Tolerability	MAP projections are shorter than 1 mm and do not reach dermal pain receptors; therefore, administration is perceived as less painful than an injection.
User groups	By eliminating injection, a MAP could increase ease of use and allow potential administration by lesser trainer personnel instead of a healthcare worker of vaccinator.
Wear time	Wear time is up to 5 minutes. The dry vaccine dissolves in the skin and the patch can be removed.
Vaccine effectiveness	Similar (non-inferior) to existing injectable vaccines.
Safety	Similar (non-inferior) to existing injectable vaccines.

Vaccine delivery costs for immunisation programmes have several components including cold chain at each supply chain level, transport between supply chain levels, waste disposal, human resource costs/time for vaccine administration, and transport costs for the vaccination teams when conducting outreach and mobile sessions.

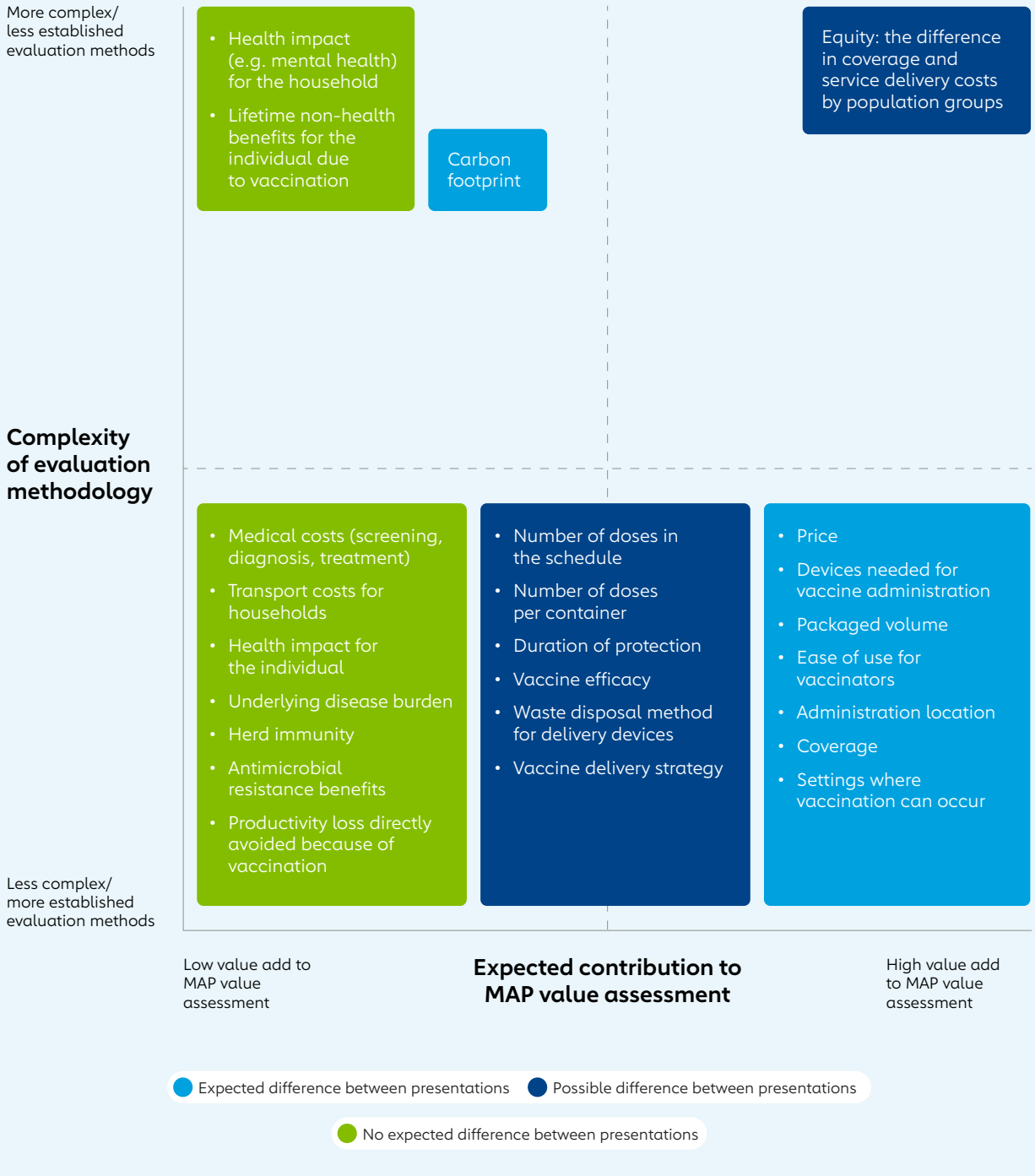
For a TCV-MAP, the average delivery costs across 73 low and middle-income countries are estimated to range from US$ 0.12 to US$ 1.07 depending on the intended use case and MAP attributes compared to a range of US$ 0.34 to US$ 0.73 for TCV in a vial.

Appendix 2

Matrix of qualitative framework components considered in socioeconomic and public health impact analysis

Figure 24. **Qualitative framework components considered in socioeconomic and public health impact analysis**

Methodological complexity versus value add of including the framework components into the socioeconomic and public health impact analysis



Appendix 3

TCV-MAP country archetype descriptions

Country archetype A, includes high-income countries (HICs) and Upper-middle-income country (UMICs) that have low burden of typhoid and/or antimicrobial resistance (AMR). These countries are unlikely to introduce TCV-MAPs into national routine immunisation schedules for children, adolescents or adults, including food handlers and laboratory workers, given the low level of disease burden. However, published articles and consultations indicated that some countries in this archetype have mandatory vaccination for military personnel being deployed to into typhoid endemic areas as well as a private market for travellers going to typhoid endemic areas. As vaccination for military personnel would be mandatory, this use case has been classified as high likelihood of use. Typhoid vaccination of travellers is non-compulsory and dependent on the traveller seeking and accessing typhoid vaccination which currently occurs at very low rates, therefore it was classified as low likelihood of use.[62]

Country archetype B, includes low- and middle-income countries (LMICs) and low-income countries (LICs) in the Africa, Americas, Eastern Mediterranean and Europe regions with high typhoid incidence and/or AMR. These countries will likely introduce typhoid vaccination into their routine immunisation schedules as well as conduct a catch-up campaign when typhoid vaccines are introduced. If TCV-MAPs are introduced in these countries, they would have a high likelihood of being used in children less than 2 years old at the health facility through their regular medical check-ups and in settings without health services as part of the outreach and mobile services such as administration of the first or second dose of measles-containing vaccines (MCV1 and MCV2). There is a low likelihood of TCV-MAPs being used routinely in settings with limited health services as most of the population would be reached at the fixed health post or through outreach/mobile services. As these countries will likely conduct a catch-up campaign when they introduce typhoid vaccines, TCV-MAPs could also be used in these settings. Finally, given the endemicity levels, TCV-MAPs could be used in adult populations, including food handlers, laboratory workers, military personnel and travellers. However, given that the burden of disease lies in the younger ages and vaccination may need to be privately financed by the individual receiving the vaccine, these use cases have been categorised as low likelihood of use.

Country archetype C includes LMICs and LICs in the Africa, Americas, Eastern Mediterranean and Europe regions with medium typhoid incidence and/or AMR. These countries would likely not introduce typhoid vaccine into their routine immunisation schedules. This assumption is based on the global historical trends that show a decline in typhoid burden due to increases in other measures such as water, sanitation and hygiene. Further, given the limited evidence on the use of TCV in outbreak settings, it is assumed that TCV-MAPs would not be used in this situation. While it is unlikely that these countries will introduce TCV-MAPs as part of routine immunisation, it is possible that TCV-MAPs could be used in the private market for all potential target populations in health facilities or settings with limited health services, justifying the low likelihood of each of these UCs.

Country archetype D includes LMICs and LICs in the Africa, Americas, Eastern Mediterranean and Europe regions with low typhoid incidence and/or AMR. These countries would not be likely to introduce typhoid vaccination into their routine immunisation schedules. Further it is unlikely that they would target food handlers, laboratory workers and military personnel, given the low burden of disease. However, there could be use of TCV-MAPs in the private market for travellers.

Country archetype E includes LMICs and LICs located in the Asia and Western Pacific regions with high or medium typhoid incidence and/or AMR. These countries may use TCV-MAPs in the public sector and would likely introduce them into their routine immunisation schedules. For the countries within this archetype, the private market for vaccines is established and already playing an important role compared to archetype B (e.g. in India, TCV has been actively used in the private market since its licensure in 2012 but has not yet been introduced into national routine immunisation schedules). It is also assumed that there will be more pharmacy access in these countries than in archetype B countries; thus, there will potentially be more use of TCV-MAPs in the limited health services setting with a reduced cold chain. Thus, high and medium likelihood were applied to use case (UC) 1 and UC 3 as the majority of the population will be reached in these two delivery settings. While if the country conducts a catch-up campaign high likelihood was also given to the >2 to 15-year-olds in the settings with limited and no health services. Given that the burden of disease lies in the younger populations, the adult populations, including food handlers, laboratory workers, military personnel and travellers, have a low likelihood to be vaccinated.

Appendix 4

Demand forecast baseline assumptions and additional scenarios assessed

Table 8 **Demand forecast assumptions and scenarios**

Variable	Base case assumptions	Additional scenarios
Number of countries introducing TCV	• MI4A projections base case • National routine introduction for all introducing countries	• MI4A projections low case • Subnational introduction in India*
Timing of country adoption	Country disease burden weighted 1.5 times compared to Gavi eligibility and historical introductions	Country disease burden weighted 2 times compared to Gavi eligibility and historical introductions
Forecasted coverage for surviving infants	Forecasted coverage to 2042 using 2019 WUENIC MCV1 as proxy 3%/year growth (countries <70% coverage) • 1%/year (countries 70-85% coverage) • 0.5%/year (countries >85% coverage) Capped at the historical high or 95%	No forecasted growth from MCV1 coverage (held constant at 2019 WUENIC values).
Market penetration	From year 1 of TCV-MAP introduction • <2-year-old market penetration: 80% • Travellers market penetration: 80% • Military market penetration: 50%	Phased market penetration • 20% incremental increase per year until the market penetration maximum is reached (80% for <2-year-old and travellers' market, 50% for military)
Coverage in HTR and MOV populations	• Coverage of HTR and MOV in children <2-year-old: 20% • Coverage of HTR and MOV in children 2–15-year-old: 10%	+/- 10% compared to base case assumptions for changes to HTR and MOV coverage for routine and supplementary immunisation activity delivery • Routine – High: 30%; Low: 10% • One-time catch-up – High: 20%; Low: 0%

*The impact of subnational introduction in India was specifically assessed due to the large target population, which could have a large impact on the programmatic doses required if TCV-MAPs are introduced nationally or subnationally.

Appendix 5

TCV-MAP demand projections 2033-2042, all scenarios

Table 9 **TCV-MAPs demand projections**

Scenario	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042
Base	25.0	39.7	65.7	72.9	79.3	81.4	80.4	83.1	81.9	91.5
MI4A low scenario for country scope	14.1	24.1	43.0	46.0	52.6	54.1	52.7	54.9	53.3	62.5
Subnational for India	25.0	39.7	60.8	64.0	67.2	70.3	69.3	72.2	71.1	80.8
Earlier adoption by countries with a higher burden	25.1	54.7	67.4	81.7	78.9	80.6	82.4	82.2	81.9	91.5
Low MCV1 coverage	23.1	36.0	59.7	65.1	71.3	72.9	71.6	74.0	72.5	81.9
Incremental market penetration	14.8	24.9	51.0	59.9	70.7	79.4	79.1	82.6	81.5	90.3
High HTR and MOV coverage	32.8	48.4	80.8	81.2	86.7	88.7	86.2	90.2	87.5	103.3
Low HTR & MOV coverage	17.3	31.0	50.5	64.6	71.9	74.0	74.6	76.0	76.3	79.7
Targeted TCV-MAP introduction	20.5	32.7	52.1	56.3	61.7	63.3	62.2	64.5	63.2	72.7
100% TCV-MAPs penetration	28.8	46.2	75.7	85.6	93.1	95.6	94.5	97.5	96.4	107.1

HTR= hard-to-reach; MOV= missed opportunities for vaccination

Appendix 6

Probability tree model of disease outcomes

Figure 25. **Probability tree model of disease outcomes**

IP: Ileal perforation

Appendix 7

Key input parameters for the global and subnational analyses

Table 10 **Key input parameters for the global and subnational analyses**

	TCV-N&S (5-dose vial)	TCV-MAP	Rationale
Introduction dates	2023-2032	2033-2042	Projected for each country based on historical vaccine introduction trends, forecasted Gavi eligibility and burden of disease.
Coverage – routine	At 9 months: 26.3–99.7% (MCV1 proxy) At 15 months: 9–93% (MCV2 proxy)		Demographic and health surveys (DHS) or multiple indicator cluster surveys (MICS) for MCV1 coverage (at 9 months) and MCV2 coverage (at 15 months) in 20 countries. For countries with no data, it was assumed that coverage was 20 percentage points lower for MCV2 than for MCV1. The difference of 20 was the average difference in the 20 countries where the data was available. Coverage rates are conservatively held constant throughout the time horizon.
Coverage – campaign	10 percentage points lower than routine coverage		Aligned to prior assessments of TCV cost-effectiveness analysis.[63]
Coverage among populations currently unreached	0%	20%	Based on expert guidance and estimates of zero-dose children outside of conflict settings and potentially reachable by addressing programmatic barriers associated with N&S delivery.
Price	US$ 1.50	US$ 2.00–4.50	TCV-N&S price for WHO-prequalified vaccine procured through UNICEF and introduced at national level to date TCV-MAP range informed by price benchmarking and cost of goods sold assessment.
Delivery costs	US$ 0.28–0.91	US$ 0.12–1.07	Weighted average of delivery costs across all countries – model includes country-specific delivery costs. Range represents variation by use case. Delivery costs include: cold chain, human resource, transport and supply costs.
Vaccine wastage	11%	1%	Based on revised WHO global indicative wastage rates.[64]
Time horizon for the ECEA	20 years (2033–2052)		Minimum timeframe to observe the impact on health outcomes and transmission trends.
Discount rate	3%		Standardised assumption for economic analysis of health interventions.
Vaccine efficacy	85%		Assumed non-inferiority of TCV-MAPs compared to TCV-N&S. Aggregated efficacy based on studies in 4 countries.[65,66,67,68]
Vaccine duration of protection	10 years		Assumed a 10-year period for both TCV-N&S and TCV-MAPS. Due to the recency of TCV availability, long-term protection studies beyond 4 years are ongoing.

Appendix 8

Country consultations

A series of country consultations, structured in-depth individual interviews conducted virtually and in-person, ensured that the processes, methodologies and assumptions related to the FVVA were informed by countries.

An initial round of country consultations conducted in eight priority countries with medium to high typhoid incidence and/or AMR was designed to provide feedback on:

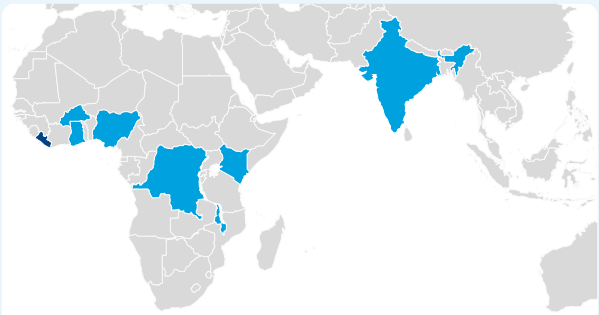
1. key components considered for new vaccine presentation introduction decisions;
2. qualitative factors to be included in the extended cost-effectiveness analysis;
3. decision-making considerations for products with an expected price premium (e.g. MAPs); and
4. potential role of TCV-MAPs in country immunisation programmes, and essential attributes for consideration.

The second round of country consultations informed the value proposition of TCV-MAPs by providing insights on country stakeholders' perceptions of the potential value of MAPs based on their proposed attributes and willingness-to-pay estimates. The country feedback also highlighted gaps in knowledge that supported the development of outstanding research questions. This round included stakeholders from 10 countries representing different typhoid burden, TCV introduction status and Gavi-support status.

Profiles of participants in the consultations can be found in the following figures.

Figure 26. **Countries engaged in country consultations**

Round 1



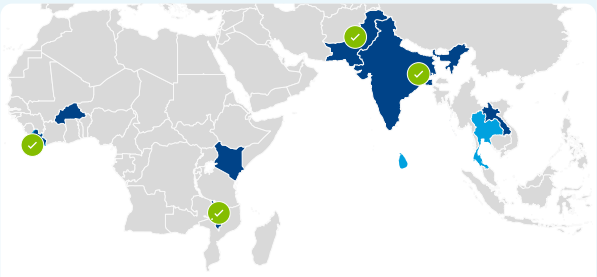
Introduced TCV in national immunisation programme
Have not yet introduced TCV in national immunisation programme

Gavi-supported countries (n=8)*

Country	n	TCV introduced	Gavi status (2022)
Kenya		No	Accelerated transition
Liberia		Yes	Initial self-financing
Malawi		Yes	Initial self-financing
Burkina Faso		No	Initial self-financing
Democratic Republic of The Congo (DRC)			
Nigeria			
Ghana			
India		No	Fully self-financing

*A Gavi-supported country in this presentation is defined as a country that currently receives **any type of Gavi support** beyond the **54 countries** eligble to apply for new vaccine support from Gavi in 2023 (i.e. Gavi-eligible)

Round 2



Gavi-supported countries
Countries not supported by Gavi

Gavi-supported countries (n=24)* TCV introduced

Country	n	TCV introduced	Gavi status (2022)
Kenya	3	No	Accelerated transition
Liberia	4	Yes	Initial self-financing
Malawi	4	Yes	Initial self-financing
Burkina Faso	4	No	Initial self-financing
Pakistan	1	Yes	Preparatory transition
Lao People's Democratic Republic (PDR)	1	No	Accelerated transition
India	4	No	Fully self-financing
Nepal	3	Yes	Preparatory transition

Non-Gavi-supported countries (n=5)

Country	n	TCV introduced	Gavi status (2022)
Thailand	3	No	N/A
Sri Lanka	2	No	Fully self-financing

Figure 27. **Overview of participants in round 1 country consultation**

Participant overview

Stakeholder interviews

Round 1:
17 participants

Round 2:
29 participants

Participant expertise

- Vaccine implementation
- Health financing
- Health economics
- Epidemiology and disease surveillance
- Vaccine policy-/ decision-making
- Clinical
- Capacity-building and service delivery
- Procurement and supply chain management

Organisations/affiliations

- **Burkina Faso:** MOH, NITAG
- **India:** MOH, NITAG, global health partner organisation
- **Kenya:** MOH, global health partner organisation
- **Lao PDR:** NITAG
- **Liberia:** MOH, NITAG
- **Malawi:** MOH, WHO, local health facility
- **Nepal:** MOH, local university, paediatric hospital
- **Pakistan:** UNICEF
- **Sri Lanka:** MOH, WHO, NITAG
- **Thailand:** MOH, public policy research institute
- **DRC:** MOH
- **Nigeria:** NITAG, local university
- **Ghana:** MOH (former)

MOH: Ministry of Health

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