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Review Article

Enteric fever: current issues in effective management and control

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ABSTRACT

Typhoidal salmonella is the causative agent of enteric fever. All are strict human pathogens. It spread through the consumption of contaminated food and water. It presents with high-grade fever, rigors, headache, malaise, some abdominal discomfort, leukopenia, thrombocytopenia, and relative bradycardia/tachycardia. None of them is diagnostic for enteric fever. Antibiotics are the mainstay in the treatment. The management of the disease has become problematic due to the development and spread of MDR genes among the bacterial populations. Efficient laboratory support is required for appropriate antibiotic administration. Among the laboratory tests, the only one to be relied upon for definitive diagnosis is blood or bone marrow culture. It is highly specific, but specificity is low, so a number of false negatives can result. Nucleic acid-based tests are not standardized and are resource-intensive, so they cannot be made available to all patients in all areas. Serological methods also lack standardization, so false positives and negatives cannot be ruled out. Vaccination too does not provide good protection, especially in the adults where it has not been extensively studied. The majority of the patients are treated on clinical suspicion, and antibiotics are administered.

Keywords: Salmonella, Non typhoidal salmonellae, Multidrug resistant strains, ESBL, QRDR strains, Typhoid, Enteric fever

INTRODUCTION

Enteric fever is endemic in some parts of Asia, Africa and south America. Inhabitants of these areas are living under substandard hygienic conditions with no access to clean drinking water. No proper waste disposal system. Health care delivery system in these areas too leaves much to be desired. If something is available it may be beyond the reach of many due to financial constraints. Majority is dependent on centres which either lack expertise or are poorly equipped. Disease is transmitted and maintained among the population through contaminated food and water.[1] Despite the efforts put in by WHO and partners to control the spread of the disease through vaccination, provision of better health care facilities and improvements in the general sanitation, the disease is still rampant with continuous emergence of antibiotic resistance.[2,3]

This article aims to review the present facilities available to treat the patients and to control the spread of the disease and attempts to identify the issues that can be addressed to reduce the threat posed by this disease.

REVIEW

Using the terms Salmonella, NTS, MDR strains, ESBL, QRDR strains, Typhoid, and Enteric fever, a thorough search was conducted across PubMed, Google Scholar,

and ResearchGate. There was no set time limit for this search; however, the articles published during the last 20 years were given preference.

Epidemiology

Enteric fever is an acute, febrile, life-threatening disease prevalent among poverty-stricken, socio-economically backward communities of the third world. People residing in many countries of South America, Asia, and Africa are the main sufferers. Improper sanitation and non-availability of safe drinking water are the common issues in these countries leading to the persistence of this disease in the environment.[1]

The importance of this disease is reflected in the fact that in 2017, 14.3 million cases of typhoid and paratyphoid fevers were reported from across the globe, although there was a 44.6% decline from 25.9 million reported in 1990. Still, it is a huge burden on the people and the economies. 76% of these were caused by *Salmonella enterica* serotype Typhi.

Overall mortality of 0.95% was reported in the same year, with higher rates seen in residents of poor countries, too, more in children and old people. A total of around one hundred and thirty-nine thousand deaths occurred globally in 2017. Overall, typhoid and paratyphoid fevers were responsible for 9.8 million (5.6–15.8) DALYs in 2017. Such is the total impact of the disease around the world. 2

In developing countries, this disease is a major public health issue; e.g., in Pakistan, Salmonella has been reported to be a leading cause of pediatric septicemia. Outbreaks have been reported from many countries in the African continent, like Moyale, Kenya, Kampala, Uganda, etc., during different parts of the years between December 2014 and Jan 2016.[3-7]

Since these figures are derived from the small number of surveillance studies based on the available diagnostic techniques, the actual impact of the disease is undoubtedly likely to be quite high.[8]

Bacteriology

Enteric fever is caused by the organism belonging to the genus Salmonella, a member of the family Enterobacteriaceae. It includes two main species *Salmonella bongori* and *Salmonella enterica*. The organisms of enteric fever belong to Salmonella enterica subsp. enterica, serovars Typhi and Paratyphi A, B, and C.[9]

A unique set of surface antigens, namely, flagellar H, virulence-capsule (Vi), and lipopolysaccharide O (somatic) antigens, is possessed by all these serovars. Salmonella serovars are classified as either typhoidal salmonellae or nontyphoidal Salmonellae (NTS) on the basis of disease presentations and host tropism. With a few exceptions, NTS can infect both humans and animals, producing a self-limiting diarrhoea in humans. In certain clinical settings, some may cause invasive disease. Typhoidal Salmonellae, on the other hand, are strict human pathogens.[10-12]

Host immune response to salmonella infection

Salmonella typhi produces around 4700 proteins from a genome size of approximately 4.8 MB, with the genome having 300-400 specific genes and around 200 pseudogenes accumulated from time to time, which are also present in *S. paratyphi* A.

The organism has acquired virulence genes present on loci like Salmonella pathogenicity islands (SPI) prophages and plasmids.[13] In this way, different pathogenic strains are in circulation globally, each having different virulence capabilities depending upon the virulence genes it has acquired. The collection of a greater number of these gene loci in one organism leads to the emergence of highly resistant strains like MDRs or XDRs.

There are four SPIs-7, 8, 15, and 18, unique to Salmonella typhi. They encode collectively. for the bacterial capsule, a type IV b pilus, hemolysin (HlyE), typhoid toxin, and some other factors also.[14-16] *S. typhi* manages to survive and replicate in the macrophages with the help of virulence factors on the SPI-2 pathogenicity island. These macrophages carry the organisms to the cells of the reticuloendothelial system in the liver, gallbladder, spleen, and bone marrow. Time taken by the organisms to reach these internal organs from the moment of ingestion can be within 24 hours.[18]

Typhoidal Salmonella is capable of inducing a variety of immune responses in the host, including humoral and cell-mediated, initiated through the interaction between the specific pathogen-associated molecular patterns on the organisms and pathogen-recognizing receptors on different cells of the host innate immune system. Flagellin, e.g., on the bacterial flagella, can be recognized by TLR5. While TLR 4 and 2 are recognized and activated by the les of the lipopolysaccharide (LPS) molecule. Similarly, type IVb pilus contributes significantly towards the entry of bacteria in the cells. In the case of non-invasive NTS, these interactions lead to the activation of proinflammatory responses localized in the intestine, leading to the rapid onset of diarrhoea within 12–72 h.

In contrast, typhoidal salmonellae typically do not trigger a proinflammatory response.[19-20] The Vi CPS and the typhoid toxin have a role in inhibiting host immune responses by toning down the PAMPs, such as LPS O-antigen, and altering the function of the recruited immune cell and/or depleting them, respectively. The genes for Vi CPS are not present in *S. paratyphi*, so in this bacterium the same function is performed by a very long O-antigen, which enables the organism to evade the host immune system. Thus, in this way, typhoidal salmonellae maintain themselves inside the macrophages for a greater part of

their life cycle inside the reticuloendothelial system with only a brief presence in the circulation.[21,22]

CLINICAL PRESENTATION

The classical signs and symptoms after an incubation period of 8-14 days can be any combination of high fever, headache, malaise, anorexia, relative bradycardia /rapid pulse, leukopenia, thrombocytopenia, abdominal discomfort, and neurological complications.[23,24] However, many other infections quite common in typhoid endemic areas, may present with similar symptoms. So, making a definitive diagnosis on clinical presentation alone is difficult. Moreover, available laboratory parameters too cannot reliably differentiate between enteric fever and these other infections.[25]

Diagnostic and treatment challenges

Clinical presentation and laboratory investigations interpreted together form the mainstay in the diagnosis of enteric fever The support of the laboratory, is required to confirm the clinical suspicion.[26]

In addition to the strains of typhoidal salmonella causing a similar clinical picture. many other infections, too can have the same clinical picture.[27,28] The current laboratory investigations cannot exclude these diseases, and hence the diagnosis of most enteric fever cases, if culture negative, remains an educated guess.

The global spread of MDR strains has led to the ineffectiveness of antimicrobials like ampicillin, chloramphenicol, and co-trimoxazole in the management of typhoid and paratyphoid in these endemic areas. These MDR strains have the IncH1 plasmid in addition to the other antibiotic-resistant genes.[29] *S. typhi* Haplotype-58 (H58) is the most common MDR strain identified in various parts of Asia and Africa and in cases diagnosed among the travelers in other countries.[30]

LABORATORY DIAGNOSTIC METHODS

Diagnostic approaches in the laboratory can be categorized into direct methods and indirect methods.

Direct methods

Culture

Isolation of Salmonella from clinical specimens still remains the gold standard in the diagnosis of typhoid fever. Isolation is carried out from blood and bone marrow from a patient with three days or more of fever. This enables us not only to identify the organism to species level but also to find the antimicrobial sensitivity. This method has 100% specificity but is low in sensitivity. On average, blood culture taken and processed under standard conditions has a sensitivity of around 50% and bone marrow 80%.[18]

The outcome depends upon proper collection of a blood culture sample employing a strict aseptic technique to avoid contamination. Blood is collected in a bottle of liquid medium (e.g., tryptic soy broth (TSB)), balancing the quantity of blood to the quantity of broth in such a manner as to maintain a 1/10 ratio or greater. Cultures are incubated at 370 C and inspected daily for a week. Indication of positivity leads to subculture on selective-differential and non-selective enriched media at 370 ℃ for 24 hrs.

Bone marrow culture in terms of yield is generally considered more rewarding than a culture set up from a peripheral blood sample. But at the same time, it is not simple to be carried out. It is an invasive procedure and requires expertise and equipment to perform bone marrow aspiration.[31]

The shortcomings of this procedure are the provision of a proper laboratory infrastructure and expertise to carry out the task professionally. Another issue is the minimum turnaround time of at least 48 hours needed for the organism to grow and be identified and another 24 hours for sensitivity testing.

Nucleic acid detection

Detection of bacterial nucleic acid is carried out by polymerase chain reaction (PCR). It is capable of detecting serovar specific DNA extracted from bacteria. They can detect a small quantity from the clinical sample as there is a step which amplifies the DNA before detection, so the method should be highly sensitive and specific. As it is detecting DNA sequences and not bacteria so it cannot differentiate between live and dead organism.[32]

Different types of PCR methodologies are in vogue, starting from the conventional PCR to real-time PCR (qRT-PCR), fully automated and can give quantitative results, nested PCR, multiplex PCR, and loop-mediated isothermal amplification (LAMP) PCR.

The standard reference method has not yet been agreed upon; at present, the results of the blood culture depict the accuracy of the method. Practically, the sensitivity of this method is between 40-100%, and the specificity is near 100% if conducted under the best conditions.[33]

The sensitivity of this method in the detection of the active disease is still controversial, and how far it can be applied as a standard investigation in clinical practice is not yet agreed upon. The primary advantage of this method is the rapid turnaround time.

Serology

The Kauffman–White Scheme is the time-honored protocol for the serological identification and differentiation of S. enterica serovars. The diagnosis is based on the detection of antibodies to Vi,

lipopolysaccharides (LPS) O, and flagellar H antigens present in the typhoid organisms, differentiating between *S. typhi* and *S. paratyphi*.

Different Salmonella serovars may share some of the antigens (Table 1). Hence, the positive serological tests are just suggestive of the diagnosis and should be interpreted carefully with the clinical picture. The advantage is that they are simple to perform, and the turnaround time is shorter.

Following are the serological tests being currently done by the medical laboratories for Typhoid fever, Widal test, Tubex T, Typhidot, IgM/IgG Elisa

Widal test

This agglutination test looks for antibodies in the patient's serum by reacting the serum with commercially prepared sera that contain antigens. It is necessary to establish the laboratory's and the patient population's sensitivity and specificity for the accurate interpretation of the test. Another crucial factor is the standardization of the antigen and, of course, its proper storage.[34]

This test should be performed on two serum samples roughly ten days apart. A four-fold increase in antibody titers is interpreted as a positive result. In the endemic areas, a single test is done in the acute phase, titers reported, and interpreted with the clinical picture. The reasons for this practice can be manifold, from economic constraints to a cultural mindset.

False positive results do occur, as other bacteria belonging to the family Enterobacteriaceae possess O and H antigens producing cross-reactivity.[35]

Tubex TF (Inhibition magnetic binding tube assay)

A quick test to identify Salmonella typhi. Using monoclonal antibodies, it looks for the IgM antibodies against the Salmonella O_9 antigen in the patient's serum.

The test measures how well an anti-O_9 IgM monoclonal antibody binds to coloured latex particles. The patient's serum sample is combined with the latex reagent and the magnetic beads (blue and brown particles) in a reaction well that has been specially made for this purpose. The mixture is then left for two minutes. A magnet is then used to extract the magnetic beads from the solution.

The reaction produces a colour which is measured against a colour standard and detected in numbers. The result is reported as TUBEX® TF score. A score between 0-10 is used for reporting. 0 is negative and 10 is highly positive. TUBEX® TF score of 4 to 10 is considered positive for typhoid fever, while scores in the range above 2 and below 4 are equivocal, in such a situation the test is recommended to be repeated.[36]

Majority of the studies performed in Asian countries comparing the Tubex TF test with Widal and Typhidot have shown high sensitivity and sensitivity of Tubex TF over the other two. The first version of TUBEX®TF test gave the highest sensitivity (100%) and specificity (100%) as compared against Widal test. A study performed in India reported lower sensitivity for TUBEX®TF compared with the Widal test. This was the only one giving such results.[37]

In order to have better accuracy in the results, control cases must be selected carefully, use of other pathogens instead of Salmonella, blood culture-negative patients as negative controls without ruling out typhoid completely. Can compromise the sensitivity and specificity of the assay. Standardization in protocol is a must to have a true and satisfactory interpretation of such clinical work. By and large, these tests do not show any advantage of one over the other.

Typhidot

This is a dot enzyme immunoassay based on the detection of IgM or IgG or both antibodies in the patient's serum using a specific antigen (50 kDa) which is present on the outer membrane protein of S. Typhi. The detection of IgM antibodies means, in the early phase, acute S. typhi infection, while the detection of both IgG and IgM also suggests acute disease but, in the middle phase. There is a greater chance of detecting IgG antibodies in people living in areas in which the prevalence of disease is high as compared with areas where it is low.[38]

An analysis done by Wijedoru et al., published in 2017 showed moderate accuracy of Typhidot and TubexTF in diagnosing enteric fever but none was found better than the other. 39

Typhoid IgM dipstick assay

A qualitative test based on immunochromatography. It detects IgM antibodies in the serum, produced against lipopolysaccharide antigen released by dying S. Typhi

This assay, at the face of it, appears to be simple and easy to perform and can give results in minutes and hence, can serve as a good alternative at the POC centers in resource-poor communities.

TP test

A recently developed test claimed to detect both typhoid and paratyphoid fevers. Mononuclear blood cells from the blood sample collected in a heparinized tube are separated by means of the density gradient configuration technique, cultured in an RPMI medium at 370°C in a 5% CO_2-enriched atmosphere. After incubating for 48 hours, the supernatant from the culture is checked for the presence of IgA specific to Salmonella using ELISA. A value of

greater than 10 ELISA units is given positive. This is the established cutoff value.

IgM/IgG ELISA

This is a solid phase immunochemical test that quantifies antibodies directed against specific *S. typhi* antigen epitopes. Wells coated with purified typhoid LPS antigen (*S. typhi* somatic O-antigen and flagellar H-antigen) are then filled with serum samples or controls. The absorbance is created through by addition of various reagents. This is quantified and correlated with the quantity of IgM or IgG-specific antibodies found in the specimen. The test may be difficult to apply for typhoid diagnosis on a regular basis since it takes a long time and requires multiple tools, such as a microplate reader.[40]

Newer potential targets for lab diagnosis

Extensive work is being undertaken to find new biomarkers, using techniques like proteomics, transcriptomics, and metabolomics. Through these methods, people aim to look for biomarkers unique to patients with acute enteric fever, with an aim to distinguish these patients from those with other infectious diseases and healthy people. Finding an ideal biomarker has many difficulties, including finding validation methods, as there is a lack of a reference standard.

The lack of an animal model capable of reproducing the organism's whole infectious life cycle is another obstacle. A composite reference standard (CRS) that incorporates several diagnostic tests has been suggested as a solution to the shortcomings of the current diagnostic methods, as no one approach is flawless.[41] These methods' have a potential to bring improvements in the sensitivity and specificity of these tests.

Finding the best biomarker/ biomarkers that are expressed early in the infection stage, can give information about the antimicrobial resistance and are capable of differentiating distinguishing between acute infections and subclinical infections, and can detect chronic carriers will require further extensive work in this field.

Protein biomarkers

Immunodominant antigen signatures linked to enteric fever have been found using high-throughput techniques like immuno screening, traditional and customized proteomics.

In order to identify bacterial antigens that are particularly immunogenic in patients with enteric fever, immunoaffinity proteomics-based technology (IPT) was used, in which columns were loaded with antibodies from enteric fever patients and probed with bacterial antigens.[42] The bound bacterial proteins were identified using proteomics based on mass spectrometry.

HlyE and LPS are two antigens expressed by intracellular salmonella that have a promising diagnostic potential.[43] HlyE is relatively specific to *S. typhi* and *S. paratyphi* because the majority of NTS, such as S. Typhimurium and S. Enteritidis, lack this gene product.[15]

Detection of IgA titres against membrane components of *S. typhi* and *S. paratyphi*, by ELISA and an immunodot blot approach (TPTest) can be useful in certain situations. It has shown 78–97% specificity and 100% sensitivity in identifying the bacteria, it can distinguish between acute infection and convalescence cases also.[44] These biomarkers could become POC-compatible quick diagnostic techniques with further advancements.

Nucleic acid signatures

RNA-Se and microarray hybridization have been used to analyse the gene expression profiles of host and bacterial cells at different phases of infection. From the infected blood cells, microarray analysis identified 2026 *S. typhi* genes (~44% of the genome), with the number of upgraded transcripts to be up to 141. These included the typhoid toxin, PhoPQ regulatory genes, and HlyE.[45] Host genes have also been identified through the use of microarray analysis. Repeatable blood signatures unique to enteric fever were generated by analysing the relative gene expression patterns of peripheral blood samples from acute, recovery, convalescent, and uninfected groups. Clinical indicators were associated with the transcripts found in this investigation.[46]

Five host genes (STAT1, SLAMF8, PSME2, WARS, and ALDH1A1) were examined in a more recent investigation to look for a signature that is expected to detect enteric fever with 97% sensitivity and 88% specificity.[47] Amplification of these genes using a qPCR-based diagnostic assay may be developed as a potential diagnostic technique if these signatures are also found in other endemic locations. Using magneto-DNA probes, a novel technique called micro-NMR (NMR) can be useful to detect bacterial mRNA. It can detect as low as 1 CFU/ml of *S. typhi* and *S. paratyphi*.[48]

CHALLENGES IN MANAGEMENT

The mainstay in the management of this disease is early and accurate diagnosis with sensitivity testing and administration of appropriate antibiotics in adequate doses. The disease is manageable with low morbidity and mortality if diagnosed early and treated by appropriate antimicrobials to which the organism is fully sensitive. In case of delay in the start of antimicrobials or if the drug is ineffective because of organisms showing resistance, then complications and the fatality rate are increased.[49]

The first effective antimicrobial against typhoid was chloramphenicol. It was introduced into patient care by 1950. Two more drugs were licensed for typhoid treatment: ampicillin and co-trimoxazole. In 1980 these

two, along with chloramphenicol, were considered the first-line drugs to be dispensed unless otherwise indicated. These were highly effective to start with. Resistance to these three started appearing by the end of 1980. Due to the indiscriminate use without carrying out culture and sensitivity testing, isolates resistant to these drugs called multidrug-resistant isolates (MDR) started emerging. This situation brought the fluoroquinolones in the field. Ofloxacin and ciprofloxacin were extensively prescribed, with amazing results, defervescence could be achieved in three days.[50]

The relief was short-lived and by 1990 Isolates with decreased susceptibility to quinolones started emerging with MICs of 2 mg/ml detected by Nalidixic acid resistance during in vitro testing.[51] These bacteria were observed in countries in which the prevalence of the disease was negligible. Almost all could be traced back to travel to endemic area.

Isolates highly resistant to fluoroquinolones are being increasingly reported from South Asian countries. The resistance is chromosomal in origin. Bacteria are getting resistant to these drugs by undergoing mutations of the genes encoding DNA gyrase (gyrA) and the topoisomerase IV (parC). These mutations affect the chromosomal quinolone-resistance-determining regions (QRDR) of the bacterial chromosome.

An isolate of *S. typhi* was reported from south Asia with an MIC of 256 mg/ml against fluoroquinolones, which means that it is highly resistant. This was in 2011. A novel mutation of the genes encoding DNA gyrase (gyrA) was reported to have occurred in this isolate.[52-54]

There has been an ongoing epidemic since 1990 of a specific Salmonella typhi lineage known as H58 (genotype 4.3.1) in South Asia. This very persistent lineage in terms of survival is also associated with resistance to fluoroquinolones through the common gyrA/parC mutations. The strain H58 S. Typhi is moving to regions within Asia and from Asia to Africa. The dispersal of high-level resistance to quinolones in the region and to other countries is not far.[30]

Third generation cephalosporins and azithromycin

Third-generation cephalosporins and azithromycin are the available options for therapy after the compromise of fluoroquinolones. In South Asia, these medications are now the first option for empirical treatment. The single oral cephalosporin, cefixime, has gained a lot of popularity among doctors who want to avoid intravenous antibiotic therapy.

Third-generation cephalosporin resistance has already emerged but has not yet spread as much as fluoroquinolone resistance. However, there are more and more reports of *S. typhi* that produce extended spectrum beta-lactamase (ESBL), especially in patients in Asia and among tourists returning from South Asia. According to reports, the MIC for ceftriaxone has progressively increased in certain isolates, rising from less than 1 mg/ml to isolates with a MIC of more than 20 mg/ml. 54,55 Certain strains of Salmonella typhi have been reported to acquire a number of ESBL genes, including those that encode the TEM, SHV, PER, and CTX-M enzymes as well as Amp C.[34] It is very worrying when ESBL-producing organisms appear, especially if they have already gained determinants and mutations linked to MDR and/or fluoroquinolone resistance.

An early clinical response is seen with treatment using Azithromycin, with little faecal carriage and relapse rates. 37 Azithromycin-induced clinical and microbiological failures in *S. typhi* have only been documented once to date.[56,57] Although the macrolide efflux pump genes, macA and macB, have been identified in certain *S. typhi* strains that are circulating in India, the mechanism of resistance was not specified in this particular paper.

Other options

Antibiotics belonging to the carbapenem group and the glycycline antimicrobial, tigecycline, are becoming increasingly common empirical therapy in cases of severe typhoid. A recent study reported that tigecycline was highly active at a concentration of 2 mg/ml against *S. typhi* in vitro, inhibiting the growth of more than 97% of isolates.[58]

These findings were consistent with those published by the European committee on antimicrobial susceptibility testing (EUCAST) and an additional investigation conducted on several isolates of Salmonella spp. It has good in-vitro activity against Salmonella spp. isolates resistant to ceftriaxone. Although widespread resistance to ceftriaxone in typhoidal salmonellae has not yet been documented, you never know what the future holds.[42]

Clinical trial data are now needed to evaluate the effectiveness of tigecycline in the management of severe typhoid fever. The use of antimicrobials that were once considered outdated, such as co-trimoxazole and chloramphenicol, is being reconsidered for the treatment of simple typhoid fever. Some recent reports from Asia have shown that they are again effective in treating typhoid fever.[59-60]

Attention has also turned back to the use of the lost in time antimicrobials, the old time first liners; chloramphenicol and co-trimoxazole, are under review to be re-employed for the treatment of uncomplicated typhoid fever. The persisting avoidance of these agents from the last two decades or even more has led to the re-emergence of *S. typhi* susceptible to them and some recent reports from Asia have demonstrated their successful use in the treatment of typhoid fever.[59,60] In contrast to the already prevailing situation about the MDR strains, several investigations have indicated that the prevalence of MDR

may now be as low as 10% in some situations.[61] As alternative therapeutic approaches are being examined, a trial comparing azithromycin with co-trimoxazole for the treatment of undifferentiated fever in Nepal, of which *S. typhi* is responsible for around one-third of the cases presently in progress, might yield useful information.[62,63]

Available vaccines

There are two readily accessible typhoid vaccines: Vi polysaccharide (parenteral) and Ty21a (oral). The development and application of more recent typhoid conjugate vaccines are in different phases. Recently, the World Health Organization selected Typbar-TCV, a unique Vi tetanus toxoid (Vi-TT) conjugate vaccination, as the recommended immunization for people of all ages.

The licensed Ty21a and Vi polysaccharide vaccines are efficacious in adults and children older than two years in endemic countries. The Vi rEPA vaccine is just as efficacious, although data is only available for children. The new Vi-TT vaccine (PedaTyph) requires further evaluation to determine whether it gives protection against typhoid fever or not.[64]

Table 1: Serological identification of Salmonella.

Serovar	LPS OAg	Flagella H	Ag Vi Ag*	Cross-reactivity
S. typhi	9	D	Positive	O9 Ag is present in *S. enteritidis*, *S. Dublin*, and *S. Gallinarum*. Vi Agis present in *S. paratyphi* C, S. Dublin, and *Citrobacter freundii*.
***S. paratyphi* A**	2	A	Negative	
***S. paratyphi* B**	4	B	Negative	O4Agispresent in *S. typhimurium.*
***S. paratyphi* C**	6/7	c	Positive	O6/7 Ags are present in *S. choleraesuis*. Vi Agis present in *S. dublin*, *Citrobacter freundii*, and *S. typhi*.

* Vi antigen is mainly used to screen for chronic carriers

CONCLUSION

The control of Enteric fever depends upon case finding and treatment along with improvement in general hygienic standards in the endemic areas and vaccination. Case finding depends upon the correct diagnosis for which Laboratory support is inevitable. Correct diagnosis is important otherwise antibiotic resistance will keep on emerging. Existing laboratory tests and the way they are employed in clinical practise leaves much to be desired.

There is a need to develop new laboratory tests which are cost effective, can be done at the point of care easily, would not require special expertise and have good sensitivity, specificity, negative and positive predictive values. Newer vaccination strategies and improvement in the general sanitation is a must to block transmission. Meanwhile the quest for the development of newer antimicrobials should be undertaken with Zeal and dedication transmission. All these measures if put together have a great potential to control this disease in future.

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