International Journal For Advanced Research In Science & Technology
A peer reviewed international journal www.ijarst.in
ISSN: 2457-0362

BACTERIAL DRUG RESISTANCE AND ANTIBODY STUDIES IN S. TYPHI

Nitin Singh Gaur[1], Dr. Sangeeta Gupta[2]
[1]Research Scholar, OPJS University, Churu, Rajasthan
[2]Assistant Professor, OPJS University, Churu, Rajasthan

ABSTRACT
Since typhoid fever is a major killer in developing countries, it poses a significant threat to public health. Cephalosporins and azithromycin are preferred drugs for treating infections caused by S. Typhi because of the strain's lower susceptibility to fluoroquinolones. The rise of cephalosporin resistance in S. Typhi and azithromycin-associated clinical and microbiological failure are major causes for concern in low-income regions. Cephalosporin-azithromycin combination therapy is an alternative method for treating simple S. Typhi infection in endemic areas. Here is a quick rundown of the current state of the art. Infection with the bacteria Salmonella typhi is what causes typhoid symptoms. Most people in developing countries lack access to clean water and sanitation facilities, and they are often exposed to filthy and unclean environments that increase their risk of contracting typhoid. Salmonella typhi expresses a number of virulence antigens, including H-antigens, O-antigens, and Vi antigens, which play crucial roles in bacterial infection and pathogenesis. High fever, nausea, headache, fatigue, and gastrointestinal problems are common among patients with Salmonella typhi.

KEYWORDS Salmonella Typhi, Typhoid fever, Multidrug, Bacterial Drug Resistance

INTRODUCTION

Typhoid fever, often known as Salmonella Typhi, is an illness caused by the Salmonella enterica subspecies enterica serovar Typhi bacterium. It's a leading killer in many developing nations and a major health problem in others. Typhoid infections and deaths were concentrated in just five UN regions: South-East Asia, Eastern Asia, Western Africa, and Eastern Africa. South Asia accounted for 68.0 percent of the global total. Typhoid is difficult to clinically diagnose since symptoms are sluggish to manifest after Salmonella Typhi infection and lack a distinctive clinical appearance. Infected patients may have a wide range of symptoms, including fever, muscle weakness, headaches, stomach discomfort, constipation (and less often diarrhea), nausea, a dry cough, and a sore throat. Typhoid can only be confirmed by isolating Salmonella Typhi from an otherwise sterile site like the blood or bone marrow. Typhoid fever, an infection caused by bacteria that may be lethal, is a global health crisis. There is an urgent need for early diagnostic techniques to aid in the management and prevention of the sickness since the infection is associated with a high mortality and morbidity rate. In this post, we'll take a look at the literature around immunodiagnostics for typhoid fever to see how well they work. To find relevant material published between

January 1, 2011, and December 31, 2020, a literature search was conducted using three databases (PubMed, ProQuest, and Scopus), as well as manual searches using the references of chosen full texts.

Multidrug resistance, which is defined as resistance to the three first-line classes of antimicrobial medicines (chloramphenicol, ampicillin, and trimethoprim sulfamethoxazole), is currently present in 50-80% of S. Typhi isolates. In South Asia, where the prevalence of MDR S. Paratyphi ranges from 13% in India [12] to 44% in India, up to 25% of cases have been reported globally.

LITERATURE REVIEW

Cristina Masuet-Aumatell et.al (2021) Typhoid fever, caused by Salmonella enterica subsp. enterica serovar Typhi (S. Typhi), is prevalent in poor and developing countries. Although most occurrences of typhoid fever in high-income territories are transmitted by infected travelers returning from typhoid-endemic regions, data show that the level of typhoid immunization among passengers is low. Typhoid fever is becoming more difficult to treat with medicines due to the spread of drug resistance, which is an issue for both locals and visitors to endemic regions. This article provides an overview of the epidemiology and diagnosis of typhoid fever; the emergence of drug-resistant typhoid strains in the endemic setting; the observation of drug resistance in travelers; vaccines currently available to prevent typhoid fever; vaccine recommendations for people living in typhoid-endemic regions; strategies for introducing typhoid vaccines and stakeholders in vaccination programmes; and travel recommendations for a selection of destinations.

Francesca Micoli et.al (2021) Antibiotics have been utilized to treat bacterial infections, and as a result, many lives have been saved and people's health has improved. The emergence and spread of pathogens resistant to antimicrobials has been identified as a global threat by a number of health organizations. There is an urgent need for innovative treatment approaches and prevention measures due to the rising incidence of multidrug resistance. In this Review, we will discuss the possible role that vaccines may play in the fight against antimicrobial resistance. Vaccines inhibit the spread of AMR by reducing the need for antibiotics via their ability to protect against infectious disease. We also describe the current state of development of vaccines against resistant bacterial pathogens that cause a substantial disease burden both in high- and low- and middle-income countries, and we speculate on the impact of next-generation vaccines against bacterial infectious diseases on AMR.

Pietro Mastroeni et.al (2020) Salmonella is a bacterium that causes severe systemic infections in people and other animals and acts as a model for similar germs that cause other diseases since it can survive both inside and outside of host cells. Newer generations of vaccines rely heavily on the antibody responses for their success. The quality, antigen

International Journal For Advanced Research In Science & Technology
A peer reviewed international journal www.ijarst.in
ISSN: 2457-0362

specificity, and functions of antibody responses to this virus have remained a mystery for a long time. Research in humans and genetically modified animal models, as well as new techniques that take into account where and when the pathogen occurs inside the host, are shedding light on the mechanisms of humoral immunity against Salmonella. Even though there has been a lot of development in this area, there is still a lot of opportunity for argument and dispute. In sum, the data provide credence to the theory that antibodies are essential for providing immunity against systemic Salmonella infections and may be most effective when working in tandem with cell-mediated immunity. Factors such as antigen specificity, isotype profile, Fc-gamma receptor usage, and complement activation remain elusive with regards to antibody-mediated protection against Salmonella.

Sumitha Nayak (2019) The globe is still reeling from the deadly impact of typhoid. In addition to increasing the likelihood of mortality, the condition disproportionately affects young children. Diseases of the Most Impoverished (DOMI) study has uncovered fresh, very useful data on illness prevalence. That is to say, the bacteria had developed resistance to the older antibiotics. Typhoid has developed extreme drug resistance in certain regions, making common anti-malarials ineffective. This includes the fluoroquinolones and, more recently, the third-generation cephalosporins. In the ongoing fight against typhoid, vaccinations have proven to be an indispensable tool.

Elin Näsström (2017) Enteric fever, sometimes known as typhoid fever, is caused by bacteria, the most frequent of which being Salmonella Typhi and Salmonella Paratyphi A. The widespread spread of the illness is mostly attributable to the lack of proper sanitation and the distribution of contaminated water. The virus might potentially be propagated only by human beings. Having asymptomatic chronic carriers adds a layer of complexity to the transmission. Limitations exist in the current diagnostic methods for both acute infection and chronic carriage. The field of metabolomics examines how various stressors affect the levels of different metabolites in living organisms. This strategy has been used to the study of many infectious diseases in an attempt to locate diagnostic biomarkers. In this thesis, we use a mass spectrometry-based metabolomics methodology, incorporating chemometric bioinformatics tools for data processing, to assess the potential of metabolite biomarker patterns for detection of enteric fever at different stages of the disease.

MULTIDRUG-RESISTANCEM

Antimicrobial-resistant Salmonella typhi strains are spreading rapidly over the world. Studies describing the antibiogram pattern of Salmonella typhi and S. paratyphi A demonstrate that multiple antibiotic resistance is on the increase in India. Typhoid and paratyphoid infections generated by strains resistant to several antimicrobials are more severe and often deadly than those caused by

International Journal For Advanced Research In Science & Technology
A peer reviewed international journal www.ijarst.in
ISSN: 2457-0362

strains susceptible to those drugs. It is possible that the increasing prevalence of multidrug-resistant Salmonella strains is related to the general increase in the number of germs in the environment.

Another worrying trend is the proliferation of drug-resistant typhoid. Between 1970 and 1985, there were periodic outbreaks of chloramphenicol-resistant typhoid, during which several strains of S typhi acquired plasmid-mediated multidrug resistance. Co-trimoxazole (ampicillin, chloramphenicol, and sulfisoxazole). For this reason, oral quinolones were created; however, chromosomally acquired quinolone resistance in S typhi and S paratyphi has lately been found in several parts of Asia.

Salmonella isolates demonstrating resistance to several antibiotics are cause for concern because of their widespread appearance and dissemination. Because of the increasing difficulty in treating salmonellosis with traditional antibiotics like ampicillin, chloramphenicol, and trimethoprim sulfamethoxazole, doctors prescribed fluoroquinolones (such as ciprofloxacin) and extended-spectrum cephalosporins. However, the evolution of resistance to these 'critically needed antibiotics for human health' is increasing the severity, morbidity, and mortality of infections and forcing the use of last-resort antimicrobials.

Evidence is mounting linking chicken production in particular to human sickness, particularly Non-typhoidal Salmonella, which has been linked to antibiotic resistance for decades but has been the subject of heated controversy. Bacteria resistant to ciprofloxacin and other broad-spectrum antibiotics may be spreading in middle-income nations like Asia due to the use of poultry products.

ANTIBODY DETECTION

Bacterial culture from body fluids is the gold standard for diagnosing typhoid fever, however many hospitals also utilize less reliable serological assays like the Widal test.

The Widal Test: Uses the lipopolysaccharide (LPS) (O) and flagellar (H) antigens of Salmonella serovar typhi to detect the presence of agglutinating antibodies in the sera of patients with suspected enteric fever. Although its use is often frowned upon due to its lack of precision, in certain countries it is widely practiced due to its low cost and ease of execution. The performance of the approach has been hindered by a lack of reagent homogeneity and inaccurate result interpretation. During the acute and convalescent periods, serum samples for the Widal test should be taken 10 days apart. A increase in antibody titer of at least fourfold would indicate a good outcome.

Tubex: Antibodies (IgM) from the patient and monoclonal antibodies from the kit both bind to an O9 lipopolysaccharide that is specific to Salmonella typhi, and their inhibitory reaction is the basis for the TF test. De-colorization of the patient blood test reagent solution as a macroscopic indicator of a successful magnetic particle separation test. To identify

International Journal For Advanced Research In Science & Technology
A peer reviewed international journal www.ijarst.in
ISSN: 2457-0362

anti-O9 antibodies, a semi-quantitative competitive agglutination test is used.

Typhidot, on the other hand, relies on the detection of IgM and IgG in patient sera against a 50 kD outer membrane protein unique to Salmonella typhi. You may further modify this test by using a dipstick assay or cassettes of mixed antigens.

Enzyme-Linked Immunosorbent Assays: The possibility of using ELISA as an alternative approach for typhoid detection has been discussed. The IgM response normally fades away within a few weeks to a few months after a bacterial infection has been treated. IgM antibodies to Salmonella antigen may be more diagnostically valuable than IgG antibodies in an endemic environment. However, there are theoretical limitations to the use of indirect ELISA for IgM. If the concentration of a specific IgG in a sample is substantially greater than the concentration of IgM, false-negative results may be produced due to competition for antigen determinants on the plate. If a rheumatoid factor of the IgM class interacts with antigen-IgG complexes, however, the sample may provide a false-positive result.

Since ELISAs are quantitative, require less time for sample preparation, and don't need sample purity, they are more cost-effective than other procedures. Since ELISA results linearly correlate to a standard curve, it takes minimal effort to interpret them. For research purposes, ELISAs are not only able to confirm infection at any stage of the disease, but they can also identify asymptomatic human carriage of the bacterium.

The market now offers a variety of antibody detection assays, as shown in Table 01.

Table 1: Tabular comparison of various antibody detection tests available in market

International Journal For Advanced Research In Science & Technology
A peer reviewed international journal www.ijarst.in
ISSN: 2457-0362

S. No.	Test Name	Principle	Features
1.	Multi-Test-Dip-Sticks	Dipstick detecting anti-LPS IgG and IgM	Sensitivity, 89%; specificity, 53%
2.	Tubex TF	Detects antibody against *Salmonella typhi* LPS with an inhibition assay format and a visual result readout	Sensitivity, 56–100%; specificity,58–100%
3.	Typhidot	Measures IgM and IgG antibodies against a 50-kDa outer membrane protein of *Salmonella typhi* in an immunodot test format.	Sensitivity, 67–98%; specificity,58–100%
4.	Typhidot M	Measures IgM antibodies, after removal of IgG antibodies, against a 50-kDa outer membrane protein of *Salmonella typhi* in a dot blot format.	Sensitivity, 47–98%; specificity,65–93%
5.	Typhi Rapid IgM and IgG IgM (Combo)	Measures IgM antibodies, after removal of IgG antibodies, against a 50-kDa outer membrane protein of *Salmonella typhi* in an ICT LFA a cassette format.	Sensitivity, 89–100%; specificity,85-89%
6.	Widal test	Measures agglutinating antibodies against O and H antigens of *Salmonella typhi* and *Salmonella Paratyphi A*; uses a tube or slide format.	Very variable sensitivity and specificity; lack of standardized reagents

Mechanisms of antimicrobial resistance in S. typhi

For example, S. typhi may avoid being killed by antibiotics by doing the following:

- Inactivation of the antimicrobial agent
- Efflux or transport of the antimicrobial
- Modification of the antimicrobial target site
- Reduced permeability of the antimicrobial agent

Drug resistance is usually the result of some kind of genetic alteration in the organism, such a chromosomal mutation or the acquisition of a plasmid or transposon.

Challenges in detection of typhoidal Salmonella

Despite S. Typhi's declining prevalence, blood cultures still provide significant challenges when trying to isolate the organism. Suspected cases of typhoid fever are first treated with antibiotics in the community before being sent to a tertiary care center for blood culture testing. Ofloxacin-based combinations, such as ofloxacin plus cefixime and ofloxacin plus azithromycin, are commonly used and marketed over-the-

International Journal For Advanced Research In Science & Technology
A peer reviewed international journal www.ijarst.in
ISSN: 2457-0362

counter in India. The Center for Disease Dynamics, Economics & Policy found that between 2000 and 2014, the rate of cephalosporin usage increased from 1887 to 7269 standard units/1000 people. Macrolide use also increased, from 1166 to 1862 standard units/1000 people from 2000 to 2014, respectively. Standard units of fluoroquinolones administered per one million persons ranged from 2608 to 2661 throughout the years of 2000 and 2014. A sign that cephalosporins, fluoroquinolones, and macrolides are heavily used in the Indian medical system. As a result, a false-negative blood culture may occur in patients who have taken a cephalosporin-based combination (e.g., cefixime plus ofloxacin). It is important to obtain a blood culture before starting antimicrobial therapy since antimicrobials may reduce the yield of S. Typhi in blood cultures. Adding synthetic resin molecules to commercial blood culture systems renders the antimicrobials ineffective. Previous research has demonstrated that resin-based culture flasks may reduce the effectiveness of antimicrobials. However, the resins have not neutralized all antimicrobials, thus this is still a limitation. Commonly used drugs for treating suspected instances of typhoid fever include fluoroquinolones and cephalosporins. We were unable to find any studies that looked at the likelihood of detecting S. Typhi in blood cultures taken from individuals who had just finished antibiotic therapy.

The standard method of diagnosing typhoid fever using a blood culture is laborious and time consuming, often requiring 24-48 hours before the culture bottle reveals positivity. Although this is the gold standard for detecting S. Typhi in blood, the lengthy turnaround time severely limits its usefulness. Doctors request WIDAL slide agglutination tests more often than any other laboratory test. The problem is that it has limited sensitivity and specificity. Rapid diagnostic tests (RDTs) are thus an area of intense interest. However, poor sensitivity and specificity rates still limit conclusive identification. Test-it, TUBEX-TM, and Typhidot-M have all been investigated as potential serological tests. Studies have demonstrated that in Asia, where typhoid is common, a high disease load results in inaccurate and unreliable test findings. In contrast, studies done in the Philippines have shown high levels of sensitivity and specificity. The sensitivity and specificity of TUBEX were 78% and 87%, respectively, the highest of the three tests. These limitations are why the World Health Organization does not endorse commercial RDTs. Even though RDT uses serum and urine samples in addition to blood, it is still the gold standard since the susceptibility profile of the infected organisms cannot be determined from serologic-based tests.

MDR SALMONELLA TYPHI

The total MDR rate in India was at 65% between 1990 and 1992, with rates being higher in the northern (71%), central (55%), and southern (15%) regions. The widespread presence of multidrug-resistant bacteria (ofloxacin and ciprofloxacin) has been linked to a decline in the use of ampicillin, chloramphenicol, and cotrimoxazole and an increase in the use of fluoroquinolones. This has led to a decrease in ciprofloxacin susceptibility (DCS) and the emergence of resistance to cephalosporins.

International Journal For Advanced Research In Science & Technology
A peer reviewed international journal
www.ijarst.in
ISSN: 2457-0362

The prevalence of serious depression has decreased drastically since 2004 when it peaked at 26%.

Table 2

Burden of antimicrobial resistance rates reported in typhoidal Salmonella from Indian studies of past 15 years.

Antibiotic	Salmonella Typhi	Salmonella Paratyphi A
Ampicillin†	5–72%	0–74%
Chloramphenicol†	3–27%	0–23%
Cotrimoxazole†	2.3–35%	0–36%
Nalidixic acid	78–100%	63–100%
Ciprofloxacin‡	0–97%	0–100%
Ceftriaxone	0–4%	0–6%

Table 3. Antimicrobial resistance mechanisms reported in typhoidal Salmonella.

Antibiotic class	Resistance mechanism	AMR genes responsible	Ref.
ß-lactams (ampicillin)	Enzymatic hydrolysis	*bla* TEM , *bla* CTX-M , *bla* SHV	[30]
Chloramphenicol	Enzymatic hydrolysis	*cat*	[30]
Sulfonamides (trimethoprim/sulfamethoxazole)	Enzymatic hydrolysis	*dfr*A, *sul1* and *sul2*	[30]
Quinolones (nalidixic acid, ciprofloxacin, pefloxacin)	Drug target alterations (QRDR)	*gyr*A, *gyr*B, *par*C,*parE*	[31]
	Enzymatic hydrolysis (PMQR)	*qnr*A, *qnr*B, *qnr*S, *aac(6)-Ib-cr, qepA*	[32]
Cephalosporins (ceftriaxone, cefixime)	AmpC ß-lactamases ESBLs	*bla* CMY , *bla* FOX *bla* CTX-M-15	–
Macrolides (azithromycin)	Enzymatic hydrolysis overexpression of efflux pumps	*ereA*, *ereB*, *ermB*, *mefA*, *mphA*, *mphB* and *mphD*	[32–35]

A similar picture may be seen at Christian Medical College (CMC), Vellore, India, where the MDR is now below 1% (V. Balaji, Unpublished

International Journal For Advanced Research In Science & Technology
A peer reviewed international journal www.ijarst.in
ISSN: 2457-0362

Data), as it is in New Delhi and across the rest of India. In addition, a research conducted by the Indian Network for Surveillance of Antimicrobial Resistance between 2008 and 2010 found that there were less than 5% cases of MDR S. Typhi in India. Antibiotic resistance rates from Indian studies are summarized in Table 2. We have included the literature-documented antibiotic resistance mechanisms in S. Typhi in Table 3.

TYPHOID FEVER THERAPY: CHALLENGES IN CLINICAL PRACTICE

If antibiotic therapy begins shortly after the onset of symptoms, typhoid fever may respond well. Concerning trends include the emergence and survival of Salmonella typhi that is resistant to lower concentrations of fluoroquinolones, as well as treatment failures with azithromycin and NARST. Fever resolution is also slower and there is a higher risk of clinical and microbiological failure. Patients with mild cases of enteric fever due to MDR S. Typhi are often prescribed fluoroquinolones. Overuse of fluoroquinolones in primary care has contributed to the spread of germs in several Asian and African nations that are highly resistant to the medicines ciprofloxacin and ofloxacin. The gold standard for the treatment of typhoid fever.

Weight-based dose titrations are not possible since most of these formulations include azithromycin, although at subtherapeutic amounts. An analysis of 22 different Indian brands of FDCs consisting of azithromycin with ofloxacin or cefixime revealed that the dosage of azithromycin was 250 mg/tablet, despite the formulations having an adequate quantity of the fluoroquinolone or cephalosporin component. A daily consumption of 1200 milligrams (10 milligrams per kilogram of body weight) is recommended by the World Health Organization, thus this amount would be about similar to one-fifth of that amount. Administering five tablets of the aforementioned FDC to a person weighing 60 kilograms (130 pounds) would be dangerous due to the high pill load and poor adherence rates that would result.

NATURAL PRODUCTS IN TREATING TYPHOID FEVER

Treatment with medicinal plants is common because they are both efficient and economical, unlike conventional medical options. Plants include phytoconstituents with chemical properties similar to those of synthetic antibiotics. Due to reports of declining antibiotic potency in monotherapy, it is now more important than ever to evaluate plant biology. The holy basil plant Tulsi (Ocimum sanctum) has been shown to be very effective in killing S. Typhi [FL1]. In vitro research showed that chloramphenicol, trimethoprim, and O. sanctum leaf extract all worked together well against S. Typhi. Inhibitory activity against multidrug-resistant Staphylococcus typhi has been shown at an acetone mango leaf

International Journal For Advanced Research In Science & Technology
A peer reviewed international journal www.ijarst.in
ISSN: 2457-0362

extract concentration of 10-50 g/ml. The MIC for S. Typhi for a combination of Cymbogogon citratus leaf extract, Carica papaya leaf extract, and Zea mays silk was determined to be 0.02-0.06 g/ml by Nkuo-Akenji et al. According to the available literature, some leaf extracts have shown strong in vitro activity against S. Typhi. However, little research has been done on the human bioavailability, pharmacokinetics/pharmacodynamics, antibacterial interaction, or safety profile of these natural substances. Therefore, there is ongoing discussion on the most effective dosage for treating severe typhoid.

CONCLUSION

Although typhoid fever cases tend to be isolated incidents, the illness is nevertheless considered prevalent in a few regions. The disease has been almost eradicated in developed countries because to increased attention to sanitation, better personal hygiene, safer food and water, and widespread inoculation against Salmonella typhi. Patients with severe typhoid fever are given ceftriaxone intravenously (2 g/day) for 10-14 days, then azithromycin orally (20 mg/kg/day) for 7 days. Fluoroquinolones should not be given to patients with DCS S. Typhi-caused uncomplicated typhoid fever. A higher dose of ciprofloxacin (20 mg/kg daily) may be more effective in treating moderate cases of typhoid fever. However, fluoroquinolone use has been associated with prolonged fever, relapse, and fecal carriage. Therefore, azithromycin (20 mg/kg daily for 7 days) is recommended for treating mild cases. Considering the prevalence of S. Typhi strains resistant to fluoroquinolones and azithromycin, it is interesting to see a recent trend of diminishing numbers of multidrug-resistant Typhi Salmonella isolates in India.

REFERENCE

1. Micoli, F., Bagnoli, F., Rappuoli, R. et al. The role of vaccines in combatting antimicrobial resistance. Nat Rev Microbiol **19**, 287–302 (2021). https://doi.org/10.1038/s41579-020-00506-3
2. Cristina Masuet-Aumatell et.al **“**Typhoid fever infection – Antibiotic resistance and vaccination strategies: A narrative review” https://doi.org/10.1016/j.tmaid.2020.101946
3. Pietro Mastroeni et.al “Antibodies and Protection in Systemic Salmonella Infections: Do We Still Have More Questions than Answers?” DOI: https://doi.org/10.1128/IAI.00219-20
4. Sumitha Nayak **“**Typhoid Fever: Drug Resistance and Current Vaccine Recommendations”2019
5. Elin Näsström “Diagnosis Of Acute And Chronic Enteric Fever Using Metabolomics”

Department of Chemistry Umeå 2017

6. Liberati, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gotzsche, P.C.; Ioannidis, J.P.A.; Clarke, M.; Devereaux, P.J.; Kleijnen, J.; Moher, D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ 2009, 339, b2700
7. Bujang, M.A.; Adnan, T.H. Requirements for minimum sample size for sensitivity and specificity analysis. J. Clin. Diagnostic. Res. 2016, 10, YE01–YE06
8. Parry, C.M.; Wijedoru, L.; Arjyal, A.; Baker, S. The utility of diagnostic tests for enteric fever in endemic locations. *Expert Rev. Anti-Infect. Ther.* **2011**, *9*, 711–725.
9. Darton, T.C.; Baker, S.; Randall, A.; Dongol, S.; Karkey, A.; Voysey, M.; Carter, M.J.; Jones, C.; Trappl, K.; Pablo, J.; et al. Identification of novel serodiagnostic signatures of typhoid fever using a Salmonella proteome array. *Front. Microbiol.* **2017**
10. Singh, A.; Verma, H.N.; Arora, K. Surface plasmon resonance-based label-free detection of Salmonella using DNA self-assembly. *Appl. Biochem. Biotechnol.* **2014**, *175*, 1330–1343.
11. Chin, K.L.; Redhuan, N.E.M.; Balaram, P.; Phua, K.K.; Ong, E.B.B. Detection of salivary IgA antibodies against the HlyE antigen as a diagnosis of typhoid fever. *J. Clin. Diagnostic. Res.* **2016**, *10*, DM01–DM03
12. Ismail, A. New Advances in the Diagnosis of Typhoid and Detection of Typhoid Carriers. *Malays. J. Med. Sci.* **2000**, *7*, 3–8
13. Wijedoru, L.; Mallett, S.; Parry, C.M. Rapid diagnostic tests for typhoid and paratyphoid (enteric) fever. *Cochrane Database Syst. Rev.* **2017**, *2017*, CD008892.
14. Sharma, T.; Sharma, C.; Sankhyan, A.; Bedi, S.P.; Bhatnagar, S.; Khanna, N.; Gautam, V.; Sethi, S.; Vrati, S.; Tiwari, A. Serodiagnostic evaluation of recombinant CdtB of S. Typhi as a potential candidate for acute typhoid. *Immunol. Res.* **2018**, *66*, 503–512.
15. Zaka-ur-Rab, Z.; Abqari, S.; Shahab, T.; Islam, N.; Shukla, I. Evaluation of salivary anti-Salmonella typhi lipopolysaccharide IgA ELISA for serodiagnosis of typhoid fever in children. *Arch. Dis. Child.* **2012**, *97*, 236–238.