ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

A Review On Recent Research And Advancements In Typhoid Fever.

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ABSTRACT

All animals are at risk to infection with Salmonella, belonging to the family Enterobacteriaceae, a genus of gram-negative, motile, non-spore forming, facultative anaerobic bacilli. Salmonella is distinguished into 2,200 serotypes on the basis of differences in capsular, somatic and flagellar antigens. Salmonella typhoid is the cause of one of the most dreadful type of enteric typhoid fever. The host for this pathogen is only humans. This infection is spread mainly by contaminated food and water. This infection occurs via oral route, usually when food or water is contaminated by sewage. This review paper summarizes the literature work done in epidemiology of typhoid, pathogenesis of Salmonella, its infection chain, symptoms, diagnosis and treatment of typhoid. Recent advancement for the treatment of typhoid has also been focused.

Keywords: Salmonella, Vaccination, Pathogenesis, Typhoid fever, Epidemiology.

https://doi.org/10.33887/rjpbcs/2021.12.2.15

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ISSN: 0975-8585

INTRODUCTION

Typhoid fever is a bacterial infection, mainly caused by *Salmonella enterica* serotype *typhi*, cause for more than 33 million cases annually and more than 500,000 deaths. *Salmonella enterica* can incorporate various infectious agents in to homeothermic animals [1]. Typhiod is a type of fever and still abide to be a reason for ill health in many developing countries where there's poor standard of personal hygiene, poor sanitation and contaminated water and food. It is endemic in many parts of the world and is a cause of morbidity and mortality worldwide [2]. The transmission of the bacteria occurs by food and drinking water that has been contaminated or by close contact with someone infected.

The study intends to provide reader some knowledge about the infection, the diagnostic techniques, the multi-drug resistant nature of *Salmonella* and the vaccines used for typhoid and the recent advances in the topic concerned. The MDR strains of salmonella has increased the need for efficacious drug which can reduce the incidences of typhoid fever.

EPIDEMIOLOGY

This bacterial disease is a multisystemic illness, encountered worldwide, but mostly found in those counties where the sanitization condition is poor. As per a report from US Centers for Disease Control and Prevention, there are approximate 21.6 million typhoid cases yearly [3]. This infection is assessed to cause 21 million diseases and 200,000 passings yearly, overall [4]. Likewise, it was seen that in the world overall up to 27 million contaminations happen on a yearly premise, with generally among kids younger than five years [5]. Youngsters are at higher danger because of an absence of procured insusceptibility.

This bacterial sickness was found to have happened in numerous pieces of the world like Thailand, India, Spain, Australia, Central in South America, Zimbabwe, Turkey, Nigeria, Florida and furthermore been accounted for to come to pass in Vietnam, Bangladesh, UK, China and Netherlands [5].

The largest typhiod outbreak in India were reported in "SANGLI" from December 1975 to February 1976 and found to be endemic. The disease caused by *S.typhi* and *S. paratyphi* in an overall ratio of 10 to 1 [3]. The case fatality rate was found to vary between 1.1-2.5 percentile. The prevalence was found to be 88 cases/lac population. In the latest assessment it was discovered that around, 11 and 21 million cases and 128,000 to 161,000 typhoid-related passings happen yearly overall [WHO].

PATHOGENESIS

The causative life form of typhoid is *S. paratyphi* and has three subtypes – *S. paratyphi* C, B, and A.

The hatching time of this sickness is around 10-14 days. This fever can be serious in immunocompromised patients, for example, those with HIV or patients with intestinal sickness and sickle cell iron deficiency. The virulence of *Salmonella* is caused by typhoid toxin. The entry of bacteria is mainly through contaminated food and water which then invade the small intestinal mucosa. There, they are taken up by macrophages of payer patches and survive and spread via lymphatics while inside the macrophages. Microorganisms can attack the reticuloendothelial framework through both the lymphatic framework and circulation system and can attack other various organs, most ordinarily nerve bladder, liver, spleen, bone marrow and histiocytic granulomas, known as typhoid nodules [6]. Bacteria that enter are phagocytosed by macrophages and monocytes in the reticuloendothelial framework called primary bacteremia. This phase is usually asymptomatic. Microorganisms in the reticuloendothelial framework when returning to the circulation system are known as secondary bacteremia. The first week can be seen as an elevation of body temperature. The second week marked by red spots on body and enlargement of the spleen with abdominal pain. Finally the third week, necrosis of payer patches occur, if the disease remains untreated for longer time perforation and bleeding could occur and can lead to death also.

One of the harmfulness components of *S. typhi* is Vi capsular polysaccharide (Vi). It shapes a case around *S. typhi* and it is shed by microbes while connecting with the host cell [7]. Vi capsular polysaccharide contains a straight polymer of α1, 4,2-N-acetyl galacturonic acid. Virulence of typhoid is due to typhoid toxin discovered by the genomic analysis of *S. typhi* to that of *S. typhimurium* [7]. Vi capsular polysaccharide

encodes by via locus which contains genes for synthesis and export of Vi capsule. It is located in *Salmonella* 'Pathogenicity Island' [8]. 'Salmonella Pathogenicity Island' is located on pathogenic bacterial chromosomes and has distinct genetic components [6]. These SPI have a different base composition from the core genome. Till now 15 SPIs have been found in *S. enterica* serovar *typhi* [6]. Virulence factors of *Salmonella*, such as, toxin genes, invasion, and adhesion are clustered in the SPI [6]. Mapping of sixty virulence genes is done and they all have different functions [6]. Two most studied 'Salmonella Pathogenicity Island' are SPI-1 and SP1-2 found to be responsible for pathogenicity and encode proteins for type III secretion system (T3SS). Another name for typhoid toxin is Salmonella cytolethal distending toxin (S-CDT) [6]. Bacterial AB toxin comprising of "A" enzymatic subunit and "B" receptor restricting subunit. Typhoid poison has a place with this group of AB toxins (A2B5 poison) have a pentameric ring [6]. Typhoid toxin has a DNAse activity which causes damage to the DNA of eukaryotic cells [6]. Two subunits: A subunit contains PltA (pertussis-like poison A), CdtB (cytolethal distending poison B) and PltB (pertussis-like poison B) alluded to as B subunits. PltA, CdtB and PltB structure complex for toxicity [6].

INFECTION CHAIN

Reservoir:

The reservoir of *Salmonella typhi* is mainly Humans and rarely domestic animals [9].

Portal of Exit:

Major portal of exit is faeces but urine shedding is also reported [9].

Mode of Transmission:

Transmission of *S. typhi* and *S. paratyphi* can happen through a two-cycle naimed as short cycle and long cycle. In short cycle pollution of water and food is by poor disinfection and cleanliness rate and in the long pattern of transmission defilement of the climate like the debasement of water supplies and inadequate treatment of sewage water, so lead to devoured by individuals and sullied groundwater, and so on [10].

Portal of Entry:

The mouth is the gateway of passage for *Salmonella typhi* infection by taking contaminated water or food. so, with an increase in ingested dose, the risk for infection increase and incubation period get shorten [11].

SYMPTOMS

After a person gets infected with typhoid by *Salmonella typhi*, the symptoms may develop after 1 or 2 weeks. The early symptoms include Fever, weakness and fatigue, headache, dry cough, etc. Cases of *S. typhi* sepsis and rhabdomyolysis with acute renal failure were also observed in some patients [12] and also on ileal perforation in children [13] is seen. No recent advancements in symptoms observed during recent years.
The detailed review for the symptoms week wise is give below -:

1st week

The first week of illness comes with the gastrointestinal manifestation. This includes abdominal pain and may be sensitivity in pain and in some cases it comes with choledocholithiasis; the right upper quadrant pain. Monocytic infiltration [14] inflames Payer patches and narrows the bowel lumen, thus leading to constipation that lasts till the duration of the illness. The patient then expresses weakness along with cough without mucus, mild headache and increasingly stuporous malaise. During the end of 1st week of illness, the temperature may rise up to 103-104°C. Some patients may be seen with salmon-rose coloured spots.

2nd week

The signs and symptoms mentioned above become more effective during the 2nd week. The abdomen becomes distened with enlarged spleen known as splenomegaly. Relatively slow heart rate and dicrotic pulse may be observed. With this pain and rashes all over the body parts can be seen. The other diseases also include haemorrhage in intestine or perforation, pneumonia, myocarditis, hepatitis, acute cholecystis and meningitis [16].

3rd week

At the start of the third week, the contition of the individual grows more toxic with notable weight loss. The conjunctives are been infected that is seen in the outer membrane of eye with some inflammation. Abdominal distension becomes severe. In some cases, some neuropsychiatric disorders of typhoid such as delirium, semi-coma, coma, meningitis, convulsions, generalized myoclonus, focal neurological deficits and transient Parkinsonism are seen.

4th week

If the patient survives till 4th week of illness, temperature decreases gradually until in a week or so, returns to normal baseline level. May be the fever has subsided but signs and symptoms may appear. A person needs to consult a doctor when he gets temperature raise constantly (100-104°C) for a week or more so or find symptoms for diarrhoea or constipation, dry cough and body ache [17]. The signs and symptoms develop about one to three weeks after someone exposed to the bacteria and continue for about four to six weeks.

DIAGNOSTICS TESTS

Conventional tests:

Even now the diagnosis for typhoid is done by the process of blood culture and antibody detection through WIDAL test. Some other processes include isolation of *Salmonella typhi* that is done with the culture of bone marrow or a combination of specimens from blood, stool or urine. But these methods are not fully trusted and not available in all areas.

WIDAL test:

It is an indirect agglutination antibody test against the O and H antigens of the bacteria of typhoid fever (*Salmonella typhi*). The typhoid fever bacteria have two types of antibodies against which measurements can be done; those are flagellar (H) and somatic (O). Both the antibodies H and O have their own preferences during detection which leads to different conditions. When the antibody O goes higher in first stages and decreases in later stages eventually to nonexistence of this, it is known to be as acute infection and when the antibody H goes higher in later stages and stays for a longer period of time thus they identify enteric fever in our body. This is how both the antigens have their importance in detection in case of typhoid. Accuracy of WIDAL test is seen to be 67% when done on or after 5 days.

Nucleic acid amplification test:

For the detection of any particular nucleic acid sequence this technique is used. For the diagnosis of enteric fever, polymerase chain reaction (PCR) and real-time PCR are conducted. This technique can amplify DNA from dead or unculturable bacteria that helps to identify even the poor cultured positivity because of its pre-treatment with the antimicrobials. [17, 19].

ADVANCEMENTS IN TYPHOID DIAGNOSIS

An ideal diagnostic test should be rapid, specific as well as sensitive so that prompt and effectively management of typhoid fever can be possible to control the deaths caused by this disease. The conventional processes were used to take longer time and were not giving proper results, therefore some new specific antigens and new diagnostic techniques are being used now-a-days. Some of these antigenic components may

contain compounds like outer membrane proteins, lipopolysaccharides and heat shock proteins. The new tests developed include ELISA, TUBEX and TYPHIDOT.

RECENT STUDIES ABOUT PERFORMANCE OF DIAGNOSTIC TESTS:

These are the sensitivity results obtained from different tests at a specificity of ≥0.93 (Table 1):

Anti LPS IgM ELISA – 0.75
Anti LPS IgG ELISA – 0.55
Anti LPS IgA ELISA – 0.52
Anti flagellum IgG ELISA – 0.28
WIDAL TO – 0.47
WIDAL TH – 0.32

Anti-serotype typhi IgM dipstick assay – 0.77

For TUBEX results were obtained as 0.87 sensitivity and 0.76 specificity i.e it is >0.90

For a single acute phase serum sample, it was observed that The serological assays (based on the detection of IgM antibodies against either serotype Typhi LPS (ELISA) or whole bacteria) has a much more higher sensitivity than the WIDAL TO test [19]. A study was conducted taking 177 febrile patients where the evaluation of four recent antibody-detection kits for typhoid fever was done, in 75 of whom Salmonella enterica serotype typhi grew. TUBEX had the highest sensitivity of 94.7% and specificity of 80.4% [20]. Typhidot gave the mst poor performance[21], although anathor study by Membrebe and Chua(in the Philippines) had found very similar results i.e.72% sensitivity; 52% specificity.

Table 1. List of diagnostic test to identify *Salmonellae*

Tests	References
Widal	Widal, 1896
Typhidot	Dutta *et al.,*2006
Tubex tests	Dutta *et al.,* 2006
Real time PCR	Zhou and Pollard, 2010

ELISA test:

The ELISA test or IgM ELISA test is an enzyme linked immunosorbent assay (ELISA). This test detects only the IgM class antibodies of Salmonella typhi in human serum or plasma. This technique is helpful in showing that the person contaminated with typhoid has higher levels of immunoglobulin G (IgG), IgA and IgM than normal or healthy person or from febrile nontyphoidal groups.

TUBEX test:

This is a test by IDL Biotech that is a kind of a process of 5 minutes semi quantitative colorimetric test to detect the presence of *Salmonella typhi*. This test detects the presence of anti-salmonella O9 antibodies from a patient's serum. This is so because these antibodies have the ability to form the binding between the indicator antibodies bound particle and the magnetic antigen bound particle. Detection of specified soluble O9 lipopolysaccharides in antigen-spiked buffer is also possible by the ability of these antigen to perform the same binding between these particles.

TYPHIDOT test:

Typhidot is a kind of test that consists of a dot ELISA kit. The kit acts against the outer membrane protein of the bacteria and is helpful in detecting the IgM and IgG antibodies. The best thing is that the positive result can be obtained within just 2 to 3 days and an extra advantage is that, it can separately identify IgM and IgG antibodies. The basics of the test is based on the reaction of IgM and IgG antibodies towards a specific 50Kd OMP antigen, which is saturated on nitrocellulose strips. Notable point here is that the recent infection is shown by IgM whereas remote infection is marked out by IgG.

RECENTLY DEVELOPED DIAGNOSTIC TESTS FOR TYPHOID:

The Loop-Mediated Isothermal Amplification test (LAMP):

The contemporary LAMP test of DNA was correlate with real time quantitative polymerase chain reaction (qPCR) which manifested better performance, good quality, temperature stability around specific conditions like temperature 57-67°C and pH unit of (7.3-9.3). The test can be achieved with less preparations regarding to other tests. The extra biological materials present in the fluid cannot do any harm either to the sensitivity or to the specificity [22, 23].

Typhoid paratyphoid test (TPTest):

It detects the responses of immunoglobulin A that is specific to *Salmonella* in lymphocyte culture supernatant. This can be performed in the following three cases of patients: patients with suspected enteric fevers, patients with other illnesses and healthy controls. The simplified form of this test has been developed and used in less improvised laboratories of developing countries [24] and is ideal for them to adopt.

Gas chromatography with time-of-flight mass spectrometry:

This is a two-dimensional technique that involves the investigation of metabolite signals associated with enteric fevers, and is performed on plasma taken from *S. Typhi* and *S. Paratyphi* A infected patients and asymptomatic controls. A study was conducted where this recognised 695 individuals with high metabolic activity. An examined pattern was applied that showed three categories of highly activeand indicative metabolite profiles. This takes us to a conclusion that is more specific, this system acts with a total of six metabolites that act as serovar-specific systemic biomarkers. Then these biomarkers accurately detected the cause [25] for typhoid.

MDR STRAINS OF TYPHOID:

Multidrug resistant bacteria are micro-organisms that have developed resistance over time and are no longer susceptible to the antibiotics that it was sensitive to before. Due to the extensive and inappropriate use of antibiotics, along with unsanitary conditions the rise of multidrug resistant pathogens has occurred. Multidrug resistance in bacteria may occur in one of two ways. 1) The bacteria accumulate various genes which each code for resistance to a single drug. This usually occurs due to the resistance (R) plasmid; 2) Genes coding for multidrug efflux pumps can have an increased expression which cause multiple resistance against drugs. MDR typhoid is defined as typhoid strains that have developed resistance to the 3 first line antibiotics that has been used to treat typhoid, chloramphenicol, ampicillin, and cotrimoxazole. These MDR typhoid strains first appeared in the 1970s. Since then there have been various other strains which have emerged that have become resistant to second and third generation antibiotics. A strain of typhoid known as an XDR (extensively drug resistant) had been identified which has resistance to chloramphenicol, ampicillin, cotrimoxazole, streptomycin, fluoroquinolones and third-generation cephalosporins. XDR strains can lead to disease outbreaks that are difficult to deal with as treating diseases caused by XDR organisms requires special treatments. Orally administered azithromycin can be used to treat diseases caused by XDR strains. MDR strains like H58 are identified in parts of Asia, sub-Saharan Africa and the most recently, Latin America. The H58 strain is considered globally dominant strain of MDR typhoid. *S.Typhi* CT58 consists of a transferrable R plasmid known as pHCM1 and it encodes the resistance genes to all first-line antibiotics which are used for the treatment of typhoid fever. The pHCM1 plasmid encodes genes for the antibiotics such as *dhfr1b* (trimethoprim), *sul2* (sulphonamide), *catI* (chloramphenicol), *bla* (TEM-1; ampicillin), *tetA/tetC* (tetracyclines) and *strAB* (streptomycin) [26].

RECENT RESEARCH:

Genome sequencing of the MDR strain of typhoid, known as CT18, indicates that it harbours a transferrable R plasmid known as pHCM1. This plasmid gives resistance conferring genes for the first-line of antibiotics used in treatment of typhoid fever [26]. *S. typhi* can transform from Multi-drug resistant to extremely drug resistant by acquiring a plasmid, which gives it resistance against various antibiotics. The XDR variant of the H58 strain is said to harbour an *IncY* plasmid which provides it resistance against

fluoroquinolone. It is also said to contain the CTX-M-15 gene *bla* which confers it resistance against ceftriaxone [27].

DRUGS USED AGAINST TYPHOID:

Chloramphenicol:

It was one of the first drugs that was being administered for the treatment of typhoid. It was being administered orally. The use of chloramphenicol has reduced because resistance towards has been developed by many strains of the organism.

Ampicillin and co-trimoxazole:

They were used as an alternative to chloramphenicol in the treatment of enteric fever which started in the early 1970s. Ampicillin could be used as a safe and effective alternative to chloramphenicol. It was used for the treatment of cases as well as carriers. It is safe and can be used by people of pediatric and pregnancy age groups and can be administered via oral and parenteral routes [28].

Amoxicillin:

It is another drug that is used to treat typhoid. Amoxicillin trihydrate is an antibiotic of the penicillin group. It is structurally similar to Ampicillin but it is more potent than ampicillin in vitro against *S. typhi*. It is mainly used for the treatment of chronic carriers of typhoid. Oral amoxicillin is well tolerated by patients. It is better absorbed than ampicillin [29].

Fluoroquinolones:

Tgey belong to a family of antibiotic drugs that are usually used for the treatment different of diseases. They are not significantly better than chloramphenicol or azithromycin except for the fact that Fluoroquinolones have less of a clinical failure [30].

Bactrim:

It is a combination of two antibiotics which are sulfamethoxazole and trimethoprim. Bactrim comes in tablets that's is used to treat infections such as traveller's diarrhoea, shigellosis etc. It is used against drug resistant bacteria.

RECENT RESEARCH:

S. typhi shows major susceptibility to drugs such as ceftriaxone and cefixime. Antibiotics such as ampicillin, co-trimoxazole and chloramphenicol are also in use for the treatment against typhoid fever. Due to antibiotic resistance combination of antibiotics are also being used to treat the disease. Antibiotics such as ofloxacin or azithromycin are added to cefixime are administered to patients who do not show any clinical improvement after administration of the first antibiotic [31]. Studies show the reduction in mortality of patients with severe typhoid fever treated with chloramphenicol and dexamethasone in comparison to patients treated with chloramphenicol. Corticosteroids are administered to patients suffering from severe toxaemia and fever. They cause a major response in the patients with sepsis [32]. Antimicrobial tests show that azithromycin-loaded poly(lactide-co-glycolide) nanoparticles are more effective than pure azithromycin against *S. typhi* with the nanoparticles showing equal antibacterial effect at 1/8th concentration of the intact drug [33]. Antibacterial effect of Mn_3O_4 nanoparticle is nearly half to that of standard ciprofloxacin which is effectively used for the prevention of typhoid fever. It can be used to treat health complications caused by *S. typhi* [34].

VACCINATION:

The first licensed vaccine was Vi-polysaccharide in 1994 in the United States, after that many other vaccines such as Ty21a, a live attenuated was licensed in 1983 in Europe [35]. But these vaccines had various limitations, which included their impossibility of widespread use in prevalent countries moreover were not

suggested for administration in kids that are below or >2 years of age. Typbar TCV, fabricated in Bharat Biotech International Limited is a typhoid conjugated vaccine accepted by WHO in January 2018. It can be used for an individual whose age is in the range of 6 months to 45 years [36]. First-generation vaccine is existing since the late 19th century but reactogenicity in the recipients of these vaccines led to its withdrawal [37]. Vaccines of second-generation are approved for use against typhoid and are used since the late 1980s, an oral live attenuated vaccine (Ty21a typhoid vaccine) and an injectable subunit Vi-capsular polysaccharide vaccine are the two types of second-generation vaccine. But the need for better vaccines continues as these vaccines have some limitations and are not used for the Expanded Programme on Immunizations (EPI) in the typhoid-prevalent country's schedules. The live attenuated vaccine, Ty21a is a capsulated formulation so cannot be used for children <5 years of age also revaccination is advised every 5 years [35]. Vi polysaccharide vaccine responds poorly in the case of children < 2 years of age. Moreover, it does not develop any immune memory. Revaccination every 3 years is recommended [38]. Typhoid conjugate vaccines are being made by the Vi polysaccharide vaccines, enhancements in these vaccines are made by conjugating the polysaccharide with a protein carrier due to this a change occurs in polysaccharide's antigenic properties making it T-cell dependent antigen, which evokes an immunogenic response to immunization in addition to that it gives an extended period of protection [39]. Different Typhoid conjugate vaccines are now manufactured and licensed and are available such as PedaTyph by Biomed India, Typbar TCV by Bharat Biotech International Limited India, Typhoid Vi Capsular Polysaccharide Tetanus Toxoid Conjugate Vaccine by M/s Cadila Healthcare Limited, etc. [40]. As a substitute to TCVs in vaccination, next-generation vaccines are developed which are Protein Capsular Matrix Vaccine, Generalized Modules of Membrane Antigens, and Protein-based Subunit Vaccine. In current times, the problem caused by both *Salmonella paratyphi* accompanied by *S. typhi* has increased noticeably, especially in Asia. As a result, interest in A bivalent vaccine has increased [41]. Also, an increase in invasive nontyphoidal *Salmonella* (iNTS) disease is a significant public concern, it is triggered by *Salmonella enterica* serovar Enteritidis and *Salmonella enterica* serovar *typhimurium*. It is endemic in sub-Saharan Africa. Approximately 600000 to 3.4 million cases of iNTS disease are noticed each year [42]. Consequently, a trivalent vaccine for *S. Typhimurium*, *S. Enteritidis*, and *S. typhi* is a rational move that can be taken to regulate enteric fever cases in sub-Saharan Africa.

RECENT ADVANCEMENTS:

Leaf extract of *Moringa oleifera* and its antimicrobial effect with typhoid vaccine in immunized mice:

In this work, *Moringa oleifera* (MO), a member of the Moringaceae family also referred to as 'Horse radish' or 'Drumstick' was evaluated for a possible adjuvant property for typhoid vaccines [43]. Moringa oleifera ester leaf extract was shown to possess upregulated the immuno-protective effect of a respiratory syncytial virus vaccine when administered together with it [44]. Here, they evaluated the synergistic effect of MO leaves extract when co-administered with typhoid fever vaccine and their findings revealed that MO extract demonstrates a promising antimicrobial effect when combined with ST vaccine and may be evaluated for adjuvant properties for the vaccine given conferring a longer immunity.

Assessment of prophylactic potential of cytolethal distending toxin B (CdtB) subunit of typhoid toxin against Typhoid fever:

In this study, they used a mouse model to show the immunoprotective potential of the CdtB toxin. This toxin showed activity like deoxyribonuclease causing DNA damage by promoting cell cycle arrest and also cellular distention which results in apoptosis of all the infected cells [45, 46, 47, 48]. The link of life-threatening symptomatology of typhoid with the nano-bound form of typhoid toxin gives us an idea for some strong pre-emptive strategy with regard to typhoid fever.

The inference that may be made from the study is that CdtB subunit of typhoid toxin showed immunoprotective response, which was clearly shown by the immune reaction of the cells and also by the antibody titer being developed against the disease [49].

Comparing the trial of mono versus dual antibiotic therapy for Typhoid Fever in adults:

In this study, they combined two antibiotics, namely cephalosporin and azithromycin, and both of these antibiotics act synergistically on the two niches which are tenanted by the bacteria i.e. the intra and the

extra-cellular compartments. A study which was conducted among the Israeli travellers who were coming back from Nepal in 2009 after the outburst of *S. Paratyphi* A showed that monotherapy with intravenous ceftriaxone was very less effective as compared to dual therapy with azithromycin and ceftriaxone, particularly in terms of defervescence, as fever clearance time was condensed by more than 5% in patients who were subjected by dual therapy of azithromycin and ceftriaxone.

The conclusion they made from the study showed that dual therapy is more effective and promising than monotherapy in terms of bacteraemia elimination and time to defervescence.

Transcutaneous vaccination with conjugate typhoid vaccine vi-dt induces memory, mucosal and systemic anti-polysaccharide responses:

Systemic and mucosal immune responses can be induced by transcutaneous vaccination. In the present study, they vaccinated mice transcutaneously with Vi (virulence antigen) polysaccharide of S. typhi either in conjugated or unconjugated form. They showed that presenting the virulence antigen polysaccharide during a nonconjugate versus conjugate form derived in different serumn IgG responses but high IgG memory responses, serum and lamina propria lymphocyte IgA anti- virulence antigen responses. They concluded that vaccination of a conjugate typhoid vaccine transcutaneously can bring about mucosal, systemic and memory B-cell anti-Vi polysaccharide responses [50].

Antibacterial activity of plants and herbal medicine:

Testing of extracts of *T. mollis*, *D. batocana* and *A. venosum* against bacteria responsible for an infectious illness that justify them as a source of drugs. Different concentration of plant's extracts was tested. *S. typhi* showed great sensitivity against the excerpt of *D. batocana*. In the case of the extract of *A. venosum* whatever may be the dilution, *S. typhi* showed sensitivity against it [51].

STIV, an outer membrane protein of *Salmonella typhi* for vaccine development for fever caused by *S. typhi* and *S. paratyphi*:

The study showed that STIV, a highly preserved gene in *Salmonella* serovars triggers both innate and adaptive immunity of the host organism and offers protection from *S. paratyphi* and *S. typhi*. Immunization by rSTIV results in the production of antigen-specific antibody isotypes in mice. Great levels of different antibodies such as IgG1, IgG3, IgA, and IgG2b were detected in the antisera of the mouse by ELISA. The IgG2 antibody of the mouse shows alike activities as antibody IgG1 present in humans which encourages immune effector functions and ADCC (Antibody-dependent cellular cytotoxicity).

The study presented that the rSTIV (recombinant protein STIV) present on the outer membrane of *S. typhi* stimulates high serum titers of different subtypes of immunoglobulin. STIV antibodies opsonize *S. typhi* and *S. paratyphi* A to endorse complement-mediated lysis and antibody-dependent cellular cytotoxicity. Immunization with the protein rSTIV also results in robust cell-mediated immunity, with antigen-specific T-cell proliferation accompanied with cytotoxic T-lymphocyte response. In the end, the mice immunized with rSTIV were found to be protected against *S. paratyphi* and *S. typhi*. The results showed the capability of rSTIV as a new vaccine developer for typhoid fever. [52]

Multidrug resistance proteins identification for the production of vaccine for *Salmonella Typhi*:

They projected 9 epitopes of T-cell - VKWMYAIEA (MdtH), FGVANAISI (EmrB), WDRTNSHKL (MdtA), YVEQLGVTG (MdtG), LAHTNTVTL (MdtL), MVNSQVKQA and YQGGMVNSQ (TolC), YVSRRAVQP (EmrA), and FLRNIPTAI (MdtB) which were proficient enough of provoking mutually adaptive and humoral immune responses. These epitopes of T- cell precisely bind to HLA alleles - DRB1*0401 and DRB1*0101. As a result, EmrA, TolC, and MdtA were reported to be the most appropriate candidates for vaccine development for typhoid fever. The study was proved to be useful for developing a peptide-based vaccine for the treatment and prevention of typhoid fever [53].

CONCLUSION

Over the passage of time, with vaccination and improved public hygiene and sanitization, the cases of typhoid has reduced significantly and is almost rare to find. The need for a better typhoid vaccine with longer impact still continues Today, typhoid fever is treatable and its possible that it will soon be eliminated from the world. With improvement in sanitation, hygiene, diagnosis together has improved the result of typhoid. However, MDRST reports is still a cause of concern. With the advancement in biotechnology and various high-throughput techniques research is on its way to eradicate this disease in future.

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