

Typhoid Fever: Pakistan's Unique Challenges and Pragmatic Solutions

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ABSTRACT

Typhoid fever is a life-threatening disease caused by gram-negative bacteria *Salmonella enteric* serotype Typhi. There are almost 21 million individuals affected by this disease annually all over the world from which majorly belongs to South Asia. According to WHO, almost 11 to 21 million cases of typhoid fever and about 200,000 deaths with typhoid fever have occurred all over the world. Pakistan health authorities have confirmed that from 2016 to 2020 almost 22,354 cases of typhoid fever are reported, out of which 15,717 cases are extensive drug resistance typhoid fever reported from the different regions of Sindh. These calculations are used to measure the disease rate of typhoid fever, ratio is about 15.5/1,000 and that XDR strain of typhoid fever is highly resistant to the antibiotic so known as extensive drug resistant. The diagnosis of typhoid fever is done by culture test, serological test, nucleic acid assays, protein markers, and biomarkers. The proper diagnosis is very important to ensure the strain of typhoid fever so that treatment should be started according to it.

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Introduction

Typhoid fever is a life-threatening illness caused by gram-negative bacteria *Salmonella enterica* serovar Typhi and to some extent also caused by the *Salmonella enterica* serovar Paratyphi A.² In developed countries, the ratio of occurrence of typhoid fever is far lower whereas in developing countries it still contributes a major disease burden and is known as a serious health threat in developing countries. It is considered serious health issue in developing countries due to the presence of poor resources and improper

sanitation conditions which results in contamination with food and water with the typhoid causing strain.³ Fecal contaminations of food and water play a major role in its transmission from person to person. It is a serious morbidity as almost eleven million people are suffered with this disease from which almost 129,000 affected individuals did not survive at the global level. According to WHO almost 11 to 21 million cases of typhoid fever and about 200,000 deaths with typhoid fever occurred all over the world. Pakistan health authorities have confirmed that from 2016 to 2020 almost 22,354 cases of

typhoid fever were reported, out of which 15,717 cases are extensive drug resistance typhoid fever mainly reported from the different regions of Sindh. This calculation is used to measure the disease rate of typhoid fever and the ratio calculated is about 15.5/1,000 and that XDR strain of typhoid fever is highly resistant to the various antibiotic so known as extensive drug resistance. The current outbreak of typhoid fever in Pakistan is known to be caused by extensive drug-resistant strain and caused infection of almost more than 19 thousand individuals in different regions of Sindh. Children below the age of 15 years are more susceptible to this disease due to lower immunity levels while adults are less susceptible due to better immune responses.⁴ XDR typhoid fever is also known as enteric fever caused by gram-negative bacteria *Salmonella enterica* serovar Typhi that is highly resistant to at least five antibiotic classes currently used in the treatment of typhoid fever. The causative agent is either water-borne or food-borne and the severity of the disease highly depends on the infective dose, virulence of the microorganism and the immune level of the affected individual⁵. The dissemination of disease by typhoid carriers is one of the major reasons for the continued higher incidence of typhoid fever. It is important to detect these carriers because as early as these carriers are detected, the risk of prevalence of the disease can be reduced. The most common route of infection is water as drinking water especially in urban areas is contaminated due to the presence of a poor sewage system.⁶ The second common route of infection is food so it is also important to screen the food and water samples to control the outbreak of typhoid fever. The data from a hospital and community-based studies about XDR typhoid fever is limited in Pakistan. There are very few studies conducted to measure the challenges and trends of typhoid fever and XDR typhoid fever in Pakistan. Hanif *et al.* (2021) has done a hospital-based study to measure the

emerging trends of XDR typhoid fever in pediatrics. This study explained that out of total number of pediatric cases, about 80% of children have XDR typhoid fever. Among these cases, almost 90% showed resistance to Meropenem and Azithromycin. According to Saleem (2021), the ratio of non-resistant enteric fever reduced from 100% to 44% from 2009 to 2019 in Pakistan. Whereas the ratio of XDR has increased from 16% to 40% within the same time span. Tareen (2014) explained that typhoid fever can occur at any age but majorly occurred at 11-12 years or 51-60 years. This study also explained that the dominance of typhoid fever in male population as compared to females.

Clinical Chronicles of Typhoid: Signs, Symptoms, and Scenarios

Clinical presentation of any disease is very important as it is involved in assessing the prevalence and outcomes of the disease. Some typical symptoms of typhoid fever are high fever, chills, severe headache, pain in the abdomen, constipation or diarrhea, and myalgias. Diarrhea and vomiting are not so much severe at the start of typhoid fever but in severe conditions, intestinal perforation, confusion, and even delirium can also occurred⁷. The incubation period for paratyphoid fever is 1-10 days whereas for typhoid fever is 6 to 30 days. In some cases, the symptoms of typhoid fever are misinterpreted with other illnesses, and due to inappropriate treatment, it can lead to severe complications such as shock, GIT hemorrhage, cerebral dysfunction, and perforation of the gut wall. The most common complication of typhoid fever is terminal ileal perforation. Relapsing of typhoid fever is occurred due to incomplete course of treatment and usually occurs 1 to 3 weeks after its recovery. Some common complications of typhoid fever are myocarditis, pancreatitis, endocarditis, some psychiatric problems such as paranoid psychosis, delirium, and hallucinations, pneumonia, meningitis, mycotic aneurysm, and

kidney or bladder infections.⁸ The relapse is milder than the first attack and is also known as the recrudescence when the strains of both cycles of diseases are identical. If the strains of the first and second infection are different from each other than reinfection occurred.⁹ So, in this case typhoid patients are recommended to follow up for 3 months even after the completion to identify the relapse or any complication associated with the infection. So, an individual need to have proper protection against typhoid by both cell-mediated as well as humoral responses.¹⁰

Navigating Typhoid Diagnostics: Challenges and Innovations

It is very important to diagnose a disease because the accurate diagnosis of a disease will lead to the proper treatment and cure of the disease. The surveillance of accurate typhoid fever disease burden in an area is very important to reduce the morbidity and mortality of typhoid patients. There are multiple diagnostic tests available to detect the cause of infection, all of these tests should be highly sensitive, cost-effective, specific, and simple to perform to detect the pathogen.¹¹ In developing countries, availability of specific and sensitive diagnostic tools is limited that result in its increased prevalence of the disease so in these regions it is important to examined the clinical presentation of typhoid fever. Every country needs to have the availability of such sensitive and specific diagnostic tests to ensure the accurate and timely diagnosis which will leads to the proper treatment of disease. The accurate treatment can also overcome the emergence of antimicrobial resistance.¹² The diagnostic is also important because it is involved in the identification of the natural history of infection in humans, as well as evaluate the efficacy of treatment. Unidentified cases of enteric fever have caused a major hindrance in the estimation of disease burden. Most common methods used for the diagnosis of typhoid fever is by the method of blood culture and antibody detection by Widal

test. For bacterial culture testing, sample of blood is taken and then cultured on a special medium that helped in the bacterial growth.¹³ After overnight incubation, bacterial growth is checked by specific biochemical tests to ensure the presence of *Salmonella typhi* in culture. Presence of *S. typhi* in blood represents that patient is suffering from typhoid fever.¹⁴ The culture testing is known as the most common diagnostic test used for the confirmation of typhoid fever and other tests are done to measure other parameters such as detection of antibiotic and antibody quantification in the blood. Limitations of the culture method is that it can only identify the presence of bacteria within 3 to 10 days of illness and before the start of empiric antibiotic therapy.¹⁵ The sensitivity of the culture test is also lower in children as compared to adults but it is still used for the identification of typhoid fever.

Widal test is a serological technique used to detect typhoid fever. This test involved the principal of serum agglutination to detect enteric fever. There should be homologous antibodies present in the serum of patients infected with *Salmonella typhi*.¹⁶ Widal test is performed by two methods named as slide method and tube method. It is stated that if serum reacts with the respective antigen, then agglutination occurred which confirmed that the patient has typhoid fever. It is a highly sensitive and rapid diagnostic test as results are reported on the same day.¹⁷ This test has both quantitative and qualitative diagnostic capabilities and the Widal test range is more than or equal to 1:160 for antigen O and antigen H. Thus, in this way detection of *Salmonella typhi* is done by both culture test and Widal test.

From Lab to Clinic: Advancing Typhoid Diagnosis with State-of-the-Art Techniques

There are some limitations present in these conventional diagnostic tests for typhoid fever such as in sensitivity, specificity, and time span. The development in technology has developed

some new diagnostic tests for detection of typhoid fever. The culture test is time taking while an ideal diagnostic test should be specific, sensitive, and rapid.¹⁸ So, there is a need for the development of such rapid, sensitive, and specific tests for early diagnosis, effective management, and control of typhoid fever. The antigens included in the detection of typhoid fever through serological testing are outer membrane proteins, and lipopolysaccharides. Some other tests are done by nucleic acid detection as well. The nucleic acid detection of typhoid fever involved Polymerase Chain Reaction that amplifies the growth of *Salmonella* serovar-specific DNA for the diagnosis. This is a more rapid, specific, and sensitive test and detects the *Salmonella* typhi specific DNA extracted from the live, attenuated, or dead microbes.¹⁹ The presence of dead microbes is due to the antibiotic treatment in response to typhoid fever. One of the major disadvantages of this method is the use of special equipment and trained staff to perform the PCR test. This approach includes extracting DNA from patient samples and Flagellin, 16s rRNA (GroEL), cytotoxins, Vi polysaccharide (via), heat shock proteins, and other preserved genes are the most frequently used target genes for diagnosing enteric fever.²⁰ Several studies have shown the sensitivity range of 40 to 100 percent, whereas if test is performed under optimal conditions, the specificity may be nearly 100 percent.²¹

Beyond Cultures: Harnessing Serology for Rapid Typhoid Diagnosis

Serological identification of typhoid fever is done by various serological tests. It is a simple, rapid, and highly valuable test to manage the fever effectively and timely. The most common and effective serological test for the detection of typhoid fever is the Widal test that involved agglutination of bacterial cell wall O antigen as well as flagellar H antigen. This test is done twice to improve the accuracy of the results: 1st time in the acute phase and then during the recovery

phase of the infection, which can be approximately 10 days after the acute phase.¹⁶ Fourfold increase in antibody titers between the two tests results, the test results are considered positive. However, a single Widal test performance is widely used in the areas where typhoid fever is endemic, particularly in the early stage of acute infection, because of the unusual circumstances present in endemic areas.

Diverse background anticorps in people of different endemic areas complicating the interpretation of a single Widal test, therefore determination of cut-off values of antibodies to determine a positive resurgence is required.²² The Widal test can be significantly improved and better than the most available fast diagnostic (RDTs, Tubex, and Typhidot) tests if optimum cut-off values are documented for the particular endemic regions.

Unraveling the Diagnostic Puzzle: Hurdles in Typhoid Fever Diagnosis

Patients have faced some challenges in the typhoid fever diagnosis that leads to inappropriate treatment which then results in extensive drug resistant typhoid. Some of the main challenges in the diagnosis of typhoid fever in Pakistan are delayed presentations to clinics, the use of some suboptimal tests, and the presence of improper diagnostic facilities that negatively impact the prevention and control of typhoid fever.²³ Self-medication is another common issue and when no effective results observed then the patient visit the doctor for treatment. The performance and efficacy of diagnostic test is then reduced because of this self-medication that also result in the antimicrobial resistance as well as some serious complications. Sometimes physicians don't have the appropriate protocols or facilities to perform the culture test of the patient which is also considered as a major challenge in the diagnosis of typhoid fever. The new emerging tests need a special instrument and are at high price and it's

not possible for every patient to afford such expensive diagnostic tests. It is stated that a POC test is done to differentiate between the typhoid fever and other fever or disease that is unavailable in Pakistan.²⁴ This will reduce the development and marketing stimulation factor. It is difficult to obtain a non-invasive and accurate standard of reference to promote blood culturing. In addition, its implementation as an effective diagnostic test for typhoid is also a challenge. Especial attention is needed to promote its use instead of using inappropriate empirical treatment.

Bridging the Gap: Addressing Practical Challenges for Enhanced Typhoid Surveillance in Pakistan

The surveillance of any disease is very important for the proper management of the disease. The surveillance of typhoid fever comprised of early detection of fever, proper diagnosis, assessment of risk factors, and the outbreak conditions of typhoid fever. Furthermore, it also provides the serological and molecular characterization of any mutational change in the typhoid causing strain of *S. typhi*.²⁵ Efficacy of laboratory diagnostics and documentation of affected cases depend upon the level of monitoring. For instance, data monitoring of blood cultures is recommended in the case of hospital surveillance. In peripheral areas, however, where cultural facilities are not available, the Widal test is the only reliable test for its identification. In the peripheral health care system, upgradation of laboratory facilities is the need of an hour. There are multiple surveillance activities conducted for typhoid fever in Pakistan but still, some challenges are present. The diagnostic test is an important part of surveillance of typhoid fever in Pakistan as the positivity of typhoid diagnostic tests is highly dependent on the onset of the fever.²⁶ The reporting of the results of both the serological tests and blood culture is also important as culture test has the delay of 3 to 5 days from sample collection till

reporting and physicians have to started the treatment even before the results. One of the major challenges in the surveillance of typhoid fever in Pakistan is the unavailability of good diagnostic laboratories in rural as well as underprivileged areas of Pakistan. And in some areas where these laboratories are present have faced other problems such as unskilled staff, improper equipment that will result in false positive or false negative results of disease.²⁷ The government of Pakistan should be focused on developing some good diagnostic laboratories in rural and backward areas with skilled staff members and proper equipment so that proper surveillance of typhoid fever could be possible.

Resistant Resilience: Exploring the Evolution of Antimicrobial Resistance

Typhoid fever is a highly challenging and life-threatening disease before the development of antibiotics. Chloramphenicol has emerged as an effective antimicrobial agent as it showed significant therapeutic and efficacious effects to typhoid fever caused by *Salmonella typhi*. Clinical research on the efficacy of chloramphenicol has been done which has reported that *Salmonella typhi* strains gradually showing resistance to chloramphenicol.²⁸ The chloramphenicol-resistant strain of *Salmonella typhi* got the attention of researchers all over the world because this resistance is increasing with the passage of time. Reports claimed that during the 1970s almost 10,000 cases of multidrug-resistant cases were reported in Mexico. Due to the production of resistance, physicians started ampicillin as well as trimethoprim-sulfamethoxazole as an alternative therapeutic agent for *Salmonella typhi*. This combination of antibiotics is also known as co-trimoxazole and is highly effective in treatment of *S. typhi*.²⁹ The researches have shown that in the early 1990s the strains of *Salmonella typhi* showed resistance to all commonly used antibiotics due to the inappropriate use of antibiotics. The resistance

against these antibiotics resulted in the increase in fatality rate due to which development of newer antibiotics for the treatment of typhoid fever is compulsory. It is stated that fluoroquinolones especially ciprofloxacin used effectively all over the world to treat typhoid fever.³⁰ In recent years the resistance against fluoroquinolones also increased in the majority of typhoid cases not only in South Asia but all over the world. Cephalosporins and azithromycin used as an alternative treatment option for such fluoroquinolones resistant strains of Salmonella typhi. The bioburden of typhoid fever is highest in South Asian countries due to the poor sanitation conditions and limited resources for its identification and treatment.³¹ The first outbreak of a cephalosporin-resistant strain of Salmonella typhi has been reported from Sindh till then it became a major health concern for Pakistani population. Other studies from different developing countries such as Iraq, India, Guatemala, Bangladesh, and the Philippines also reported the cases of cephalosporin resistant S. typhi. The global spread of MDR Salmonella typhi has emerged rapidly and this strain of microbe is known as H58 lineage or haplotype that is most common reported in Asia and some developing countries of African subcontinent. The multi-drug resistance strains of salmonella typhi showed resistance against all first-line antibiotics: chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole. The MDR strains of S. typhi which also showed resistance against quinolones group of antibiotics is also a serious health issue in Pakistan which limited the treatment options³². Study conducted at Agha Khan University, Karachi reported that ratio of MDR Salmonella typhi has increased from 34.2% to 48.5 % from 2001 to 2006 while a remarkable increase in quinolones resistance from 1.6% to 64.1% has been observed After the emergence of fluoroquinolone resistance, third-generation cephalosporins has become the choice of treatment for Salmonella

typhi. 1st case of cephalosporins resistance was observed in November 2016 that resulted in the transformation of MDR to XDR typhoid fever. It was reported that Cephalosporins resistance is plasmid associated, conferring resistance against all the recommended treatment options. The specific haplotype H58 is mostly associated with the outbreak of XDR typhoid fever because of mutational variations in IncY plasmid present in this haplotype. The presence of this IncY plasmid conferred resistance to not only against fluoroquinolones but also to cephalosporins by producing various genes such as CTX-M-15 gene.³³ As a result, evolution of XDR strains of Salmonella typhi results in more devastating outbreaks of diseases and also increased the disease burden in developing countries. After the evolution of first XDR strain in Pakistan, 8,188 typhoid cases were reported from Pakistan in 2016 among which 5,274 cases were of XDR typhoid fever as reported by WHO. These statistics are calculated from Sindh province from which 69% of cases were reported from Karachi, the capital city of Sindh, 27% cases from Hyderabad, and other 4% were reported from other districts of Sindh.

Typhoid Without Borders: The Challenge of Intercontinental XDR Typhoid Transmission

The XDR strains of Salmonella typhi were also transmitted across the borders from January to October 2018 by travelers, travelling from Pakistan. During this era, six major cases were reported which confirmed that transmission of XDR strains by travelers from Pakistan. First case was reported in the United Kingdom of Great Britain, Northern Ireland, whereas the other five cases were reported in the United States of America. Further data analysis has explained that Islamabad, Karachi, and Lahore were the most common affected areas of these cases. Acquisition of such XDR strains while travelling to developing countries can also results in an outbreak of the disease in the native country of the affected individuals.

Confronting the Challenge of XDR Typhoid in Pakistan: Effective Approaches

The only reported host of *Salmonella typhi* infection are humans and route of transmission is by contaminated water and food, mainly resulted from the extremely poor hygiene and sewage conditions. So, it is important to focus on the water purification, hand hygiene practices and appropriate sanitation system because all these factors played a significant role in controlling and reducing XDR typhoid fever bioburden in Pakistan. As per regards of policy frameworks, in 2011, the Government of India launched a National Containment Policy on Antimicrobial Resistance followed by the 2012 Chennai Declaration, which still included a five-year anti-microbial stewardship plan.³⁴ Schedule H1 was introduced in 2014, to limit over the counter sale of antibiotics specially azithromycin and ciprofloxacin without having a prescription. Therefore, the effective control of MDR and XDR challenges can be seriously addressed infectious diseases specialists and accredited microbiology laboratories. Hence, we can say that proper sanitation, maintenance of hygiene conditions follow-up of food safety protocols and vaccinations are some of the effective ways to control the typhoid burden and prevent the emergence of rapid drug resistance in disease causing strains of typhoid fever.³⁵

Water, Sanitation, and Hygiene

Water, sanitation, and hygiene are important factors in the prevention of outbreaks of typhoid fever. Sanitation is about the public health concerns related to clean drinking water, adequate water treatment, as well as disposal of human wastage and sewage management. The government of Pakistan should focus on proper sanitation practices because poor sanitation will lead to fecal contamination in drinking water. In the 1990s, WASH strategies were also developed as Sustainable Developmental Goals (SDGs) to prevent typhoid fever. Pakistan has been reported

among the top 10 countries in poor sanitation and least accessibility to clean drinking water. Water treatment plans are also not available in all areas of Pakistan and majority of the people especially, in rural areas consumes untreated drinking water. The untreated water supplies are also more prone to water-borne infections that also results in the increased prevalence of typhoid fever.³⁶ Thus, the government of Pakistan should be focused on the development of proper sanitation, appropriate sewage system to avoid the contamination of water with feces, and to ensure the availability of clean water. There is a need to implement WASH strategies before eating, after using toilets, and after every kind of chores, as it will improve the hygiene conditions that results in the prevention of typhoid fever and other water-borne diseases such as diarrhea. Hygiene conditions are also important in controlling typhoid fever as when individuals are focused on maintaining good hygiene conditions it will positively affect the overall sanitation system.

Food safety

Food safety is also an important step in controlling and preventing typhoid fever. The food that is properly cooked is considered safe due to the provision of high temperature. The high temperature decreased the survival ability of microbes but if properly cooked or thoroughly cooked food is allowed to sit at room temperature for a longer period of time then the chances of microbial contamination increased. The dry fruits and food cooked or baked in industries under good hygiene conditions are safe for the health and seldom cause typhoid fever.³⁷ Where on the other hand, the chances of infection increased by eating raw food, vegetables, street foods that don't maintain the hygiene conditions, and fruits without washing. Thus, it is important to wash the raw food such as vegetables and fruits with clean water before consumption.

Vaccines

Immunization is an important step to control and

prevent typhoid fever. The immunization is attained by the vaccination so every individual should be vaccinated to control the prevalence of disease. Vaccination of high-risk populations is known as one of the most effective and promising strategies to control MDR and XDR typhoid fever. In 1896 first-ever effective typhoid vaccine was developed especially for military use.³⁸ After the effective use of this vaccine, new generation of the vaccine was developed. The two new licensed vaccine was developed in 1980s that are more tolerant and provide significant protection and prevention against *Salmonella typhi*. These two effective typhoid vaccines were live, attenuated vaccine Ty21a, as well as other was Vi-polysaccharide (P5) vaccine. The researchers have shown that the doses of both vaccines had provided almost 62% protection for 7 years whereas provide 80% protection against a surveillance span of almost 5 years. It is stated that the protective efficacy of the Ty21a vaccine varies with the variation in the demographical area as it is lower than 53% in some regions and higher than 95% in some regions.¹ Different doses of this vaccine were developed that can also be administered to children above 6 years. Ty21A was licensed as a liquid formulation in which lyophilized vaccine and buffer powder had been recreated. This has however been discontinued and only the capsule form is currently available. Until the four doses have been taken, one capsule must be taken orally every day. Injectable subunit vaccine was the second developed typhoid vaccine by using the polysaccharide as a capsule Vi is also considered as essential for both virulence factor as well as a protective agent. The vaccines Ty21a and capsule Vi were equally protected against typhoid and had different immune mechanisms. In Vi, the IgG antibody is stimulated, but in Ty21a the immune responses are cell-mediated and activated by the cell instead of Vi antibody³⁸. The Vi vaccine has several benefits over Ty21a and has, consequently, been

targeted at speeding up the immunization plan in public health. Even in areas with high typhoid incidence in one-dose schemes, it showed consistent efficacy results (64-77 percent) and less stringent cold chain requirements. However, due to the age restriction as well as decrease in efficacy within two to three years, the virus Vi vaccine is not widely used. Both of these vaccines are not so effective as they don't provide long-term protection due to which booster dose is needed after some time that is difficult to administer after a specific period. Thus, because of these reasons, the prevention and control of typhoid fever caused by *Salmonella typhi* strains in Pakistan have not been achieved.

Leading Change: Effective Healthcare Management Practices

The health care management of typhoid fever is important during the treatment. In the treatment of typhoid fever in Pakistan, it is important to understand the susceptibility pattern of XDR typhoid strains which showed sensitivity to carbapenems and azithromycin. The clinicians also reported that 90% of strains of *Salmonella typhi* in Pakistan showed least susceptibility or increased resistance to fluoroquinolones, that is why fluoroquinolones are not considered as a drug of choice for the treatment of XDR typhoid fever in Pakistan. While using azithromycin, it is also important to adjust the dosage form to treat XDR typhoid fever according to the age and weight of patients. Because of the emergence of rapid drug resistance in *Salmonella typhi*, it is important to keep updated about the current treatment plans used for XDR typhoid fever. Rapid use of azithromycin along with tigecycline and carbapenems for treatment of typhoid fever as a 1st line of drugs inspite as a last therapeutic agent also warns about the emergence of resistance against these antibiotics as well.

Immunization Impediments: Understanding and Overcoming Introduction Challenges

The immunization through vaccination is another

challenge in Pakistani population because most of the people in Pakistan showed hesitancy to get vaccinated. Introduction of a new vaccine in Pakistan, particularly in the EPI program, as a tool of public health should be warranted. Drawback in the development of new vaccine is lack of significant data availability regarding disease's national burden and type of resistant strains circulating in our local population. Technically speaking, the main challenge was to provide a vaccine for the EPI program's age. The development of the Vi conjugate vaccine has solved this problem. It is necessary to assess whether the vaccine can be administered concurrently without adverse effects with other EPI vaccines. The major concerns will be logistical problems such as storage availability and the cold chain space. The cost of the vaccine is also a major challenge in the introduction of the vaccine in Pakistan to reduce typhoid fever.

Conclusion

Typhoid fever is a life-threatening disease caused by *Salmonella typhi*. The prevalence of typhoid fever is high in developing countries as compared to the developed countries. The main reason for the increased prevalence of typhoid fever is because of poor sanitation conditions in developing or underdeveloped countries. The resistance in strains of *Salmonella typhi* has increased by developing some mutational changes in the cell membrane antigens and plasmid. Due to the emergence of resistance, MDR and XDR typhoid strains resulted that makes the treatment of typhoid fever more challenging. It is important to develop and implement new strategies to control and prevent typhoid fever. Some of the common strategies which can be implemented to control typhoid fever includes proper sanitation system, consumption of clean drinking water, implementation of WASH strategies, and maintaining proper hygienic practices. The diagnosis of *Salmonella typhi* has

been done by different methods such as culture test, serological test, nucleic acid diagnostic test, bio markers, and protein biomarkers. The anti-Vi serological test is still in used in the absence of a better laboratory diagnostic facilities. An ideal detection test for *S. typhi* should be highly specific, sensitive, cost effective. For convenient carrier detection in the field, the development of the test with immunochromatography or dipstick may be more useful. In developing multi tests for simultaneous detection of typhoid patients and typhoid carriers, the control and management of typhoid fever can be done in much proper way and will have a greater positive impact on surveillance of public health. Development of effective identification tests from environmental samples to track the organism would also enhance typhoid control as it would allow tracing the source of contamination. While carriers are important for public health concern, reports showed a strong interlink between biliary and chronic carriers of *S. typhi*. Thus, a cost-effective, sensitive, user-friendly test to detect typhoid carriers would not only support efficient management but also reduce gallbladder carcinoma and dysfunction. It is important to ensure the proper management, treatment plan, and healthcare management of typhoid fever to prevent and control the incidence of resistant strains.

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