WHO Preferred Product Characteristics (PPC) for Bivalent *Salmonella* Typhi/Paratyphi A Vaccines

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Executive Summary

Enteric fever, caused by *Salmonella* Typhi and Paratyphi A, B, and C, is a major health concern in LMICs. The disease is transmitted through the faecal-oral route, often via contaminated food and water, and can lead to severe complications if untreated. The increasing prevalence of antimicrobial resistance has complicated treatment options, making vaccination a critical preventive measure.

Currently, there are vaccines available for typhoid fever, including the oral live-attenuated Ty21a vaccine, the polysaccharide Vi antigen vaccine, and the typhoid conjugate vaccine (TCV). However, there are no licensed vaccines for paratyphoid fever. Several vaccine candidates for *Salmonella* Paratyphi A are in various stages of development, including live-attenuated, protein subunit, outer membrane vesicle (OMV), and conjugate vaccines.

Salmonella Paratyphi A-containing vaccines have been identified as a strategic priority for WHO due to the high incidence of enteric fever in certain regions, especially in Asia. The rise of antimicrobial-resistance has further highlighted the necessity for effective vaccines to prevent the disease and curb the spread of AMR

The WHO's Preferred Product Characteristics (PPCs) for bivalent Salmonella Typhi/Paratyphi A vaccines outline the desired attributes for these vaccines. These include targeting infants, toddlers, school-age children, and young adults in high-burden areas. The vaccines should provide robust protection against both Salmonella Typhi and Paratyphi A, with a strong and lasting immune response. They must have a favourable safety profile, be stable under conditions commonly found in LMICs, and have a long shelf life. Additionally, the vaccines should be easy to administer, ideally in a single dose or simple schedule, and be affordable and cost-effective to ensure widespread access and uptake.

The development of bivalent *Salmonella* Typhi/Paratyphi A vaccines is crucial for reducing the burden of enteric fever and combating antimicrobial resistance. WHO develops preferred product characteristics (PPCs) to provide strategic guidance on preferences for new vaccines, particularly for those intended for use in LMICs. The intention of the PPCs is to accelerate vaccine development towards products and regimens most in need and seen as most feasible to implement by LMIC policy-makers. The PPCs for a bivalent *S.* Typhi/Paratyphi A vaccine were defined by convening a technical advisory group on *Salmonella* vaccines that includes experts from various disciplines and representatives from high-burden areas. Through a series of consultations, the group aimed to articulate the priority public health needs within high-burden areas, and it is on this basis that these PPCs were developed.

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Acronyms

AMR	Antimicrobial resistance
ART	Anti-retroviral therapy
CFR	Case-fatality ratio
CHIM	Controlled human infection models
CVGH	Centre for vaccines and global health
DT	Diphtheria tetanus
EPI	Expanded programme on immunization
FQNS	Fluoroquinolone non-susceptibility
iNTS disease	Invasive non-typhoidal S*almonella* disease
IVB	Department of Immunization, Vaccines and Biologicals, WHO
HIC	High-income country
LMIC	Low- and middle-income country
LPS	Lipopolysaccharide
MDR	Multi-drug resistance, multidrug resistant
NTS	Non-typhoidal Salmonella
OMV	Outer membrane vesicle
PDVAC	Product Development for Vaccines Advisory Committee
PoC	Point of care
PPCs	Preferred product characteristics
PQ	Pre-qualification
RCT	Randomised controlled trial
RDT	Rapid diagnostic test
SAGE	Strategic Advisory Group of Experts (on Immunization)
SBA	Serum bactericidal activity
SETA	Severe Typhoid in Africa Program
TCV	Typhoid conjugate vaccine
TPPs	Target product profiles
TT	Toxoid tetanus
WASH	Water, sanitation and hygiene
WHO	World Health Organization
XDR	Extensively drug resistant

A. Introduction

1. Background and Purpose of WHO Preferred Product Characteristics Statement

The Department of Immunization, Vaccines and Biologicals Department (IVB) at the WHO aims to accelerate development and uptake of safe, effective, and affordable vaccines against pathogens with significant disease and economic burden in low- and middle-income countries (LMICs).

Key to achieving this aim is the early identification of aspirational characteristics for a given product, outlined in the PPCs. Vaccine PPCs published by WHO IVB aim to provide stakeholders (including researchers, vaccine developers, funders, national and regional policy-makers) with strategic guidance spanning the process of vaccine development, from identification of public health need to encouraging innovation and research in vaccine candidate evaluation, and to facilitate the progress towards licensure and implementation. It also contributes to the identification of data gaps and ways to address these to generate the evidence-base to allow prompt policy recommendations and vaccine introduction following licensure (1).

The WHO's Product Development for Vaccines Advisory Committee (PDVAC) identifies disease areas for the development of vaccine PPCs based on public health needs, LMIC stakeholder demand, and feasibility of successful vaccine development (2).

The WHO PPCs outline parameters such as target population, delivery schedules and strategy, and safety and efficacy evaluation. The PPCs are pathogen-specific rather than product-specific and do not include minimally acceptable characteristics. PPCs are typically produced early in product development; therefore, one of their roles is to promote discourse regarding desired product attributes and, as such may be updated as new data emerge, or the public health need and/or vaccine development landscape changes. The intention is that, as the vaccine development pipeline matures, the PPCs will inform candidate-specific target product profiles (TPPs) to facilitate progression towards regulatory approval and WHO pre-qualification (PQ).

The intention is the PPCs should be a useful reference for all stakeholders in vaccine development, with the primary target audience being any entity which may seek WHO policy recommendations and PQ for a product.

Vaccines intended for use in LMICs would undergo evidence-based assessment by WHO's Strategic Advisory Group of Experts on Immunization (SAGE). The PPCs provide additional guidance but do not supersede evidence-based assessments by SAGE or other existing WHO guidance on vaccine development and evaluation (3).

2. *Salmonella* Paratyphi A-containing Vaccines – A strategic Priority for WHO

Enteric fever is a community-acquired infection caused by the typhoidal serovars of the bacterium *Salmonella enterica* subspecies *enterica* serovars Typhi and Paratyphi A, B, and sometimes C. *Salmonella* Paratyphi A is responsible for a high proportion of enteric fever illnesses in some areas of Asia, where it can account for up to 50% of all isolates obtained from blood cultures (4,5). Enteric fever is commonly treated with antimicrobials. However, antimicrobial overuse has led to the emergence of antimicrobial resistant (AMR) strains that no longer respond to the first-line antimicrobials chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole. *S.* Typhi resistance to chloramphenicol has been reported since the 1950s (6), and multidrug resistant strains to all three first line treatments, chloramphenicol, ampicillin, and cotrimoxazole have been reported in Asia and Africa since the 1980s (7,8). The subsequent use of fluoroquinolones for the treatment of typhoid fever led to the emergence of resistance to nalidixic acid and ciprofloxacin (9), and extensively drug resistant (XDR) strains, defined as *S.* Typhi strains resistant to all three first-line antimicrobials, fluoroquinolones, and third-generation cephalosporins (10). XDR *S*. Typhi was responsible for an outbreak in Pakistan in 2016, and was subsequently identified in the Middle East (11,12), Australia (13,14), Europe, the US, and Taiwan (15), where it was imported through returning travellers . The rise in antimicrobial resistance presents a challenge in treating enteric fever. With reduced treatment options, clinicians need to resort to more expensive, intravenous options that cannot be delivered through outpatient care, and for which availability is not guaranteed, particularly, in LMIC settings. This results in increased healthcare and patient out-of-pocket expenditures, and disease complications, relapse, and even fatalities (16–18). Antimicrobial resistance in *S.* Paratyphi A presents a different pattern to *S.* Typhi, with MDR being less common than in *S.* Typhi. In 2019, the prevalence of MDR *S.* Paratyphi A in endemic countries was estimated at 0.2% (95% CI 0.0-0.4), representing a substantial reduction from 9.2% (95% CI 2.4-24.7) estimated in the 1990 (19). However, fluoroquinolone non-susceptibility (FQNS) has experienced the opposite trend in the same time period, and while this remains highly variable across countries, in some endemic settings FQNS isolates represent >95% in some endemic settings (19–25). The increasing difficulties in treating enteric fevers and the heterogeneity in the distribution of MDR typhoidal *Salmonella* emphasize the need for effective surveillance, and the use of prevention and control measures (26).

Improvements in water, sanitation, and hygiene (WASH) practices and food safety can greatly contribute to reduce the burden of enteric fever. However, WASH improvements are challenging to implement in LMICs, which are disproportionately burdened by the disease (27). Vaccines that can prevent infection and confer herd protection can contribute to mitigating of the emergence and spread of AMR (28), and the WHO developed in 2020 a strategic framework to incorporate vaccines into AMR control (29). More recently, the global research agenda for antimicrobial resistance in human health published by the WHO incorporates the assessment of the impact of vaccines on colonization and infection by resistant pathogens, and on reducing the use of antimicrobial medicines, health-care encounters, and health system costs (30). The programmatic use of typhoid conjugate vaccines (TCV) in endemic countries has shown evidence of being highly effective against *S.* Typhi, and was a valuable tool to address a recent XDR outbreak in Pakistan (31). Invasive *Salmonellae* were identified as high priority in the WHO's priority list of research and development for new antimicrobials, which warrants a concerted effort to accelerate vaccine candidates through later development stages to licensure.

In 2018, the strategic advisory group or experts (SAGE) for immunizations recommended the programmatic use of the TCV in endemic countries (32). To date, there is no vaccine to prevent paratyphoid fever, and given its lower contribution to the burden of enteric fever, the WHO's PDVAC considers that a monovalent paratyphoid A vaccine is unlikely to be considered for its inclusion into national programs. However, a bivalent *S.* Typhi/Paratyphi A vaccine could be a highly valuable public health tool for the comprehensive control of enteric fever in high-burden, resource-constrained settings (33), and a step towards the WHO's public health vision for a safe, affordable, and effective vaccine(s) to protect against invasive disease caused by *Salmonella enterica* for use in high burden countries. The existing WHO guidance for the regulation and prequalification of TCV could serve as a guidance for the pathway to licensure of such vaccines, ensuring all processes: from pre-clinical evaluation to regulatory processes are streamlined (34).

S. Paratyphi A-containing vaccine candidates, the focus of this document, are a central component to the long-term vision for a vaccine protective against invasive salmonellosis. The development and evaluation for future investment will require guidance from WHO, to ensure they are well positioned for prequalification, policy recommendation, and introduction into the programmatic schedules in endemic countries.

3. Background on Enteric Fever Disease and Salmonella Paratyphi A Infection

i) *Salmonella* Microbiology

The genus *Salmonella* are Gram-negative bacteria belonging to the *Enterobacteriaceae* family. The genus comprises two species: *Salmonella bongori* and *Salmonella enterica*, and these can be further divided into subspecies: one for *S. bongori* and six for *S. enterica*. Human disease is mostly associated with *S. enterica* subspecies *enterica* (35).

Subspecies can be further divided into serogroups defined by the O (somatic) antigens, and serovars defined by O, H (flagellin protein), and K (capsular) antigens (36). There are >2,500 recognized *Salmonella* serovars. However, around 50 of them account for 99% of all human and animal clinical disease isolates (37). Serovars belonging to *Salmonella enterica* are usually designated by name, but can be described with an antigenic formula string defined by the surface antigens: O (lipopolysaccharide), H (flagellin protein), and K (capsular polysaccharide) (36,38).

Regarding human disease, *Salmonella enterica* subspecies *enterica* serovars are divided into typhoidal (serovars Typhi and Paratyphi A, B, C) and non-typhoidal serovars (such as serovars Typhimurium and Enteritidis) (36). Non-typhoidal *Salmonella* (NTS) are an important cause of enterocolitis, and can cause invasive bacterial infections, including bacteraemia, sepsis, and meningitis and other focal infections with a high case-fatality (39).

ii) Enteric Fever: Causes and Presentation

Salmonella Typhi and *Salmonella* Paratyphi A, B and C are the causes of typhoid and paratyphoid fever, respectively, referred to collectively as enteric fever. The majority of paratyphoid fever is caused by *S.* Paratyphi A, and sometimes by Paratyphi B and C, (40–42).

Humans are the only known reservoirs of typhoidal *Salmonella* (43). Enteric fever is transmitted via the faecal-oral route through the ingestion of fecally contaminated food and water. Enteric fever? Has an incubation period of 7-14 days, often with onset of high fever, accompanied by general malaise, vomiting, and mild gastrointestinal symptoms resulting from the bacterium invading the intestinal mucosa, and seeding into the liver, gall bladder, spleen, lymph nodes and bone marrow, where they continue to multiply (44). If untreated, typhoid fever and sometimes paratyphoid fever can be complicated by peritonitis, gastrointestinal haemorrhage and intestinal perforation, (45,46). The severe typhoid in Africa program (SETA) estimated that one intestinal perforation would occur for each 0.6 instances of culture-confirmed enteric fever (47).

The wide range of symptoms and signs of enteric fever make it difficult to distinguish from other systemic and febrile illnesses. Moreover, *S.* Typhi and *S*. Paratyphi A infections do not differ in their clinical presentations, making its diagnostic and aetiology confirmation contingent on access to a well-equipped microbiology laboratory (48–50).

The primary source of typhoidal *Salmonella* are the faeces of infected individuals, and as many as 10% of untreated individuals excrete the bacterium in their faeces for up to three months following infection (51). Even after successful treatment, up to 5% of individuals experience gall bladder colonization, that results in prolonged shedding (52). While *S.* Typhi remains the main causative agent of enteric fever, studies indicate that *S.* Paratyphi A infections have increased steadily in recent years, particularly in Nepal, Cambodia, and China (53–55) but without evidence of a widespread global expansion (56,57). There is also already an indication that vaccination against *S.* Typhi might be associated with increases in the prevalence of paratyphoid infections, and even surpassing *S.* Typhi as the most commonly cause of enteric fever (4,58,59).

Enteric fever is prevalent in LMICs where lack of access to microbiologically safe water and food, unsanitary conditions, and overcrowding favour transmission. However, while typhoid fever is highly prevalent in Asia, Africa, Middle East and Oceania, paratyphoid fever presently concentrates in south Asia and, to some extent south east Asia, and it is uncommon in Africa (27). In high-income countries, enteric fever is often associated with travel to high disease prevalence areas (60).

The overall case-fatality ratio (CFR) of enteric fever has decreased from 12.8% in the 1940s to <1.0%, in no small part thanks to the use of antimicrobials, although the emergence of AMR strains could revert this trend (61). Case fatality estimates for enteric disease are highest in the post-neonatal period (28-364 days of age), with an overall CFR of 1.45% in this age-group. Typhoid fever CFR is 1.89 times higher than that of paratyphoid fever (61). In 2017, the estimated CFR for paratyphoid and typhoid infections among post-neonates (aged 28-364 days) living in LMICs was 0.9% (CI 95% 0.4-1.9), and 1.6 % (CI 95% 0.8-3.0) respectively (27).

iii) Diagnostics

The clinical diagnostic of enteric fever is challenging, as symptoms and signs make it indistinguishable from other systemic and febrile illnesses, and these can differ across age groups (48,49,62). Early, accurate diagnosis is imperative to i) ensure the timely administration of appropriate antimicrobial therapy, ii) prevent mortality, especially among young children, and iii) identify those patients who may become asymptomatic carriers following recovery, which occurs in 2-5% of cases (48,62–65).

Currently, enteric fever is diagnosed by the presence of a fever $\geq$ 38°C for at least 72h, and the isolation of bacteria from culture of blood or bone marrow. While blood culture can be performed in settings with adequate microbiology capacity, this is not often available in settings where the disease is highly prevalent. Blood culture sensitivity was estimated as 59% in a 2018 meta-analysis that included 40 publications from the 1930s to 2008. However, sensitivity was highly variable across publications, ranging from 14-89%, and estimates were dependent on blood sample volume, disease onset, and pretreatment with antimicrobials

(66). Moreover, data obtained through passive surveillance embedded into at TCV efficacy trial in Nepal demonstrated that, in addition to clinical criteria, clinician's decision to perform blood culture was influenced by the age of the child; with 78% children aged ≥10 years having blood drawn, compared with 68% of those aged <5 years; hence, leading to an under-estimation of disease occurrence in the younger age groups (67). Bone marrow culture has a higher sensitivity and is the gold standard test for the diagnosis of enteric fever. However, this test is highly invasive and requires skilled clinical personnel, hence, it is seldom performed (68,69). Culture from faecal matter or rectal swabs can be used to diagnose enteric fever, however, its sensitivity is lower than that of bone marrow and blood culture, and asymptomatic, chronic carriage of enteric fever pathogens also affects specificity (70). Serological tests such as the Wildal test detect antibodies to the flagellar antigens of *Salmonella* serovars Typhi, Paratyphi A, and Paratyphi B, and the O antigen to *S.* Typhi. However, such tests have low sensitivity and specificity (71–73). Moreover, serological test cannot discern whether the response is due to a previous exposure to an agent of enteric fever or another pathogen, and the challenges to have them validated in low-resource settings constrains their use as a replacement for culture in a clinical context (74–77). Commercial, serological point-of-care (PoC) rapid diagnostic tests (RDTs) are available as an alternative, and several studies have attempted to evaluate their performance of these tests, however, the lack of a standard case definition across studies, and lack of geographic diversity made inter-evaluation comparisons difficult (78). Moreover, the performance of such tests has been found to be subpar and consistent with previous work: sensitivity and specificity values are highly variable and inconsistent across tests, and no test currently meets the minimum desired accuracy criteria (76,79,80). In addition, typhoid and paratyphoid fever are commonly encased under the umbrella of enteric fever, with *S.* Typhi perceived as the default aetiology. Hence, clinically diagnosed cases are often defaulted as typhoid fever, and diagnostic development often emphasizes the accurate detection of *S.* Typhi while neglecting *S.* Paratyphi A (57,81).

iv) Epidemiology and Burden of Enteric Fever disease

Salmonella Typhi is the most common cause of enteric fever worldwide. The Global Burden of Disease Study estimated >9 million typhoid fever illnesses and 110,000 deaths occurred in 2019 (82). *S.* Typhi infections affect mostly children of school age (83–85); however, the burden of typhoid fever among young children in endemic settings and, particularly, in Asia might be underestimated (48,86,87). In Asia, typhoid fever is associated with urban settings and high population density, lack of access to microbiologically safe water and food, and poor sanitation and hygiene practices, which are common in LMICs. However, surveillance studies conducted in Africa indicate that show that typhoid fever is also frequent in rural, low-population density sites (88,89). While Asia remains the most affected continent, typhoid fever remains a significant public health problem in sub-Saharan Africa, where several sites in African countries have been reported to cross the “high incidence” threshold of 100 cases *per* 100,000 population (88,90,91).

In 2019, 3.8 million cases of paratyphoid fever occurred worldwide, resulting in >23,000 deaths (92). The clinical presentation of paratyphoid fever, which is indistinguishable from typhoid, and the lack of access to well-equipped laboratory facilities capable of *Salmonella* serotyping, result in an underestimation of disease burden as cases might be wrongly attributed to *S.* Typhi infections or indeed other diseases like malaria (93,94). In contrast to typhoid fever, paratyphoid fever outbreaks appear to be mostly confined to Asia and the Middle East, as well as, occasionally, Europe, and appear to be proportionally more common among adults (95,96). However, routine surveillance for paratyphoid fever is limited, hence, the burden and proportion of enteric fever due to this serovar is likely to be underestimated in both: low and high resource settings (94,97). Typhoid surveillance conducted in Asia and Africa to inform the use of the TCV are also generating important information on the epidemiology and burden of paratyphoid fever (98). However, because paratyphoid fever is less common than typhoid fever, even these large studies may lack precision for paratyphoid fever incidence estimation, especially by narrow age groups. Moreover, reported incidence and proportion estimates for paratyphoid fever show high geospatial and temporal variability, further indicating that advocating for the implementation of robust national and regional surveillance strategies (94).

Some studies show that, in some settings, *S.* Paratyphi A infections have steadily increased since the 1990s, and disease rates might be comparable to those of *S.* Typhi (4,99,100). However, others seem to suggest that paratyphoid fever remains rare (101). More recently, ongoing surveillance of bacterial infections in children <14 years in Patan hospital, Nepal, showed that in 2022, the first year of the introduction of TCV into their national program, the relative contribution to positive blood cultures for *S.* Paratyphi A isolates surpassed that of *S.* Typhi for the first time since surveillance started in the hospital in 2015. After having experienced a progressive decline of 9.5% (IQR 3.7-12.5), *S.* Paratyphi A isolates accounted for 61% of blood culture-positive enteric fever in 2022 (102).

Studies on the epidemiology of paratyphoid fever are often confined to localized health facilities in South Asia, and mostly conducted in paediatric populations, hence, it is unlikely they would be representative of the national population (103,83,84). The SEAP study, a prospective, laboratory-confirmed population-based surveillance of enteric fever conducted in Bangladesh, Pakistan, and Nepal between 2016 and 2016 reported *S.* Paratyphi A incidence rates *per* 100,000 person-year ranging from 128 in a site in Dhaka, Bangladesh, to 1 in one site in Pakistan. Adjusted incidence rates were variable within countries, with the two sites in Nepal reporting incidence rates of 46 and 81 *per* 100,000 person-year, as well as heterogeneity in the most affected age ranges. In this study *S.* Paratyphi B and C were not detected (83). A similar study conducted in India between 2017 and 2020 among children aged 6 months to 14 years, the incidence rate was 68/100,000 person-year and, similarly, variation across sites and age-groups was also reported (84). An earlier study conducted in Hongta district in China between 2008 and 2009 reported an incidence of *S.* Paratyphi A of 220/100,000, and peak incidences occurring among the 15-44 age group (104). In sub-Saharan Africa, data on the incidence of enteric fever is more limited, and while some surveillance studies covered all invasive *Salmonella* disease, *S.* Paratyphi A is hardly encountered (88,89).

While it was initially accepted that typhoid fever incidences in Africa fall in the medium range (10-100 cases *per* 100,000 person-years) (90), recent data from the SETA surveillance program reported incidences ranging from 315 cases *per* 100,000 person-years (CI 95% 254-390) from one surveillance site in Republic Democratic of Congo, to 16/100,000 P-Y (CI 95% 13-21) in an Ethiopian site, and four sites in four different countries showed rates exceeding 100/100,000

P-Y (88,89). While data from a limited number of studies seem to indicate that paratyphoid fevers represent <2% of all reported enteric fever cases in Africa, this is likely a broad underestimation as surveillance has greatly focused on typhoid fever among children, in views of the development and subsequent deployment of novel typhoid conjugate vaccines. As paratyphoid fever often has a milder presentation than typhoid fever, clinicians might not see the need for a blood culture, hence, adding to the underreporting of *S.* Paratyphi A infections (88,90,94,105–108). Serotyping capability to among *Salmonella* serovars are not widely available, further contributing to disease under-ascertainment.

v) Treatment and Antimicrobial Resistance

Recommendations for antimicrobial treatment of enteric fever are commonly guided by local AMR data obtained from *S.* Typhi isolates when available. Traditionally, chloramphenicol, amoxicillin, and trimethoprim-sulfamethoxazole were recommended and used as first line antimicrobial treatment for enteric fever, and remained an effective treatment until the 1980s, when MDR *S.* Typhi strains were identified and became progressively widespread (7,8). In this context, fluoroquinolones became the preferred treatment. However, the prevalence fluoroquinolone resistance has risen in recent years, and non-susceptible strains now predominate among *Salmonella* Typhi isolates in South Asia. As a result, ceftriaxone and azithromycin have become mainstays of treatment. However, third generation cephalosporin-resistant *S.* Typhi have recently been reported from Asia, middle East, and Latin America (109–111). In 2017, an outbreak in Sindh, Pakistan, became the first report of XDR *S.* Typhi, which presented resistance to all three first-line antibiotics, as well as fluoroquinolones and third generation cephalosporins (10,112,113). The strain was subsequently isolated among travellers in the US and Europe (10,20,114), and has now become well established in Pakistan (10,112).

Due to its lower prevalence, investigations into the emergence and spread of AMR in *S.* Paratyphi A are limited. When such studies exist, they are constrained to a short time period, limited to a small number of isolates, and obtained through surveillance and non-standardized sampling methods that do not allow to generalize the findings beyond the study population (115,116). However, changes in estimating the relative prevalence of *S.* Paratyphi A as the aetiology of enteric fever cases and the wide geographic variation of both prevalence and resistance patterns (102,117,118) warrant the enhancement of surveillance and continual monitoring of AMR in both serovars: *S.* Typhi and *S.* Paratyphi A, in conjunction with other AMR emergence preventive measures, including *S.* Paratyphi A vaccination (4,26). Antimicrobial drug resistance has also been described in *S.* Paratyphi A, although MDR in this serovar less frequent than in *S.* Typhi isolates, and remains rare (20–24,119). A study conducted in 2000 by Chandel *et. al.* examined antimicrobial resistance among all *S.* Paratyphi A isolates obtained from several hospitals in and around Delhi from April 1996 through July 1997. They observed a sharp increase in *S.* Paratyphi A isolates that presented resistance to at least one antimicrobial, rising from non-detection in 1996 to 24% in 1998, and 45% of these were MDR. Additionally, they observed decreasing susceptibility to ciprofloxacin among isolates already resistant to one or more antimicrobial (22). Ciprofloxacin resistance had previously been reported in the UK in 1994 in travellers returning from India and Nepal (120) and India (121). A more recent study looked at surveillance data for enteric fever from 1999 to 2021 in Dhaka, Bangladesh. The study analysed the antimicrobial susceptibility of 2,725 *S.* Paratyphi A isolates obtained from hospitals and outpatient facilities between 1999 and 2021. They found 3% of isolates were resistant to first line antimicrobials, and no MDR was detected. Investigators also found a high prevalence of susceptibility to azithromycin and ceftriaxone; however, 98.9% of isolates were non-susceptible to ciprofloxacin (118).

More recent estimations and a review of antimicrobial resistance patterns in typhoidal *Salmonella* were published by the GRAM collaborators in 2024. The study looked that the subnational prevalence of MDR and FQNS in *S.* Typhi and *S.* Paratyphi A between 1990 and 2021. The study reported a decline on MDR *S.* Typhi in Asia, from 55.4% in 1990 to 26.4% in 2019; but an increase in sub-Saharan Africa, from 6% to 72.7% in the same period. In contrast, MDR *S.* Paratyphi A remained low in all endemic countries. For both serovars, FQNS has experienced a drastic increase, representing >95% of *S.* Paratyphi A isolates, and >99% of *S.* Typhi in Pakistan. In contrast, FQNS *S.* Typhi in Africa, while increasing, remains overall lower than in Asia, reaching 19.7% in 2019 (19).

4. Paratyphi A- Containing Vaccine Development

i) Current Available Vaccines Against Typhoid Fever

The increasing availability of microbiologically safe water and food, and sanitation improvements have contributed greatly to the prevention of enteric fever. Nonetheless, safe, effective vaccines remain necessary to combat the disease, and to hamper the spread of the increasingly prevalent multidrug resistant strains (18,109,122). There are currently three typhoid vaccines recommended for the prevention and control of typhoid fever, as described in the subsections below.

1. Oral live-attenuated Ty21a vaccine

Live vaccines using an attenuated Ty2 *S.* Typhi strain have been recommended by the WHO since 2008 (123). The vaccine is administered orally, and has been proven efficacious for children aged > 6 years.[1] The vaccine uses a mutated strain derived from the wild-type strain Ty2 that lacks enzymatic functions and the Vi antigen (124,125), and has been shown to elicit protection 10-14 days after the third dose. Vaccine efficacy (VE) estimations up to three years after vaccination were heterogeneous across studies and geographies, ranging from 67-78% in Chile for the capsule and liquid formulation respectively (126,127), to 96% in Egypt (128). The vaccine was proven safe and well tolerated in all field trials, and protection is reported to last up to seven years (126–132). Moreover, there is indication that this vaccine might confer protection against *S.* Paratyphi B infection, with an estimated efficacy of 49% (133,134), but early reports that the vaccine might also be cross-protective against *S.* Paratyphi A have been disproved through Controlled Human Infection Models (CHIM), as re-challenge of participants who were originally challenged with a *S.* Typhi strain did not result in reduction in the attack rate when challenged with *S.* Paratyphi A compared with naïve controls (135). There is currently one live attenuated oral vaccine commercially available in the form of an oral capsule, which makes it unsuitable for children <6 years. This vaccine requires a course of three doses administered at intervals of several days apart, and re-

[1] .A liquid formulation is approved for children >2 years of age: however, this is currently not available (32)

vaccination is necessary after five years. Additionally, the vaccine requires strict cold chain during handling and storage (123).

2. Polysaccharide vaccine based on the purified Vi antigen (ViPS vaccine)

The non-conjugated polysaccharide vaccine uses purified Vi capsular polysaccharide derived from the wild-type strain Ty2 (136,137). The ViPS elicits a T-cell independent IgG response, and it is administered as a single, parenteral dose either as a monovalent ViPS, or in combination with hepatitis A antigen, with the latter being mostly directed at travellers (138,139). The vaccine confers protection seven days post-immunization in individuals aged 2 years and over, and has a good safety profile (101,140). Vaccine efficacy is estimated to be between 50-80% in the first year, and between 31-75% two years following vaccine administration, with higher estimates in school children (101,141,142). Moreover, the vaccine might confer some level of indirect protection for unvaccinated individuals through herd protection (101). However, immunity wanes considerably after vaccination, and does not last beyond three years (143,144).

3. Typhoid Conjugate Vaccine (TCV)

Conjugation of the polysaccharide capsular antigen to a protein carrier is known to induce a strong, long-lasting T-cell dependent immunological response that can be enhanced by subsequent booster doses, and it is effective in children under the age of 2 years; hence, overcoming the limitation of polysaccharide vaccines (145).

Currently, vaccination with TCV is recommended for programmatic use by the World Health Organization (WHO), and three conjugate vaccines have been prequalified and are licensed for use as a single intramuscular dose in children aged from 6 months and up to 45 years (32). These vaccines consist of Vi-capsular polysaccharide, conjugated to a carrier protein such as tetanus toxoid (TT), or recombinant, non-toxic mutant of diphtheria toxoid, referred to as cross-reactive material (CRM_{197}), or diphtheria toxoid (DT). Early studies using CHIM among *S.* Typhi-naïve, British participants aged 18-60 years showed a vaccine efficacy of 54.4%

against the primary endpoints of bacteraemia or fever, and 87.1% against fever preceding culture-confirmed *S.* Typhi bacteraemia. While licensure of TCVs had been approved on the basis of demonstrated safety, immunogenicity, and clinical efficacy (146,147), and further supported by CHIM studies (148–151). However, post licensure studies were needed to demonstrate vaccine efficacy (151,152). Such trials were conducted by the Typhoid Vaccine Acceleration Consortium (TyVAC). The efficacy of the first WHO-prequalified TCV, Typbar-TCV, manufactured by Bharat Biotech in India was evaluated in Phase IV trials in in Nepal, Bangladesh, and Malawi. The study conducted in Lalitpur, Nepal, recruited >20,000 participants aged 9 months to 15 years. The vaccine showed a protective efficacy of 79% at two years post-vaccination, and there was no indication of waning protection throughout the study (153). In Malawi, >28,000 children aged 9 months to 12 year received either the Typbar-TCV or meningococcal A conjugate vaccine. The VE over a four years forllw-up period was 78.3 % (CI 95% 66.3-86.1) and 80% (CI 95% 68.3-87.3) in the Intention to treat and per protocol analyses respectively, and these findings were further validated by a secondary data analysis using a test-negative design. The vaccine showed a good safety profile, with no excess serious adverse events in the intervention group, and none of them were attributed to the vaccine (154–156). Study findings in Bangladesh were in accordance with those conducted in Nepal and Malawi. The study recruited >61,000 participants aged 9 months to 16 years in a 1:1 cluster-randomized trial design; half the children received Typbar-TCV, and the other half received a Japanese encephalitis vaccine. Vaccine effectiveness was estimated at 85%, and was consistent across age groups. The study did not find evidence of indirect protection, and further validated the safety profile of the vaccine (157). Based on the findings from these studies, the SAGE Working Group on Typhoid Vaccines recommended the introduction of TCV, and the prioritization of high disease burden and/or associated antimicrobial resistance (158,32). To date, TCVs have already been incorporated into the national immunization schemes of seven countries across Africa, Asia, and Oceania, and at least three additional countries are planning their introduction in the near future (159).

ii) *Salmonella* Paratyphi A- Containing Vaccines Development Approaches

Currently, enteric fever vaccination only covers disease caused by *Salmonella enterica* serovar Typhi. The licensure and subsequent implementation of effective vaccines against typhoid fever supports the biological feasibility of safe and effective vaccines against *S.* Paratyphi A. Given the lower burden of paratyphoid fever in comparison to typhoid, the development of a monovalent Paratyphoid A vaccine is deemed unfeasible due to the high number of study participants that would be required in a phase 3 an efficacy study. Moreover, its low commercial potential due to the geographic confinement and heterogeneous disease burden distribution of the disease, and its uncertain value proposition make it unlikely that a monovalent *S.* Paratyphi A vaccine would attract financial support (160,161). However, there is growing interest in addressing the public health burden of *S.* Paratyphi A disease through the development of a bivalent *S.* Typhi/Paratyphi A vaccine (162–164). The need for a bivalent vaccine development strategy has been highlighted by the SAGE (158), and it is likely to be of interest for inclusion into the EPI in countries where paratyphoid fever represents a substantial public health problem, or even for countries where introduction of Paratyphi A through travellers is a concern. Moreover, the use of Vi-PS vaccine in China was associated with a sharp increase in *S.* Paratyphi A prevalence, and >80% of outbreaks being caused by *S.* Paratyphi A (162); hence it is hypothesised that TCV introduction might also result on serovar replacement (25,100,102). In such scenario, a Paratyphi A- containing vaccine can become an attractive product even in countries where the disease is not currently a concern.

There are currently no licensed vaccines against paratyphoid fever; however, several vaccine constructs are under various stages of pre-clinical and clinical development (122). Evaluation of these vaccines will prove a challenge, as there are currently no animal models to investigate the immunobiology of the disease, and no correlates of protection have been established. There are, however, *in vitro* assays that demonstrate the positive correlation between vaccine and naturally-induced antibody titres and serum bactericidal activity (SBA). Additionally, given the low attack rates, the need of sample sizes of the magnitude of six figures make it unlikely that such trials can be conducted (151,164,165). Human challenge models are a viable alternative to overcome these hurdles. Response to *S.* Paratyphi A infection has already been tested in a CHIM model, and deemed safe and effective to evaluate vaccine efficacy using bacteraemia and paratyphoid fever symptoms as the endpoints (166). A CHIM to evaluate the efficacy of a live-attenuated *S.* Paratyphi A vaccine, CVD1902, is currently ongoing (167).

Several *S.* Paratyphi A-containing vaccine candidates are under various stages of clinical development. The two monovalent candidates: a live-attenuated vaccine using the CVD1902 strain, and a O:2-TT conjugate construct, are currently undergoing Phase 2 safety and immunogenicity studies with views at obtaining data on individual antigens prior to combining with a live-attenuated *S.* Typhi strain, or with the conjugate Vi antigen currently used in licensed and WHO prequalified typhoid vaccines (122,161).

1. Live-Attenuated Vaccine Candidates

The CVD1902 vaccine uses a live-attenuated vaccine (LAV) strategy using a mutant strain of *S.* Paratyphi A created by deleting the *guaBA* and *clpX* genes, which encode for nucleotide biosynthesis and regulatory systems respectively. This vaccine construct was tested in humans during phase 1 trial, in which volunteers ingested either a single dose of increasing number of colony forming units (CFU) up to 10^{10} or a placebo. The study showed that a single dose of at least 10^{9} CFUs was capable of eliciting cell-mediated antibody responses that had the potential to be protective against *S*. Paratyphi A infection (168). This vaccine is currently undergoing Phase 2 trial evaluation using a CHIM design (167). A bivalent LAV using the CVD909 typhoid strain, the same as in the licensed Ty21a typhoid vaccine, in combination with the CVC1902 paratyphoid mutant is currently undergoing preclinical evaluations (161).

Entervax is an oral bivalent vaccine candidate based on the Vaxonella platform. This is a proprietary vaccine delivery system that uses a plasmid reconstruction technology in *E. coli,* and allows them to be transformed into other enteric bacteria (169). The vaccine harbours two genetically-engineered *S.* Typhi strains: ZH9, which is an attenuated *S.* Typhi strain known to be safe, and the mutant ZH9PA, in which the genes encoding the flagellin and the O:2 LPS of *S.* Paratyphi replace their *S.* Typhi homologous to produce a *S.* Typhi strain encoding for these two well-known *S.* Paratyphi A antigens (170). This vaccine candidate is currently undergoing a Phase 1 safety and immunogenicity evaluation, and results are currently undergoing quality control reviews prior to their publication (171).

2. Protein Subunit and Outer Membrane Vesicle Vaccine Candidates

Surface or secreted protein components of *Salmonella*, such as the Vi polysaccharide have demonstrated their immunogenic potential. Several homologous components found in *S.* Paratyphi A have been evaluated in parenteral administration in murine models, with the aim of demonstrating their immunogenic and protective efficacy. Yang *et. al.* screened the outer membrane proteins of *S.* Paratyphi A, and found several outer-membrane proteins that proved to be protective. In total, they identified five proteins, LamB, pagC, TolC, nmpC and fadL, as possible vaccine candidates. These proteins showed up to 85% protection against *S.* Paratyphi A infection in mice, but further research is needed to elucidate the optimal protein combination for a potential *S.* Paratyphi A-containing vaccine (172). Ruan *et. al.* investigated the potential for the outer membrane protein SpaO, and H1a, the flagellum antigen from *S.* Paratyphi A as vaccine candidates. When tested in mice, both antigens exhibited some level of protection, up to 66.7% of SpaO, and up to 58.3% for H1a. When immunized with both antigens, protection could reach up to 91.7%. Moreover, SpaO showed cross-protection against *S.* Typhi (173).

An early outer membrane vesicle (OMV) vaccine prototype developed by Howlader *et. Al.* used OMV from *S.* Typhi and *S.* Paratyphi A strains in a 1:1 ratio (174). The vaccine was tested in mice by administering three doses at a 2-week intervals, and it elicited strong mucosal, humoral, and cell-mediated immunological responses. Moreover, vaccination protected immunized mice against lethal challenges with both: *S.* Typhi and *S.* Paratyphi A (175). More recently, Gasparini *et. al.* produced a modified strain of *S.* Paratyphi A displaying the Vi polysaccharide of *S.* Typhi. The strain was specifically engineered to increase blebbing, a natural mechanism through which Gram-negative bacteria release OMVs (176). To this end, the GSK Vaccines institute for global health (GVGH) developed a system to delete the genes involved in the production of proteins that maintain the integrity of inner and outer membranes in Gram-negative bacteria, leading to increase shedding of blebs. These purified OMV vesicles were used to immunize mice, and showed a good immunological response against Vi and lipopolysaccharide O-antigen O:2, which was comparable to that elicited when the Vi and O:2 antigens were administered separately, indicating that there was no interference between the responses (177). This vaccine platform, known as generalized modules for membrane antigens (GMMA) is currently being used for the development of vaccines against iNTS (178–180), and a bivalent *S.* Typhi/Paratyphi A? vaccine that delivers both: Vi and O:2 antigen proof-of-concept GMMA preparation demonstrated that such vaccine platform can induce the production of functional antibody responses against both antigens without interference (176).

3. Conjugate Vaccine Candidates

Current conjugate vaccines against *S.* Typhi use the Vi capsular polysaccharide attached to a carrier protein to generate long-lasting T-cell immunity. However, Vi polysaccharide is not present in *Salmonella enterica* serovar Paratyphi A; therefore, the O:2 LPS is used as the target polysaccharide antigen for *S.* Paratyphi A (181). The O:2-TT conjugate uses tetanus-toxoid as a protein carrier, and underwent Phase II evaluations in adults, teenagers, and children aged 2-4 years in Vietnam, showing good safety profile among vaccinees. At six weeks post-vaccination, a fourfold rise in antibody titres were observed in 75% of adults, 85% of teenagers, and 90% of children, although a second vaccine dose did not boost the response (182). Conjugation of the O:2 to Diphtheria-Toxoid (O:2-DT) with and without adipic acid dihydrazide (ADH) as a binder were tested in mice by Ali and colleagues. Their findings show a poor immune response, although this was improved by the addition of ADH to the conjugate (183). Conjugation to CRM_{197} was first attempted by Micoli *et. al.* and evaluated in mice immunized with three doses administered at 2-weeks intervals with a dose containing either 1 or 8 mg of O:2. The vaccine induced high IgG titres with a strong bactericidal activity, making this combination a suitable candidate for a bivalent Vi Typhi-O:2 Paratyphi A conjugate vaccine (184). Such a construct is currently undergoing phase 1 evaluation. A similar construct developed by the Serum Institute of India using TT and DT as carriers for the Vi and O:2 antigens respectively has been recently assessed in a Phase 1 clinical study. The Sii-PTCV, as the vaccine is termed, found to be safe and immunogenic, inducing a response against *S.* Typhi comparable to currently prequalified TCVs, and eliciting functional antibodies against *S.* Paratyphi A (185).

4. Multiple Antigens Presenting System (MAPs)

The MAPs system is an alternative to protein conjugation approaches that uses the Affinity pair biotin-rhizavidin to produce a complex of proteins and polysaccharide, and has proven to enhance the immunogenicity of polysaccharides similarly to a protein carrier (186). A bivalent MAPs *S.*Typhi/Paratyphi A vaccine has undergone preclinical evaluation using three different protein constructs fused to Rhizavidin: CRM197, rEPA from *Pseudomonas*, and a pneumococcal fusion protein (SP1500-SP0785), with the latter being selected for the final vaccine construct. The vaccine used the Vi and O:2 antigens from *S.* Typhi and *S.* Paratyphi A respectively, and preclinical evaluation demonstrated the immunogenicity of the vaccine, as well as its ability to produce high-affinity antibodies and generate long-term immunity in mice without indication of safety concerns (187).

5. Vaccine Use Considerations

Live-attenuated vaccines have shown protective potential against enteric fever; however, these type of vaccines are not recommended for individuals suffering from immunocompromising conditions (188), and present biosafety concerns that need to be carefully considered and evaluated (189,190). Bi-valent *S.* Typhi-Paratyphi A vaccines are more desirable than monovalent vaccines, and more likely to receive a favourable verdict from policy makers, as these can prevent enteric fever in high or uncertain *S.* Paratyphi A burden in a single administration. A live-attenuated *S.* Paratyphi A vaccine is currently being tested with a two-dose primary schedule. While such a vaccine is unlikely to be commercially viable, it might provide insights into the correlates of protection. In any case, the licensure and WHO prequalification of the current parenterally-administered TCVs make this delivery platform more attractive for a *S.* Paratyphi-A containing vaccine. Expert advice and WHO guidance will be required to guide clinical development, prelicensure, and policy recommendations for these platforms.

B. Preferred Product Characteristics for Bivalent Typhoid/Paratyphoid Vaccines

Parameter	Preferred Characteristic	Notes
Vaccine Type	• Bivalent *Salmonella* Typhi and *Salmonella* Paratyphi A conjugate vaccine for the prevention of enteric fever. version of this document. • Bivalent live-attenuated vaccines for the prevention of *Salmonella* Typhi and *Salmonella* Paratyphi A disease.	• At least one oral live attenuated vaccine is currently in early stages of development and progressing through the pipeline. Such vaccines are likely to be mature within 4-5 years. • Quadrivalent pan-*Salmonella* vaccines covering the four serovars most commonly associated with invasive disease (*S.* Typhi, *S.* Paratyphi A, *S.* Typhimurium, and *S.* Enteritidis) are envisaged but not yet advanced in the pipeline. Hence, these are not covered in this PPC document. • It is unlikely that there will be much demand for a monovalent paratyphoid A vaccine, since populations in which this pathogen is endemic also suffer a high burden of typhoid fever. Hence, monovalent *S.* Paratyphi A are not covered in this document.

Target population	<u>Conjugate Vaccine</u> • Infants and toddlers (typhoid disease in toddlers is common in some South Asian settings but paratyphoid A illness is more frequently seen among school-age children and young adults). • School age children (both typhoid fever and paratyphoid A fever are highly prevalent in children aged 5-14 years). • Young adults up to 20 years (peak age for paratyphoid A disease in many settings where that infection is prevalent). • In special situations, such as high vulnerability or outbreak, the vaccine might be used. <u>Live-attenuated Vaccine</u> • Age indication remains the same as for conjugate vaccines, to ensure peak protection is achieved and sustained throughout the 5-15 years of age period.	<u>Conjugate Vaccine</u> • Infants and toddlers – via routine EPI • School children – School-based vaccination. Limited coverage if scholarization/school attendance rates are low • Catch-up campaigns – GAVI countries up to the age of 15 years • Vaccination campaigns in response to health events (*e.g.*, outbreaks, transmission of AMR-resistant strains) – these would be tailored to the specific situation and affected population ,which might include age groups outside those targeted by routine vaccination. Current TCV vaccines are licensed for use from 6 months to 45 years of age. <u>Live-attenuated Vaccine</u> • The vaccine formulation will need to be appropriate for infants and toddlers to be able to swallow the product. The current live-attenuated vaccine against typhoid fever, Ty21a, is only available as an enteric-

		coated capsule, and it is indicated for children >5 years. A liquid formulation to be administered to children aged 2-4 years is currently discontinued.
Schedule	Conjugate Vaccine • A one-dose regimen is highly desirable • A two-dose schedule in young children is also logistically feasible if two spaced doses are needed to immunize optimally infants and toddlers with bivalent parenteral or oral vaccine • The immunization regimen should balance early onset of protection with long duration of protection Live-attenuated Vaccine • For the primary schedule, multiple doses administered a few days apart are likely to be needed. Current Ty21a vaccine is administered in 2-3 doses given every other day.	Conjugate Vaccine • SAGE (2017) recommended the use of TCVs as a single dose as early as six months of life. Co-administration with either the first or the second dose of the measles-containing vaccine is a particularly attractive EPI visit for administering Typbar-TCV and there is no interference with MCV. • Modelling work is currently ongoing to inform the timing of current monovalent TCV, either as a single dose, or with the addition of a booster, to maximize protection during the peak-disease age, while managing a feasible delivery strategy, and cost-effectiveness. • It is not known whether a parenteral paratyphoid A vaccine will be able to confer protection with a single dose.

		Unless data indicate otherwise, the schedule of a bivalent *S.* Typhi/Paratyphi A vaccine should follow the most up-to-date recommendations available for the current TCV. • To date, only one experimental *S*. Paratyphi A vaccine has been evaluated in a pediatric clinical trial. The vaccine construct was *S*. Paratyphi A O-polysaccharide (O:2) linked to tetanus toxoid. When administered to 2-4 year old children in Vietnam, a single dose elicited ≥ 4-fold rises in serum IgG anti-O antibody in 90% of children. A second dose 6 weeks after the first dose did not boost the titers over the response that a single dose achieved. Given that these Vietnamese 2-4 year old children all had titers of serum IgG anti-O:2 (A) antibody evident prior to immunization, it is not known if the failure of the second dose to elicit booster responses was due to their young age or because they were already immunologically primed. If a booster is needed,

		longer intervals between doses might be necessary to achieve optimal serological responses. Live-attenuated Vaccine • The complexities of administering multiple-dose in a short period at large scale might make the introduction more challenging. However, this might be off-set by the the fact that the oral administration is an easier route.
Safety	Safety and reactogenicity should be at least as favorable as existing TCV and other WHO-recommended routine parenteral and oral vaccines for use in the Expanded Program on Immunization (*e.g.,* pentavalent vaccine, multivalent pneumococcal conjugate vaccine, MCV1 and MCV2, rotavirus vaccine, *etc*.).	
Efficacy Targets	Conjugate Vaccine • In the absence of immune correlates of protection, non-inferiority to the existing TCV vaccines across different age-groups for the typhoid component demonstrated in a clinical efficacy trial in	Conjugate Vaccine Superiority to natural immunity on the *S.* Paratyphi A component could be documented as a 4-fold rise on antibody titers following vaccination. Live-attenuated Vaccine

	endemic setting would be preferred, with the alternative being a CHIM constructs. • For the *S.* Paratyphi A component, superiority to naturally-induced immunity would be considered evidence that the LPS component is capable of inducing an induce response. This should be demonstrated either through a field clinical efficacy trial ,which would remain the preferred standard, or through a *S.* Paratyphi A CHIM model would be an accepted alternative. • Both *S.* Typhi and *S.* Paratyphi A components should retain their capacity to induce protection as they would individually. <u>Live-attenuated Vaccine</u> • For both, *S.* Typhi and *S.* Paratyphi A component, efficacy will need to be demonstrated, as no comparator is currently available.	• The currently licensed Ty21a live-attenuated vaccine against *S.* Typhi lacks the Vi-polysaccharide; hence, a direct comparison with the current TCV cannot be established. Moreover, while Ty21a is known to be immunogenic, it is not possible to ascertain which component(s) of the live-attenuated formulation are responsible for it (132).

	• Efficacy for both components will need to be demonstrated across age ranges. • While CHIM and modelling studies might contribute to evidence of vaccine protection, evidence of vaccine efficacy in an endemic population is likely to be required by regulators, at least for the *S.* Typhi component.	
Serovar coverage	*S*. Paratyphi A and *S*. Typhi for bivalent vaccines.	• Such construct could also result in some level of protection against *S.* Paratyphi C disease, as this serovar also can sometimes present a Vi capsule. • While a conjugate vaccine might be a preferred construct, live-attenuated genetically engineered strains have been evaluated
Adjuvant requirement	Need for an adjuvant is discouraged, as it may enhance reactogenicity. The first WHO prequalified Vi conjugate vaccine against typhoid fever contains no adjuvant and is highly immunogenic with a single dose	

	in infants, toddlers, preschool age children, adolescents and adults up to 45 years of age (191)	
Immunogenicity	<u>Conjugate Vaccine</u> • For the Paratyphi A component of the vaccine construct, the immunogenicity target would be superiority to naturally-induced immunity in and endemic population. • Established mechanistic or non-mechanistic correlate of protection based on a validated assay measuring antibody levels. For parenteral conjugate bivalent vaccines, the vaccine should induce IgG antibody against the O:2 polysaccharide. The correlate of protection is yet to be established. <u>Live-attenuated Vaccines</u> • It is expected that the immune response generated by these vaccines will be directed to several of the antigens included in the vaccine. Currently, there are	

	no data available to know which of the vaccine components are relevant for immunogenicity.	
Co-administration	In the bivalent vaccines, the typhoid and *S.* Paratyphi A components must be shown to be non-interfering with one another. Similarly, when co-administered with EPI vaccines, the typhoid and paratyphoid A vaccines should demonstrate a favorable safety and immunologic non-interference upon co-administration with routinely recommended vaccines in target age group.	
Route of administration	<u>Conjugate Vaccine</u> Intramuscular for parenteral vaccines <u>Live-attenuated Vaccines</u> Oral administration as an enteric-coated capsule to be given to those aged $\geq$5 years; liquid formulation for younger infants.	
Registration, WHO prequalification and program suitability	The vaccine should be licensed by a fully accredited National Regulatory Agency and prequalified according to the process outlined in “Procedures	

	for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies." WHO defined criteria for programmatic suitability of vaccines should be met.	
Value proposition	Dosage immunization regimen and cost of goods amenable to affordable supply. The vaccine should be cost-effective and price should not be a barrier to access including in LMICs.	A Vaccine Value Profile was published in October 2023 (160)

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