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Typhoid fever: Control & challenges in India

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Enteric fever is a common but serious disease that affects mostly children and adolescents in the developing countries. *Salmonella enterica* serovar Typhi remains responsible for most of the disease episodes; however, *S.* Paratyphi A has also been reported as an emerging infectious agent of concern. The control measures for the disease must encompass early diagnosis, surveillance and vaccine to protect against the disease. Sanitation and hygiene play a major role in reducing the burden of enteric diseases as well. The current status of diagnostics, the surveillance practices in the recent past and the vaccine development efforts have been taken into account for suggesting effective prevention and control measures. However, the challenges in all these aspects persist and cause hindrance in the implementation of the available tools. Hence, an integrative approach and a comprehensive policy framework are required to be in place for the prevention, control and elimination of typhoid fevers.

Key words Complications - diagnostics - enteric fever - surveillance system - typhoid fever - vaccines - WASH strategy

Introduction

Typhoid or enteric fever is mainly caused by *Salmonella enterica* serovar Typhi and also to a lesser extent by *S.* Paratyphi A. Humans are the only reservoir for these organisms. The main sources of infection are the stool and urine of infected persons, with the important vehicles being contaminated water, food and flies. The causative agent is either waterborne or foodborne for this gastrointestinal infection. The onset and severity of the disease mainly depends on the virulence of the organism and the infective dose[1].

Typhoid fever has been estimated to cause about 26 million (typhoid) and five million (paratyphoid A) illnesses, with 190,000 enteric fever deaths in 2010 globally[2]. Economically developing nations face the disease as a major public health problem, particularly low-income countries of Asia and sub-Saharan Africa, where majority of the population strives for safe water, limited sanitation and hygiene infrastructure as well. Usually, children below 15 yr of age are more susceptible to the disease probably due to the fact that adults develop immunity from recurrent infection and subclinical cases[3].

In India, data from hospital- and community-based studies are limited. A systematic literature review of studies on enteric fevers in India showed only a few community-based studies and only seven hospital-based studies in the last 10 years which estimated the incidence of typhoid[4]. A large-scale community study conducted in India in an urban slum

setting has described the incidence of the disease as high as 2/1000 population/year under five yr of age and 5.1/1000 populations/year under 10 yr of age[5]. A similar study from north India has reported that most of the cases occurred in children aged 5-12 yr, wherein 24.8 per cent of cases were in children up to five yr of age[6]. Unfortunately, the absence of nation-wide estimates of burden of the disease has minimized the effective prevention and control efforts of enteric fevers.

Clinical presentations

Typical symptoms of enteric fevers are pain in abdomen and high fever, with fever being the main presenting feature in the initial stages. Usually, the incubation period is 1-14 days. A prodrome of non-specific symptoms may be associated with typhoid fever such as chills, persistent headache, abdominal discomfort, constipation, diarrhoea, weakness, dizziness, nausea and cough. Late diagnosis or failure to respond to treatment may cause serious complications which include cerebral dysfunction, perforation of the gut wall, gastrointestinal haemorrhage and shock. Terminal ileal perforation is the most common complication of enteric fevers[1].

Re-infection occurs only where the primary infection is terminated using early intervention with antibiotics. Protection against typhoid is brought about both by cell-mediated and humoral responses[7]. Natural infection induces antibodies both in serum and intestines. An attack of typhoid fever may induce lifelong protection if there is persistence of the bacilli in the environment, which provide continuing low levels of immunity[8].

Diagnostics

Need for typhoid fever diagnostics and role in control

Cure for any disease starts with accurate and timely diagnostics, which areoften not available, accessible and affordable in India. Most of the countries remain uncertain on the true enteric fever disease burden, which is attributed to the lack of accurate and inexpensive rapid diagnostic tools, infrequent laboratory testing practices and imperfect disease-reporting systems. In endemic and resource-poor settings, clinical diagnosis of typhoid fever (which is often inaccurate) has the preference over the diagnostic tests. However, the clinical diagnosis of typhoid remains difficult with the occurrence of other co-endemic acute febrile illnesses. Importantly, accurate laboratory diagnostics reveal the true disease burden, which initiates appropriate therapeutics. It rules out unnecessary treatment contributing to the emergence of antimicrobial resistance problem. In addition, appropriate diagnostics can identify the natural history of infection in humans and evaluate vaccine efficacy, which is an effective control measure of the disease.

Lack of diagnosis of enteric fevers poses a practical hindrance to the estimation of disease burden. The conventional diagnostic procedure of blood culture for typhoid fever remains the gold standard which, however, has a low sensitivity of 40-60 per cent, irrespective of better and continuous automated culture systems. Another widely used serological Widal test can easily be performed with less sophisticated equipment, involving minimal technical training. However, different cut-off points used by different laboratories at different places often hinder the interpretation of results and the test shows poor performance in terms of low sensitivity and specificity[9]. Moreover, the treatment is initiated using a single acute-phase sample, not with the convalescent-phase samples. The reliable yet painful test of bone marrow culture is dependent on laboratory equipment and technical training which are limited in most of the primary healthcare centres in developing countries[10-12].

Novel diagnostics in the pipeline

It is evident that the existing diagnostics platforms for enteric fevers suffer from limitations regarding sensitivity, time cycle, infrastructure need, *etc*[12]., emphasizing the need for an accurate and rapid point-of-care (POC) diagnostic. Some of the newer promising technologies are under different developmental stages (Table I)[10-19], which are described as follows:

The loop-mediated isothermal amplification (LAMP): The innovative LAMP test of DNA was compared with real-time quantitative polymerase chain reaction (qPCR) which demonstrated better performance, robustness, temperature stability within 57-67°C and 2 *p*H units (7.3-9.3). It involves less extensive preparatory steps. The test retains its sensitivity and specificity even in the presence of untreated biological fluids[13,14].

Microwave-accelerated metal-enhanced fluorescence (MAMEF): This is an amplification-free, rapid molecular diagnostic technique to identify the specific chromosomal *oriC* locus which is common to all *S. enterica* serovars. Proficient microwave-induced lysis of *Salmonella* spp. suspended in bacteriological

Table I. Current status of typhoid fever diagnostics

Name of the diagnostics	Stage	Performance	Comments/challenges
Blood culture	Current gold standard for diagnosis	Sensitivity - 40-60%	2-5 ml of blood required; sensitivity varies when bacterial levels are low; there is delay in transporting to the laboratory and if antibiotic is used before blood drawn; expensive; takes 48 h. Needs limited laboratory expertise and equipment.
Culture of bone marrow aspirate	The test may be attempted in case the blood culture for bacterial growth is negative following three to four days of incubation	Sensitivity - 90%	The procedure is extremely painful
Serological assay: The Felix-Widal test	Used in developing countries, despite low utility	Poorly sensitive or specific; often leads to misinterpretation of the results	Varying cost, disregarded as an effective diagnostic tool; false negatives are high in endemic areas; useful if combined with other tests
Rapid diagnostic tests (Typhidot with several variants as Typhidot, TyphiRapid-Tr02, Typhidot-M, *etc*., and the Tubex test)	Available	Not remarkably sensitive or specific	Dismissed as appropriate diagnostics and treatment; expensive
Polymerase chain reaction-based assay	Available	39-42% sensitive, 100% specific	Not a very reliable diagnostic; also requires high-end laboratory equipment along with technical expertise; cannot provide antimicrobial resistance status; no use in reporting
LAMP	Done in stimulated samples, and in human challenge model, needs validation	Able to detect 500 femtogram after serial dilutions of purified *S.* Typhi DNA	Equipment and cost is high; temperature range (57-67°C) and 2 *p*H units (7.3-9.3) are advantageous
MAMEF	Evaluation is underway	1 cfu/ml of non-typhoidal *Salmonella* within 30 sec	Amplification-free molecular method; more rapid
TPTest	Validated in a few countries	100% sensitivity, 78-90% specificity	New-generation serologic test; both ELISA and Immunodot platforms available; incubation for 24-48 h is a limitation
Gas chromatography and time-of-flight mass spectrometry	Validated in plasma samples	Reports distinct systemic metabolite signatures to diagnose enteric fevers caused by *S.* Typhi and *S.* Paratyphi	Expensive analytic tools
A portable iMC^2 system	Validation stage; the system is already shown in buffer and blood samples spiked with *S.* Typhi	The method is highly sensitive (10 cfu/ml), and specific; turnaround time is fast (<7 h)	A lateral flow immunoassay detects the bacteria in the recovered sample Useful as rapid culture diagnosis

Contd...

Name of the diagnostics	Stage	Performance	Comments/challenges
Strip-based typhoid diagnostics	Upscaling and validation stage	mAb to flagellin; specific to typhoid infection	Under validation

LAMP, loop-mediated isothermal amplification; MAMEF, microwave-accelerated metal-enhanced fluorescence; TPTest, typhoid and paratyphoid fever test; mAb, monoclonal antibody; iMC^2, immunomagnetic cell capture; *S.* Typhi, *Salmonella* Typhi; *S.* Paratyphi, *Salmonella* Paratyphi; ELISA, enzyme-linked immunosorbent assay; cfu, colony-forming unit
Source: Refs 10-19

medium helps in DNA release, followed by the detection of as low as one colony-forming unit (cfu) of *Salmonella* suspended in 1 ml of medium in <30 sec through metal-enhanced fluorescence. The test is reported to be sensitive and specific[15].

Typhoid paratyphoid test (TPTest): It detects *Salmonella*-specific immunoglobulin (Ig) IgA responses in lymphocyte culture supernatant. The typhoid paratyphoid test (TPTest) is carried out in the following three categories of patients: patients with suspected enteric fevers, patients with other illnesses and healthy controls. A simplified modified TPTest has been developed which is ideal to be adopted in laboratories of developing countries with limited facilities and equipment[16].

Gas chromatography with time-of-flight mass spectrometry: To investigate metabolite signals associated with enteric fevers, this two-dimensional test was performed on plasma from *S.* Typhi- and *S.* Paratyphi A-infected patients and asymptomatic controls. This identified 695 individual metabolite peaks. When supervised pattern recognition was applied, highly significant metabolite profiles could separate the three categories. More specifically, a combination of six metabolites acted as serovar-specific systemic biomarkers which accurately detected the aetiological agent[17].

Immunomagnetic cell capture (iMC^2) system: This is an indigenously developed, portable, fully automated system in which the blood samples are kept in broth medium for 6 to 8 h. The immunomagnetic cell capture (iMC^2) device is used for the immunomagnetic enrichment of the target cells. The disposable capture chip in the device constitutes two chambers. Pathogenic cells get bound to antibody-coated magnetic nanoparticles in the 5 ml sample chamber and get flown to the 50 µl recovery chamber. A lateral flow immunoassay is performed for bacterial detection. The test exploits less turnaround time and demonstrates high sensitivity and specificity[18].

Strip-based typhoid fever diagnostic: This is an indigenously developed test exploiting the flagellin proteins of *S.* Typhi. These highly immunogenic flagellin monomers contain serovar-specific middle region. Hence, a panel of murine monoclonal antibodies (mAbs) was generated against this region. These mAbs expressed unique specificity and high affinity towards *S.* Typhi flagellin, leaving aside any cross-reactivity with other serovars. The bound mAbs to flagellin on bacterial surface, and in soluble form, was suggestive of potentially improved diagnostic[19].

Challenges in typhoid fever diagnostics

Challenges in available diagnostics

In India, delayed presentations to clinics, inappropriate diagnostic facilities and usage of suboptimal tests hinder the control of the enteric fevers. Often, pre-exposure with inadequate and unnecessary antibiotic therapy prior to visiting a proper healthcare facility may reduce the performance of diagnostic tests, which affects eventual patient management in terms of antimicrobial resistance and serious complications.

Ambiguity of the enteric fever diagnosis based on clinical symptoms calls for phenotypic detection using laboratory diagnosis which is performed through blood culture, the gold standard or invasive bone marrow aspirate culture. Several healthcare facilities are not well equipped to perform blood cultures. Due to labour and time intensity, serotyping methods are substituted by serological tests. The most frequently used Widal test in the community has its limitations. Pre-incubation of blood cultures followed by PCR to capture the small number of bacteria in clinical samples shows variable sensitivities but is highly specific. Multiplex PCR and stool dipstick tests help in the early diagnosis; however, the complexity of molecular tests remains unacceptable for routine use in India. Newer assays are rarely available in developing countries.

Antigen-based rapid diagnostic test kits such as Tubex and Typhidot M tests have limited use

in clinical laboratories, but other assays such as ELISA, dot immunoassay, immuno-electrophoresis, haemagglutination and coagglutination have restricted usage due to several technical issues.

Challenges in the developmental path of diagnostics

Although a POC test is urgently needed to differentiate between enteric fevers and other febrile diseases, a clear and profit-intensive market for diagnostics is unavailable in India. This creates a limiting factor in stimulating development and commercialization. Obtaining a non-invasive and accurate reference standard is challenging, which promotes blood culture. Moreover, as a successful diagnostic test reaches the market, the challenge lies even in its rollout. The issue of incentivizing for its use rather than the cheaper empiric treatment availability needs special attention[12].

Prevention and control

Estimation of burden of disease and role of surveillance systems

The control of typhoid fever entails a robust surveillance system for assessing the disease burden followed by measures such as water, sanitation and hygiene (WASH) and advocacy for personal hygiene. Prompt diagnosis and treatment also minimize the spread of the disease from patients to the community. However, these are long-term processes and require substantial financial implications. Contextually, vaccination could provide a short-term control opportunity[3].

The challenge of controlling typhoid is often compounded by the lack of adequate nationwide surveillance in the affected countries. These are useful to provide vital input for targeted prevention programmes of the disease, as the new immunization programmes rely upon the data from surveillance networks to estimate the disease burden to prioritize risk groups. Although some of the initiatives have been undertaken globally on the typhoid fever surveillance, much is left to be desired.

Among the recently conducted studies, an initiative taken by the Sabin Vaccine Institute, USA, is Surveillance of Enteric fever in Asia Project (SEAP)[20]. This is a hospital-based enteric fevers' surveillance network in some of the Asian countries including India, Bangladesh, Indonesia, Pakistan and Nepal. The retrospective study in India[20] has revealed insight on the distribution and presentation of the disease, its outcomes and the antibiotic resistance patterns. This reflects the improved planning for future surveillance systems[20].

The Integrated Disease Surveillance Programme (IDSP) is one of the major national health programmes of India falling under the National Health Mission for all States and Union Territories, which was initiated in 2004[21]. Its main objective is to develop and strengthen a decentralized laboratory-based and computerised disease surveillance system to monitor 22 diseases (enteric fever being one of them) and to detect and respond appropriately[21].

A recent study undertaken in India titled 'National Surveillance System for Enteric Fever in India (NSSEFI)' will estimate the incidence of typhoid fever in age-specific manner in children between six months and 15 yr. The data will be generated from the community-based cohorts in varied settings as well as from different tiers of hospitals across the country[22].

Practical challenges for surveillance in India

Surveillance for typhoid fever includes early detection of cases and risk factors, as well as outbreaks. Further, it envisages molecular and serological characterization of cases to detect changes in disease strains. Laboratory diagnostics for disease documentation depend on the type of surveillance. For example, in case of hospital-based surveillance, blood culture is recommended. However, in peripheral areas where culture facilities are not available, Widal test is the diagnostic of choice which is self-limiting. Laboratory support should be an integral part at peripheral healthcare system.

Though various disease surveillance activities have been undertaken in India, several challenges still remain. First, the positivity of typhoid diagnostic tests (mainly culture and Widal) depends on the day of the onset of fever which very few patients can exactly identify. Second, reporting of culture results is time consuming and clinicians cannot procrastinate treatment for long enough. Therefore, empirical treatment is the method of choice and thus the positive typhoid cases are missed out during routine surveillance. Further, diagnostic laboratories are hardly available in rural and remote areas. Even if present, culture and other facilities are rarely available. Insufficiently trained laboratory staff may pose a hindrance in the detection of cases. Several other constraints such as utilization of limited financial support apparently for

more high-prevalence diseases curtail the need for enhanced surveillance of underestimated diseases such as typhoid.

Water, sanitation and hygiene (WASH)

WASH strategies were initiated in 1990 as Sustainable Development Goals (SDG goal 6)[23]. Data from the UNICEF regarding the WASH status in India show that basic water availability has increased from 80 per cent in 2000 to 88 per cent in 2015. Basic sanitation availability was 38 per cent in 2014[23]. However, since its initiation (in 2014), *Swachh Bharat Mission* has helped to improve the situation so as to achieve 95 per cent coverage by 2019[24]. Handwashing facilities are available to only 87.5 per cent of the population. Further, significant inequalities persist between urban and rural areas of the country[24].

While proper WASH practices including improved access to clean water and sanitation are the mainstays of typhoid control as in any diarrhoeal diseases, these require long-standing investments, huge financial outlays as well as sustained political commitment. Most policymakers in developing countries resort to a comprehensive approach that includes immunization, thus combining a short-term measure with long-term solutions.

Antibiotic resistance in India

Although appropriate antibiotic therapy is an effective targeted treatment for enteric fevers, the prevalence of resistance to available antibiotics is increasing, which results in higher morbidity, mortality and treatment cost[25-28].

Antibiotic treatment protocol for enteric fevers

As per the WHO guidelines[29], ciprofloxacin or ofloxacin is recommended for fully sensitive typhoid cases; alternatively, chloramphenicol, amoxicillin and co-trimoxazole are also recommended. However, the following two categories of drug resistance have been developed: resistance to antibiotics such as chloramphenicol, ampicillin and trimethoprim-sulphamethoxazole [multidrug resistance (MDR) strains] and resistance to the fluoroquinolone drugs. For the MDR cases, ciprofloxacin or ofloxacin or cefixime or azithromycin or cefotaxime needs to be used. In case of quinolone resistance, azithromycin, rocephin or cefotaxime is recommended[29].

Emergence of multidrug resistance in Salmonella Typhi

MDR typhoid has become a major concern in India, with chloramphenicol resistance outbreak in 1972 followed by amoxicillin, co-trimoxazole and chloramphenicol by the 1990s. Ciprofloxacin resistance was developed in the late 1990s[30]. Currently, physicians prescribe azithromycin or cefixime for uncomplicated cases and ceftriaxone in intravenous therapy as per the National Treatment Guidelines for Antimicrobial Use in Infectious Diseases released by the National Centre for Disease Control[30]. However, emerging resistance leading to more disease severity, morbidity and mortality emphasizes careful monitoring, surveillance and reporting of the cases to avoid last-line antimicrobials in therapy[30].

Way forward to overcome the challenges of multidrug resistance

Combination therapies of azithromycin with ceftriaxone or cefixime and recycling of older antimicrobials have been debatable for quite some time. Regarding the policy framework, the National Policy for Containment of Antimicrobial Resistance was initiated by the Government of India in 2011[31], followed by the Chennai Declaration in 2012[31], and a five-year plan to implement antimicrobial stewardship remained a significant initiative. In 2014, Schedule H1 was introduced to restrict the sale of third-generation and beyond antibiotics without a prescription leaving aside, azithromycin and ciprofloxacin[31]. Hence, infectious disease specialists and accredited microbiology laboratories hold serious promise for the effective control of MDR challenges[31].

Vaccines

Vaccination of high-risk populations is conventionally accepted as the most promising strategy to control the typhoid fever. The first effective typhoid vaccine was developed in 1896 for military use[32]. However, the concept of global vaccination against typhoid is as old as in the 1960s when field trials showed the effectiveness of two doses of killed vaccines, giving a protection of around 70 per cent[33].

The old parenteral heat-inactivated whole cell typhoid vaccine, which was available, contained *S.* Typhi (1000 million organisms/ml), *S.* Paratyphi A and *S.* Paratyphi B (500 million each/ml) (TAB) had reasonable protection level but had severe reactogenecity[34]. Individuals administered with TAB complained about headache, fever, malaise and localized tenderness at the injection site. The WHO recommended its discontinuation as it evoked unacceptable side effects, and it was abandoned as a public health tool for typhoid fever control[34].

Newer-generation typhoid vaccines were developed as the older-generation vaccine was abandoned. In the 1980s, two licensed newer-generation, well-tolerated vaccines were available that promised protection without significant side effects: one was the live, attenuated oral vaccine, Ty21a, and the other was the Vi-polysaccharide (P5) vaccine[35-38]. Studies done in Chile showed that three doses of Ty21a conferred a protection of around 62 per cent over a seven-year period and almost 80 per cent protection over a surveillance span of five years[35]. However, the protective efficacy of Ty21a varied from one geographical area to the other and was as high as 95 per cent in some trials and as low as 53 per cent in others. Ty21a requires multiple doses and a strict cold chain. The caveat remains as the vaccine can be administered in children above six years of age followed by boosters every five years[36]. A liquid formulation of Ty21A was licensed in which lyophilized vaccine was reconstituted along with buffer powder. However, this has been discontinued, and presently, only the capsule form is available[37]. One capsule needs to be taken orally every other day till the four doses have been consumed.

The second typhoid vaccine developed was the injectable subunit vaccine using the capsular polysaccharide of *S.* Typhi*,* Vi, which is considered both as an essential virulence factor and as a protective antigen. Both the Ty21a and Vi PS vaccines had distinct immune mechanisms leading to significant protection against typhoid. Vi stimulates the IgG antibody, but Ty21a produces humoral and cell-mediated immune responses instead of Vi antibody[38]. The Vi vaccine has several advantages over Ty21a; hence, it has been targeted for accelerated introduction into public health programmes. It has shown consistent efficacy results (64-77%) even in areas of high typhoid incidence in a single-dose regimen (all persons two years and above) and has less strict cold chain requirements. However, Vi vaccine is not used widely because of the age restriction and its effectiveness decreases rapidly in two-three years[34]. Both Vi and Ty21a vaccines do not provide long-term protection and periodic revaccination is needed, making it programmatically difficult to administer.

To overcome the limitations, the polysaccharide is covalently conjugated to a carrier protein[39]. The Vi conjugate vaccines are, therefore, expected to be safe and immunogenic in infants and younger children, to induce protective anti-Vi antibody, to stimulate memory cells and to produce immune response that lasts almost a life time, and are compatible for use in the Expanded Programme on Immunization (EPI) programme as well[39]. The first Vi conjugate vaccine was developed using a non-toxic recombinant protein which was antigenically similar to *Pseudomonas aeruginosa* exotoxin A (rEPA)[39]. The other conjugate vaccine for typhoid was the Vi-CRM197 which was found to be safe and immunogenic in less than two year olds and did not interfere with other vaccines in EPI programmes. However, the post-vaccination antibody titres were short lived and fell substantially after six months[40].

It has also been observed that Vi conjugated to Tetanus Toxoid (Vi-TT vaccine) boosts specialized T cells in the human body, which is advantageous over the Vi polysaccharide vaccine alone[41]. Hence, the Vi conjugate vaccine exhibits superior and long-lasting antibody response by engaging T cells. During a phase III clinical study, a single dose of Vi capsular polysaccharide-tetanus toxoid typhoid conjugate (Typbar TCV) vaccine exhibited four-fold seroconversion rates in the following manner of 98.05 per cent in individuals between six months and above and two years, 99.17 per cent in 2-15 yr and 92.13 per cent in 15-45 yr[41]. This vaccine has been WHO pre-qualified, taking it one step further to being used through national programmes, particularly in endemic areas[42]. Table II shows the list of available vaccines for typhoid.

Problem in developing efficacious typhoid vaccine

The side effects, low efficacy and cost efficiency issues are an integral part of developing a vaccine candidate. Further, large field efficacy trials are needed post development of a vaccine candidate. Thus, the associated cost and logistical difficulties act as hindering factors to the advancement of typhoid vaccines. The other issue is the use of a controlled human infection model of typhoid fever to assess the efficacy of the vaccine. Immunogenicity remains the major key point of a successful vaccine. The vaccine needs to provide strong humoral and cellular immunity against enteric fever, especially in children who are more prone to the infection. Recently developed licensed vaccines are not immunogenic in early childhood. The available oral capsular form of the vaccine remains unsuitable for children to swallow[44,45].

Cost-benefit/cost-effectiveness analysis of vaccination

Very few large-scale studies have been conducted on the cost-effectiveness and cost-benefit analysis of typhoid vaccination in India. It would be judicious

Table II. List of available typhoid vaccines

Characteristics	Parenteral killed whole cell vaccine	Live attenuated Ty21a	Vi capsular polysaccharide	Conjugated typhoid vaccine
Constituent	Whole cell vaccine made from a non-motile mutant of *S*. Typhi strain Ty2	Chemically mutated Ty2 strain of *S*. Typhi	Purified Vi capsular polysaccharide of the Ty2 *S*. Typhi strain	Vi polysaccharide attached to a non-toxic recombinant protein which is antigenically similar to rEPA
Vaccine type	Whole cell, killed	Live attenuated	Subunit	Subunit
Immunogenic properties	Stimulate the synthesis of 0, H and Vi antibodies	Induces mucosal IgA and serum IgG antibodies against O, H and other antigens, also cell-mediated responses Not shown any booster effect	Elicits serum IgG Vi antibodies T cell-independent (no booster response)	T cell-dependent response Booster response seen on exposure
Administration route	Parenteral	Oral	Parenteral	Parenteral
Dosing schedule	0.25 ml/dose for <10 yr 0.5 ml/dose for ≥10 yr Two doses; two-four week apart	Four doses; one capsule each on alternate days	A single intramuscular injection of 0.5 ml	Two doses; four weeks apart
Target population for licensure	≥6 months of age	Adults and children more than six years of age	Adults and children more than two years of age	Six months and above
Safety	Local side effects such as pain, swelling, redness and systemic side effects such as high-grade fever, chills, headache, vomiting and body ache are seen in 30-50% vaccines	Major safety concerns not reported	Major safety concerns not reported	Major safety concerns not reported
Contraindication	Acute severe febrile illness	Acute severe febrile illness. Congenital or acquired immunodeficient state which includes treatment with immunosuppressive drugs; acute gastrointestinal illness Individuals receiving sulphonamides and antibiotics	Acute severe febrile illness	Acute severe febrile illness
Efficacy	~70% for three years	80% at five years; 62% at seven years	64-77%	92-99%
Length of protection	At least three years	At least five-seven years	At least three years	Three-year follow up ongoing

P. aeruginosa, *Pseudomonas aeruginosa*; rEPA, recombinant exoprotein A; IgA, immunoglobulin A; IgG, immunoglobulin G
Source: Ref 43

to mention that any vaccine-costing study should first consider the incidence of the disease in the population which would affect the costing analysis substantially. Calculations should be based on at least moderate typhoid incidence with known case fatality rates because the cost of illness (COI) is highly dependent on these values.

A study was conducted to assess public expense on typhoid Vi polysaccharide vaccines for two impoverished, typhoid-endemic slums in Kolkata, India[46]. Three measures of the economic benefits of the vaccines were considered: private and public COI avoided, along with avoided COI plus mortality risk-reduction benefits. Three strategies of typhoid vaccination (targeting all children, targeting only enrolled schoolchildren and targeting adults and children) were reported as 'very cost-effective', exploiting the standard comparisons of cost per

disability-adjusted life-years circumvented with per-capita gross domestic product[46]. Another study showed that public health officials need to consider a societal perspective regarding the economic benefits of vaccination. The findings have shown that public decision makers need to realize that the incidence of typhoid fever remains underestimated by blood culture-positive cases and hence COI avoided, thereby depicting a significant underestimation of the actual economic benefits of vaccination to individuals[47]. It is imperative to conduct in-depth studies to assess the financial implications of WASH interventions as compared to vaccination strategies.

Challenges to introduction of the vaccine

Introduction of a new vaccine in India, especially in the EPI programme, poses a veritable challenge. As a public health tool, vaccination against the disease requires adequate data on the burden of the disease which are lacking substantially on a nationwide basis. Technically, the main challenge was provision of a vaccine to be administered within the age range of EPI programme. This issue has been resolved with the development of Vi conjugate vaccine. It needs to be assessed whether the vaccine can be concomitantly administered with other EPI vaccines without any adverse effects. Logistically, issues such as availability of storage and cold chain space will be the major concerns. Administrative problems of work force and the training of frontline health workers need to be resolved. Finally, substantial and long-term financial and political commitment will be the deciding factor for the consideration of introduction of the vaccine.

Conclusion & way forward

Primary strategies for typhoid fever control involve safe water supply, adequate sanitation facilities and proper hygienic practices. However, these require sustainable investments, huge financial outlays and long-term political commitment. The introduction of WASH programme has helped to improve the WASH situation in India although there still remains a significant gap in achievements. Several other issues have created a hindrance in disease burden control as well.

The key bottleneck is the non-availability of robust country-wide surveillance data in India. Additionally, the need for improved POC diagnostics which will be rapid, simple and accurate yet affordable remains a plausible challenge. Treatment of typhoid fever cases poses a veritable challenge. MDR *S.* Typhi strains leading to drug-resistant typhoid have become a major concern. Thus, preventive intervention measures turn out to be the key to control of the disease. Other than provision of safe water and sanitation, vaccination of high-risk populations is universally accepted as the most promising short-term strategy with respect to the control of typhoid fever. To make the best use of the control measures in such resource-poor endemic settings, there is a need to develop disease burden extrapolation models to choose the sites that need to be prioritized for routine intervention. The surveillance data need to be roped in to create the coordinated plans to translate into tangible actions, which is deployment of these interventions to the targeted population.

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