Invited Paper

IAPSM's Position Paper on Typhoid Vaccines for Adult Immunization in India

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Abstract

Typhoid is a major public health concern in India, particularly among those dwelling in urban slums with poor sanitation. The disease caused by *Salmonella enterica serovar Typhi* spread majorly through contaminated food and water. The economic burden of the disease is catastrophic and affects both families and the government making a strong case for including typhoid vaccines in the national immunization schedule. The World Health Organization has prequalified several vaccines and has recommended their use in endemic areas. While there is robust evidence for vaccination of children from India and other LMICs, the case for adult vaccination remains less clear. The Indian Association of Preventive and Social Medicine acknowledges the necessity to adopt a widespread typhoid immunization program, along with other preventive strategies, especially in the vulnerable pockets. IAPSM recommends focusing on newer-generation Typhoid Conjugate Vaccines (TCVs), which provide long-lasting and superior immunological benefits, and are effective across all ages including adults. IAPSM suggests routine use of Typbar-TCV™ for adults up to 45 years old in India. The organization also highlights the necessity for post-marketing surveillance of these vaccines, to monitor the long-term safety and effectiveness of various vaccines in different communities. IAPSM encourages members to take front-line efforts in their community health service areas, and finally appeals for the development of vaccines to cover a more extensive range of Salmonella infections so that control over typhoid can be strengthened.

Keywords: Adult immunization, IAPSM, India, typbar-TCV™, typhoid fever, typhoid vaccines

Introduction

Typhoid fever, which is caused by Salmonella enterica serovar Typhi, represents a major public health issue. The disease primarily spreads through the ingestion of food or water that has been contaminated and can also be transmitted due to poor hygiene practices among food handlers.[1] High case fatality is seen among children, adults, and those living in low-income regions, worsened by a lack of accurate and inexpensive rapid diagnostic point-of-care tests, and antibiotic-resistant strains.[1,2] Vaccination remains a cornerstone for the disease prevention and control strategies.[1–4] WHO recommends including the typhoid vaccine in national immunization programs, improving WASH indicators, and increasing awareness.[3] While there is enough data to support vaccination in children from India and similar LMICs, the current stance is inconclusive regarding the introduction of vaccines in the adult age groups.

Epidemiology of typhoid in India

Globally, in 2017, typhoid fever accounted for approximately 10.9 million cases and 116,815 deaths.[5] Over two-thirds of the cases are reported from South Asia, followed by Southeast Asia, East Asia, Oceania, and the sub-Saharan African region, while being uncommon in developed

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countries due to improved WASH indicators.[6,7] Over half of the global typhoid fever burden has been estimated to occur in India. The disease incidence varies across regions and periods.[8] A recent surveillance study estimated the incidence between 12 and 1622 per lakh child years of observations in children aged six months to fourteen years and between 108 and 970 per lakh person-years among people above fifteen years.[9] High incidence was observed among adults living in Chandigarh and Kullu under hospital-based surveillance.[9] The disease is mainly caused by *Salmonella enterica* serovar Typhi. It belongs to the *Enterobacteriaceae* family, which are gram-negative, facultative anaerobic bacilli with a peritrichous flagella. The H58 lineage (genotype 4.3.1) of *S. typhi* is predominant in India.[10] Man is the only host of S. typhi. The infection occurs after food or water contaminated with ill or chronic carriers' feces is ingested. It can also be transmitted through sexual contact between male partners and occupational exposure of healthcare workers to infected patients or cultures/specimens. After an incubation period of 7–14 days (range 3–56 days), the host starts experiencing fever, abdominal pain, headache, myalgia, rash, anorexia, vomiting, and diarrhea.[11] The disease is more severe among people suffering from inflammatory bowel disease, immunosuppression, achlorhydria, acid suppression therapy, and infants below one year.[11] The case fatality rate is 1–4% among those who receive treatment.

Age groups/vulnerable populations affected by the pathogen

The highest incidence of typhoid fever was observed among children.[5] It peaks between 5 and 9 years; most cases occur below 15 years.[5,9] The incidence steadily declines with increasing age among adults. Males are more commonly affected than females, but carrier state is more common in females. Estimates indicate a high case fatality rate among children, elderly, and residents of low-income countries.

Factors associated with Typhoid in the Indian context

Risk factors include lack of sanitation, unsafe water, unsanitary latrines, family size over six, overcrowding, low socioeconomic status, and illiteracy.[8,9,12] Compared to rural areas, the disease burden is higher in urban India, especially among the poorest households.[9] The disease incidence is not associated with any particular season or high rainfall.[9] Poor hygiene or carrier state among food handlers may contribute to the outbreak of typhoid fever.[13]

Diagnosis of typhoid

The gold standard for diagnosing typhoid fever remains the isolation of *S. Typhi* from a blood culture. The diagnostic sensitivity of blood culture is 60%, lower with less blood sample volume. Sample collection in the first week of infection, prior use of antibiotics, and media quality affect the sensitivity.[11,14] Blood culture is not routinely performed in most cases in developing countries. Bone marrow culture has over 80% sensitivity, unaffected by up to 5 days of prior antibiotic treatment.[15] The rapid diagnostic tests have moderate efficacy compromised by cross-reactivity with other enteric pathogens and a variable antibody response.[16]

Treatment available in India and antimicrobial resistance

Antibiotics can effectively treat typhoid fever caused by susceptible strains. In India, the prevalence of ciprofloxacin non-susceptible strains has increased, while multidrug-resistant (ampicillin, cotrimoxazole, and chloramphenicol) strains have steadily declined in the last decade.[9,10] Cephalosporins and azithromycin have become the preferred drug for treatment.[11] Extensively drug-resistant (multidrug-resistant, fluoroquinolone, and cephalosporin co-resistance) strains are rarely reported in India but are quite common in the neighboring country of Pakistan.[17]

Cost of severe typhoid disease

In a national sentinel surveillance, the direct cost of severe enteric fever was calculated to be INR 9766 in tier 2 secondary care hospitals in India and INR 33210 in tier 3 tertiary care hospitals; and 16.9% patients experienced catastrophic expenditure in tier 3 hospitals. This cost is likely to increase due to emerging antimicrobial resistance.[18]

Current vaccines available for typhoid in adults

The World Health Organization (WHO) has prequalified several typhoid vaccines, including the Vi-capsular antigen-based unconjugated polysaccharide (Vi-PS) vaccine, the live attenuated Ty21a, and the typhoid conjugate vaccines (TCVs) conjugated to Tetanus Toxoid (Vi-TT). **Ty21a is NOT available in India.**

Immunogenicity and efficacy of typhoid vaccines available

The Ty21a and ViPS vaccines have shown efficacies of approximately 50% in extensive field trials and are considered to have a good safety profile, according to the Global Advisory Committee for Vaccine Safety. The ViPS was found to be poorly immunogenic with <2 years of effectiveness.[19] A pilot study from Nepal demonstrated ViPS vaccine efficacy of 72-80% in preventing typhoid infection.[20] In individuals aged 2 to 45 years, Typbar-TCV has been shown to produce substantially higher levels of IgG Vi antibodies six weeks following both the initial and subsequent immunization, compared to the unconjugated Typbar vaccine.[21] The Vi-TT is highly immunogenic and significantly reduces typhoid fever.[22] However, the waning effect of the vaccines mandates a booster dose after every five years.[23] A single dose of the Typbar-TCV is tolerated well and includes a strong and long-lasting immune response.[24] Taking the persistence of protective levels of antibodies, Typbar-TCV can protect for five years. It is considered the most effective and highest-efficacious vaccine.[25]

The optimum age for vaccination

The WHO recommends the routine use of the ViPS vaccine for those ≥ two years old and the Ty21a vaccine for those > six years old [Table 1]. For adults aged up to 45 years, WHO recommends a single dose intramuscular injection of 0.5 mL

in endemic regions.[3] Typbar-TCV has been approved for a one-time intramuscular injection in individuals from over 6 months to under 45 years of age, encompassing pre-schoolers, school-aged children, and adults. This vaccine is available in both a single-dose format containing 0.5 ml of the vaccine in vials or syringes that are pre-filled and as a multi-dose vial containing 2.5 ml. Each 0.5 ml dose of Typbar-TCV contains 25 µg of Vi polysaccharide. In the multi-dose version, every 0.5 ml dose includes 5 mg of 2-phenoxyethanol. It is advised to store the vaccine at 2–8°C.[21] The TYPBAR-TCV® vaccine is intended for intramuscular administration, specifically in the vastus lateralis muscle (located in the anterolateral part of the thigh) for infants up to 12 months old, and in the deltoid muscle (upper arm) for individuals 12 months and older, including adults. Available in both single and multi-dose vials, this vaccine contains 25 µg of Vi polysaccharide per 0.5 ml. In the multi-dose form, each 0.5 ml dose also includes 5 mg of 2-phenoxyethanol. The manufacturer recommends it to be stored between 2 and 8°C. A single dose of TCV, including TYPBAR-TCV®, is advised starting from 6 months of age. Additionally, Typhibev, another typhoid vaccine, was authorized for use in India by the DCGI in February 2020. It is approved to be administered as a 0.5 mL intramuscular injection in a single dose for people between 6 months and 45 years.[26]

Duration of Protection and Repeat Vaccination

Typhoid conjugate vaccine (TCV)

Typbar (TCV-ViTT by Bharat Biotech): An eight-site trial in India among adults aged 2-45 years and children aged 6–23 months reported that 100% of Typbar-TCV recipients maintained seroprotection titers 2 years after vaccination.[24] In a follow-up study of 327 children aged 6–23, 92% of the boosted children (720 days) and 96% of the unboosted children showed persistent seroconversion at seven years.[25] There is no recommendation for a booster dose.[3] Current research on Typbar-TCV indicates that the vaccine's protective effects could last for at least five years following the initial immunization. Additionally, there are hints from the data suggesting that natural boosting might happen with the use of Typbar-TCV.[21]

TyphiBEV™ (TCV-Vi-CRM by Biological E): Typhibev has been licensed in India since 2020. There is no recommendation for a booster dose.[26]

Paeda-Typh™ (Vi-TT by Biomed): A seroconversion rate of 83.87% at one year was reported in a subgroup of 62 children in a study in Kolkata.[27] In another study, PedaTyph™ was found to induce long-term immune response after 30 months of vaccination.[28] No recommendation for a booster dose.

Zyvac TCV (Vi-TT by Zydus Cadilla): A study has reported that of the 117 children vaccinated with Zyvac TCV, 77.2% had maintained seroconversion at three years.[29] No recommendation for a booster dose.

Unconjugated Vi polysaccharide (ViPS): Vac Typh (Zydus Cadila) Biovac Typhoid (Dr Reddy's)

In a cluster randomized trial among children aged 2–16 years in Karachi and Kolkata, it was reported that the seroconversion rate was significantly reduced (38%) at two years of follow-up.[30] In a trial in Kolkata in persons aged two years and older a protective efficacy of 61% was reported at two years.[31] Booster is recommended every three years.[3]

Live attenuated Ty21a vaccines (Vivotif)

Three doses, given within one week of the oral typhoid vaccine, provided 67% efficacy for at least three years and 62% protection over seven years.[32] Booster is recommended every three years in Australia and Europe, five years in the USA, and seven years in Canada.[3]

Route of administration and dosing

Interference with concomitantly administered vaccines, if any: Co-administration of typhoid vaccines with other killed and live vaccines is possible. When two injectable vaccines are administered simultaneously, they should be placed in different limbs. In the case of three vaccines, two can be injected in one extremity, while the last should be given in the opposite limb. It's essential to ensure that injections in the same extremity are at least an inch apart to distinguish potential local adverse reactions.[3] Everyone can conveniently receive the oral typhoid vaccine alongside other live parenteral vaccines, such as BCG (Bacille Calmette–Guérin) vaccine, or MR/MMR (measles–mumps–rubella) vaccine.[21,36]

Safety of vaccines

Two studies reported the safety and reactogenicity of the ViPS vaccine among children and adults and found it to be well tolerated, with limited mild or moderate symptoms.[24,25] In the Philippines, a clinical trial was conducted to assess the safety and immune response generated by combining Vi-polysaccharide and Diphtheria toxoid (Vi-DT). The initial phase of the trial (Phase 1) included participants aged between 2 and 45 years, while the subsequent phase 2 focused on a younger demographic, specifically 6 to 23-month-old subjects. The outcomes of both phases indicated that the Vi-DT vaccine was safe, tolerated well, and effective in stimulating an immune response across these age groups.[37,38] Vi-DT vaccine is both safe and effective in generating an immune response in children aged 2–11 years.[35] The assessment of both prelicensure and post-licensure trials involving Typbar-TCV, which included around 1000 participants, did not reveal any concerns regarding its safety. This evaluation took into account the vaccine's immunogenicity and safety data and involved studies where Typbar-TCV was administered alongside measles-containing vaccines and compared with an unconjugated polysaccharide vaccine.

Surveillance data from India's private sector, reflecting over 3 million distributed doses of Typbar-TCV at the time of analysis, indicated that its adverse event profile was comparable to that observed with specific benchmark vaccines across various

Table 1: Route of administration and recommended dose for typhoid vaccines[3,27,33–35]

Vaccine	Recommended Number of Doses	Recommended Dosing Schedule	Target Population	Dose and Route
Typhoid Conjugate Vaccines (TCV)				
A.Vi-capsular polysaccharide conjugated to tetanus toxoid (Vi-TT)				
Typbar-TCV*	Single	Single	≥ 6 months to 45 years old	0.5 ml IM Deltoid/ Vastus lateralis
PedaTyph	Two	0 and 4–8 weeks	children older than two years 1–2 months between doses. A booster after every 10 years.	0.5 ml IM
B. Vi-capsular polysaccharide conjugated to CRM197 (TYPHIBEV)*	Single	Single	Children aged six months or older, adolescents, and adults aged 45 and younger	0.5 ml IM
C. Vi-diphtheria toxoid	Two	0 and 4 weeks	Age 6 months to 45 years old	0.5 ml IM
D. Vi-rEPA	Two	0 and 6 weeks	Children older than two years with 6 weeks between doses.	0.5 ml IM
Non TCV				
Unconjugated Vi Polysaccharide Vaccine (ViPS)*	Single	Single	Adults and children ≥ two years. Revaccination is necessary every 3 years.	IM or SC
Ty21a Vaccine** (Currently non-available in India)	3	On every alternate day	Individuals age > 6 years. Revaccination is recommended every 3–7 years.	Oral (enteric-coated capsules/sachet)

* WHO pre-qualified vaccines; ** If the interruption between doses <21 days, resume without repeating the previous dose; if it exceeds 21 days, restart the primary series

age groups, with no notable safety concerns identified. The surveillance was predominantly passive, and the information gathered was somewhat restricted, based on around 3000 reports. Common side effects like swelling, pain, and fever were observed in about 1–10% of those vaccinated across all age groups, and there were no severe adverse events reported to the manufacturer. Although Typbar-TCV's safety profile seemed similar to ViPS, it is important to note that there were limitations in the data available.[3] While these vaccines have a favorable safety profile, individual reactions may vary, and it is essential to consider each patient's specific characteristics and medical history before administering the vaccine.

Adverse Events Following Vaccination

Inactivated typhoid vaccines (ViPS, TCV)

After receiving the inactivated typhoid vaccine, individuals commonly experience localized symptoms such as pain at the injection site, along with redness or swelling. Some may also develop mild systemic reactions, including fever, headache, and a general sense of discomfort. Similarly, following the live typhoid vaccine, individuals may anticipate side effects like fever, headache, abdominal pain, diarrhea, nausea, and vomiting. While these are typical and expected reactions, it is crucial to remain vigilant for any adverse reactions that may occur and promptly report them to healthcare professionals. It's important to note that severe allergic reactions, although rare, could potentially occur after leaving the clinic. In the event that symptoms of a serious allergic reaction are noticed, including hives, swelling around the face and throat, trouble breathing, a fast heartbeat, dizziness, or feeling weak, it is critical to promptly seek medical help.[39]

Typhoid Vaccine Contraindications and Precautions[3,36]

1. Hypersensitivity: These vaccines should not be given to individuals who have a known hypersensitivity to any component of the respective vaccine.
2. Acute Febrile Illness: Vaccination should be avoided in individuals experiencing an acute febrile illness. It's advisable to wait until the individual has recovered before administering the vaccine.
3. Individuals with impaired immune function, whether due to a congenital condition or acquired immunodeficiency, should not receive these vaccines. This recommendation also applies to individuals undergoing immunosuppressive or antimitotic drugs.

Ty21a Vaccine (Vivotif): The Ty21a vaccine should not be taken during an acute gastrointestinal illness. Individuals receiving sulfonamides, antibiotics, and antimalarial (particularly mefloquine) should not receive the Ty21a vaccine, as these agents may affect the vaccine strain's ability to induce a protective immune response. The final dose of the oral typhoid vaccine should be provided at least three days before beginning antibiotic or antimalarial prophylaxis. It is contraindicated in transplant recipients.[40]

Typhoid Vaccination in Special Populations[3,41]

Pregnant Women

The safety and effectiveness of ViPS (Vi polysaccharide) and TCV during pregnancy and lactation have not been extensively studied. While there are no theoretical safety concerns, it is

a reasonable precaution, when feasible, to consider delaying vaccination until the second or third trimester to minimize the potential risks of teratogenicity. However, the live attenuated Ty21a vaccine should be avoided during pregnancy.

Immunocompromised Persons

Immunocompromised individuals, including those living with HIV or AIDS, should receive TCV or ViPS vaccine. These vaccines do not contain live attenuated organisms and are generally safe for this population. Those immunologically stable (CD4% >25% for children less than five years and a CD4 count of ≥ 200 cells/mm^3 for those ≥ five years) can receive Ty21a vaccine.

Healthcare staff

At risk of occupational exposure are recommended for typhoid vaccination.

Food Service Workers

In endemic areas, those involved in food preparation and service should receive typhoid vaccinations. When feasible, preference should be given to using a Vi-negative vaccine, such as Ty21a to facilitate the serological detection of chronic carrier status in individuals who have been vaccinated.

Travellers

Typhoid vaccination is recommended for travelers visiting locations at high risk of typhoid fever. When available, combined Typhoid–Hepatitis A vaccines are recommended for use.

Cost-effectiveness of vaccines

It has been demonstrated that Typhoid could be economically catastrophic for families and the government, thus making a strong case for introducing typhoid vaccines in the immunization schedule.[42] Vaccination is likely cost-effective in countries with 300 or more typhoid cases per 100,000 person-years.[43] Introducing TCV in urban settings is projected to prevent between 17% and 36% of typhoid cases and fatalities. In rural regions, the introduction of TCV could lead to a reduction in typhoid cases and deaths ranging from 19% to 36%. A decision analytic model specific to India has determined that implementing TCV in urban areas is a more cost-effective approach compared to rural areas.[44] The introduction of the typhoid vaccine proved cost-effective as per the studies conducted in the urban slums of Delhi, Kolkata, and Mumbai, which targeted infants, children, and young adults.[45–47]

Implementation Issues and Barriers to Inclusion in the National Immunization Program

Most vaccine effectiveness studies focused on children and adolescents there is limited evidence on the effectiveness of the typhoid vaccine among adults in India.[8,48–50] When the typhoid conjugate vaccine was first introduced as a public health campaign in Mumbai, India, in 2018, the financial cost for the direct expenditures on vaccines and other supplies was $1.87 per dose.[47,51] During the campaign's execution, several obstacles were faced, including extensive administrative hold-ups needing multiple tiers of authorization and the height of the rainy season, which introduced logistical challenges. These issues impacted the selection of session sites, the attendance of beneficiaries, and transportation arrangements.[47] Typhoid vaccines do not induce long-term protection, and revaccination is needed every three years, especially with the Vi polysaccharide vaccine. At the same time, the need for revaccination with typhoid conjugate vaccine is still not clear. The need for revaccination increases the financial burden on the health system and indirect costs at the individual level, which makes these vaccines programmatically challenging to administer.[3]

Future Research Priorities

Further research is required to estimate the typhoid vaccine's long-term protective efficacy and immunogenicity beyond five years of administration. It is crucial to generate evidence specific to the Indian context to determine whether revaccination with typhoid conjugate vaccine is necessary in adults.[3,26,28,29] Future studies should also include the effectiveness of vaccines against drug-resistant strains.[10] Available evidence depicts that the typhoid vaccine is well tolerated. It is imperative to prioritize research on the cost-effectiveness of adult typhoid vaccination at the national and state levels.[45–47] Efforts should continue to develop a more efficacious typhoid vaccine with coverage against all the Salmonella strains because current typhoid conjugate vaccines are based on Vi antigen, which is ineffective against Vi S. typhi strains.[34] Implementation research should be conducted to identify the barriers and facilitators for typhoid vaccine implementation at the community level and to integrate it with the national immunization schedule. In the initial stages of implementing the typhoid vaccine in adults, the vaccine can be prioritized in high-risk adults and later expanded to a broader population.

IAPSM position on Typhoid vaccines for the Indian population

India faces a substantial incidence of typhoid fever, particularly in urban regions. To address this, a widespread typhoid immunization program, along with other preventive strategies, is essential, especially in the vulnerable pockets of slum areas. While existing Vi-PS vaccines fall short in addressing this issue, the newer generation TCVs (Typhoid Conjugate Vaccines) are well-equipped to bridge this gap. Among the various typhoid vaccines, TCV is recommended for all age groups due to its superior immunological benefits, applicability in adults, and potentially longer-lasting protection. The Indian Association of Preventive and Social Medicine (IAPSM) suggests routinely using Typbar-TCV™ for adults up to 45 years old in India. Furthermore, Typbar-TCV™ has received WHO Pre-Qualification, making it suitable for introduction

in countries eligible under the Global Alliance for Vaccines and Immunization (GAVI).[3] While the current generation of TCVs is generally deemed safe, there is still a necessity for comprehensive post-marketing surveillance research involving a substantial number of participants. Members of the IAPSM can ensure this in their respective community health service areas.

Simultaneously, there is a need to advance the development of more sophisticated and widely effective typhoid vaccines that can address the full range of human Salmonella infections. When selecting a typhoid vaccine, factors like cost, programmatic concerns, and the length of protection offered must be taken into account. Additionally, the outcomes and effectiveness of various vaccination approaches, along with their integration with WASH initiatives or other interventions, should be carefully observed and recorded to enhance future efforts in controlling typhoid. Members of the IAPSM can also conduct such trials in their field practice areas to generate this evidence and set up a surveillance system to monitor the burden and ascertain the long-term effectiveness of the vaccine.

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Conflicts of interest

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