International Journal of Biosciences (IJB)
ISSN: 2220-6655 (Print) 2222-5234 (Online)
Vol. 2, No. 3, p. 110-120, 2012
http://www.innspub.net

REVIEW PAPER OPEN ACCESS

Recent trends in typhoid research- A Review

Kishwar Hayat Khan*

Medical Biotechnology Division, School of Biosciences and Technology, VIT University, Vellore-632014, Tamil Nadu, India

Received: 25 January 2012
Revised: 12 February 2012
Accepted: 14 February 2012

Key words: Typhoid, genes for infection, nanotechnology, vaccination, herbal drugs.

Abstract

Typhoid fever is an infectious disease caused by salmonella enterica serotype typhi. It is a disease of global distribution. In India and Bangladesh, the highest incidence has been observed among children aged less than five years, while in Vietnam, the peak incidence has been found to occur in children in between five to nine years. Prevention is the present requirement for the people of this young age group. This article is totally based on literature survey and is the updated work of the published review article of the corresponding author. This article discusses and summarizes important work in literature in response to the epidemiology, symptoms and diagnosis of typhoid. Much stress has been given to salmonella and immune system and study was done on infection of salmonella to various organs. Genes involved during infection and typhoid related to nanotechnology was also described in detail. In this communication the authors reviewed the vaccination used against typhoid fever. Much focused has been given for the plants products and herbal drugs to minimize pathogenicity caused by salmonellae. This article will be very helpful for those researchers working in the field of infectious diseases caused by salmonellae species.

*Corresponding Author: Kishwar Hayat Khan ✉ hamkishwar191@yahoo.co.in

Introduction

Enteric fever is caused by infection with Salmonella enterica serotype *Salmonella typhi* (*S.typhi*) or Salmonella enterica serotype paratyphi (*S.paratyphi).* Globally, up to 27 million infections occur per year, with over $2X10^5$ attributable deaths annually, predominantly among children under the age of five years (Clark *et al.,* 2010). Typhoid fever is a bacterial disease, caused by *S. typhi* and is transmitted through the ingestion of food or drinks contaminated by the faeces or urine of infected people as reported by this corresponding author in his research article (Khan, 2010a). This fever is endemic in many developing countries and remains a substantial public health problem despite recent development in water and sanitation (Lauria *et al.,* 2009).

S. typhi is the causative organism for human typhoid is a worldwide problem as described by this corresponding author also (Khan, 2010b). Multi drug resistant typhoid fever was also reported by the researchers (Zaki and Karande, 2011). Typhoid is characterized by high fever, diarrhea and headache. This article discusses and summarizes important work in literature related to typhoid epidemiology and its symptoms. The authors also focused on various ways to diagnose typhoid. Work related with salmonellae and immune systems were also discussed. Infection of salmonellae to various organs like liver, gall bladder, spleen etc was explained in details. The author also explained the treatment of this disease and also enlisted a number of antibiotics and drugs that has been used so far. More stress was given on the vaccination against typhoid. Due to the emergence of multi drug resistant salmonellae and lack of proper vaccine the author surveyed the plants product that can help to combat the infection of salmonellae. Genes involved during infection and pathogenicity of *S.typhi* was also highlighted. Moreover typhoid related to nanotechnology was also described in detail. This article will be very helpful for the researchers, working in the field of infectious disease caused by salmonellae. The main aim of writing this article is to create awareness among the researchers to make a better therapy against this disease which will finally eradicate typhoid.

Epidemiology

Typhoid fever occurred in many parts of the world like Far East Asia, Middle East, Central in South America, Zimbabwe, Australia, West French Guiana, Thailand, Ivory coast, India, Florida, Spain, Turkey and Nigeria as reported by the this corresponding author (Khan et al., 2008). Typhoid has been also reported to emerge in Vietnam (Holt *et al.,* 2011), China (Dong *et al.,* 2010), Bangladesh (Naheed *et al.,* 2010), Indonesia (Lauria *et al.,* 2009), Netherland (Van Wolfswinkel *et al.,* 2009) and UK (Clark *et al.,* 2010).

Symptoms

Typhoid is characterized by high fever, chill, nausea, headaches, malaise and sometimes with delirium (Cook *et al.,* 2008). The other complications include intestinal hemorrhage or perforation, pneumonia, myocarditis, hepatitis, acute cholecystitis and meningitis (Sulaiman and Sarwari, 2007). Early small bowel perforation and cochleovestibular impairment as rare complications of typhoid fever had been also reported (Van Wolfswinkel *et al.,* 2009). Other symptoms also include diarrhoea, abdominal pain, vomiting, myalgia, cough, weight loss, constipation, abdominal tenderness, palpable spleen, palpable liver and rose spots (Clark *et al.,* 2010). Reports were also made regarding *S. typhi* sepsis and rhabdomyolysis with acute renal failure (Jhawar *et al.,* 2010) and also on ileal perforation in children (Osifo and Ogiemwonyi, 2010). A number of symptoms of typhoid were also reported by this corresponding author in his review article on typhoid (Khan *et al.,* 2008).

Diagnostic test for typhoid

The diagnosis of disease requires laboratory testing. Blood and bone marrow were used for the isolation of the pathogen. Isolation of the pathogen from these

specimens is the most reliable means for the confirmation of the disease (Abdoel *et al.,* 2007). Attempts were made regarding the serodiagnosis of typhoid fever since the late 19th century when Widal demonstrated that the serum of patients with typhoid fever agglutinated typhoid bacilli (Widal, 1896). A number of new serologic tests for typhoid fever have been introduced which detect antibodies (IgG or IgM) to various purified antigens of *S. typhi*. A variety of test that detect salmonellae has been listed in the Table 1.

Table 1. List of diagnostic test to identify salmonellae

Test	References
Widal	Widal, 1896.
Typhidot	Dutta *et al.,* 2006.
Tubex tests	Dutta *et al.,* 2006.
Latex agglutination test	Abdoel *et al.,* 2007.
Dipstick assay	Pastoor *et al.,* 2008.
Immunochromatographic lateral flow assay	Pastoor *et al.,* 2008.
Real time PCR	Zhou and Pollard, 2010.
Dot enzyme immunoassay	Jackson *et al.,* 1995.

Salmonella and immune system

The immune system is a unique and effective defense mechanism to protect the body from foreign microorganisms. During the initial infection local (particularly secretary antibodies) and systemic immune responses constitute the main host defense. An effective immune response may stop bacteria from reaching the lamina propria which will block the subsequent stages of the infection process. Immune responses against circulating extracellular bacteria encompass anti-capsular virulence (Vi), anti-lipopolysaccharide (O) and anti-flagella (H) antibodies. However, the acquired immune response stimulated by typhoid pathogen may not result in protection from relapse and re-infections.

Global expression profiles of *typhi* grown *in vitro* and within macrophages at different time points were obtained and compared. Virulence factors, such as the SPI-1- and SPI-2-encoded type III secretion systems, were found to be expressed as predicted during infection by Salmonella. *S.typhi* inside macrophages exhibited elivated expression of genes encoding resistance to antimicrobial peptides (Faucher *et al.,* 2006). Intracellular survival of *S.typhi* in human macrophages is independent of Salmonella pathogenicity island (SPI)-2 have been reported (Forest *et al.,* 2010). Macrophage polarization and bacterial infection has also been reported (Mège *et al.,* 2011).

Infection of salmonellae to various organs

The authors described the spread and movement of salmonellae to various organs. Gallbladder epithelial cells acts as a novel niche for *in vivo* replication of Salmonella leading to the pathogenesis in the gallbladder during typhoid fever. Salmonella related to gall bladder cancer has been also reported by the researchers. Chronic typhoid carriage (persistence), production of mediators of chronic inflammation and a genotoxic toxin were also known for this bacterium (Nath *et al.,* 2010). Gallstones have been reported to play a significant role in Salmonella spp. gallbladder colonization and carriage (Crawford *et al.,* 2010).

Reports were also made regarding the hepatic involvement with typhoid and elevated serum bilirubin, and serum alanine transaminase levels (Shetty *et al.,* 1999). Spleen is the secondary lymphoid organ of the body. It plays important role in immune system. Spontaneous spleen rupture and spleenic abcess have also been seen in this fever. This bacterium is also able to persist in its host causing a chronic disease by colonizing the spleen and liver (Villarreal *et al.,* 2011). The colonization and growth within the spleen and liver by *S. typhimurium* has been also reported (Watson and Holden, 2010).

The kidneys are organs and are store house of various functions. They belong to an essential part of the urinary system. The kidney serves homeostatic functions such as the regulation of electrolytes, maintenance of acid-base balance, and regulation of blood pressure. Renal involvement like bacteriuria, nephrotic syndrome and acute renal failure have been studied due to *S. parayphi A* (D'Cruz *et al.,* 2009).

Genes involved during infection and pathogenesis of *S.typhi*

S. typhi which causes typhoid fever is a human restricted pathogenic microorganisms. To understand its pathogenesis is little difficult due to the unavailiblity of suitable animal models. *S.typhimurium* which is a serovar posses high degree of genome homology (Parkhill *et al.,* 2001). It has been used for a long time to study and evaluate typhoid fever pathogenesis using a murine infection model in which this bacterium causes a systemic infection. This model has been considered as a crucial model in understanding systemic infections caused by Salmonella. However, it has also been explained that the mouse model does not always reflect the human disease. A number of Salmonella virulence factors have already been detected and studied, but there is need to discover more. In human infected with Salmonella, macrophages represent an important host defense mechanism. The ability of salmonella to survive and replicate within macrophage is considered to be one of the major pathogenesis determinants (Schwan *et al.,* 2000).

SPIs are insertions of large regions of DNA. It contains virulence genes which are located on the bacterial chromosome. Fifteen SPIs have been recognized in *S. typhi* (Parkhill *et al.,* 2001). SPI-1 and SPI-2, which are present in all S. enterica serovars, represent two most important pathogenesis determinants that encode type III secretion systems (T3SS). SPI-1 and SPI-2 T3SS exhibit distinct and important roles in pathogenesis of Salmonella. SPI-1 effectors via the T3SS are required for invasion of epithelial cells, whereas SPI-2 has been demonstrated to contribute to Salmonella survival inside macrophages. Many genes present in typhi are involved in invasion were identified so far are homologous genes present in typhimurium, including SPI-1 genes (*invC, invA, invE, invG, prgH, iagAB, sipEBCDA).* The virulence of typhi is associated with the presence of the Vi antigen. This is needed for typhi to survive inside the phagocytes. Moreover it is also necessary for serum resistance, a characteristic required for systemic dissemination (Daigle, 2008). Host-pathogen interactions are very complex. Considerable effort is required for their elucidation. Studying interactions between the infected host and typhi should definitely improve our knowledge regarding typhoid.

Typhoid and nanotechnology

New techniques are always in demand to find trace amount of infectious pathogens rapidly, accurately and with high sensitivity and also to put an end to epidemics and loss of lives. Engineered nanomaterials are proving to be promising in fullfiling these demands in diagnosing the pathogenic microorganisms in blood, clinical samples and food. A number of experiments using nanoparticulate formulations have been done on experimentally induced salmonellosis due to *S. typhimurium* constituting a typical model of intracellular infection and resembling humans typhoid. Ampicillin was entrapped in polyhexylcyanoacrylate nanoparticles. This increases efficacy of the antibiotic 120 fold in experimental murine salmonellosis (Pinto-Alphandary *et al.,* 2000). Nanotechnology-driven approach was utilized for antibody-conjugated oval-shaped gold nanoparticles to selectively target and destroy pathogenic bacteria. The assay based on nanotechnology would have high potential for rapid, on-site pathogen detection and also to avoid the distribution of contaminated food (Wang *et al.,* 2010). Poly(lactide-co-glycolide) nanoparticles loaded with azithromycin with appropriate physicochemical properties and antimicrobial activity was reported.

Table 2. Drugs so far used against typhoid.

Drugs so far used against typhoid	References
Amoxacillin-clavulanic acid	Akinyemi *et al.,* 2005b.
Amoxicillin	Akinyemi *et al.,* 2005b.
Amoxycillin	Trivedi and Trivedi, 2010.
Ampicillin	Krishnan *et al.,* 2009.
Cefixime	Krishnan *et al.,* 2009.
Cefotaxime	Krishnan *et al.,* 2009.
Cefpodoxime	Bajracharya *et al.,* 2006.
Ceftriaxone	Trivedi and Trivedi, 2010; Krishnan *et al.,* 2009.
Cephalosporins	Chowta and Chowta, 2005.
Chloramphenicol	Fae Farrer. 2010; Trivedi *et al.,* 2010; Krishnan *et al.,* 2009.
Ciprofloxacin	Trivedi and Trivedi, 2010; Krishnan *et al.,* 2009.
Co-trimoxazole	Trivedi and Trivedi, 2010; Krishnan *et al.,* 2009.
Gatifloxacin	Krishnan *et al.,* 2009.
Gentamycin	Trivedi and Trivedi, 2010.
Ofloxacin	Trivedi and Trivedi, 2010; Krishnan *et al.,* 2009.
Quinolone	Bajracharya *et al.,* 2006.
Streptomycin	Akinyemi *et al.,* 2005a.
Tetracycline	Akinyemi *et al.,* 2005a.

Antimicrobial activity test has proved that the nanoparticles were more effective as compare to pure azithromycin against *S. typhi* (Mohammadi et al., 2010). Mn_3O_4 nanoparticles also exhibit a clear antibacterial activity against Salmonella sp., the causing agent for typhoid (Chowdhury *et al.,* 2009). Moreover chitosan nanoparticles were used to encapsulate porcine interleukin-2 gene which enhances immune response of mice to piglet paratyphoid vaccine (Yang *et al.,* 2007).

Treatment for typhoid

The treatment of salmonella infection can be done by using antibiotics. Moreover the treatment can be also done by considering the immune system which is a defense system provided by body against microorganisms and pathogens. The immune system utilizes the machanisms of vaccination to clear pathogen. Due to side effects of vaccination and antibiotic herbal drugs can be used as it is natural and lacks the side effects. The author is further going to explain about antibiotics, vaccination and herbal drugs against salmonellae species.

Antibiotics

Bacterial infection can be minimized or removed by the use of antibiotics. Antibiotics are naturally occurring agents, which are produced by microorganisms and act on other bacteria. Synthetic antibiotics have been also been constructed to fight against microorganisms. A number of antibiotics so far used in salmonellae infection have been listed in the Table 2. The antibiotics used has a number of side effects. Moreover the salmonellae often get resistant to it leading to multi drug resistant typhoid (MDRST).

Vaccination

Treatment of typhoid fever is done by the use of antibiotics, but increasing resistance rates to the primary agents used (ampicillin, chloramphenicol, co-trimoxazole as well as quinolones) have been associated with complications and increased severity of illness. The burden of typhoid fever remains high in impoverished settings, and increasing antibiotic resistance is making treatment costly. One strategy for reducing the typhoid morbidity and mortality is vaccination. Therefore effective and cost-effective vaccination is the control measure required to fight this infectious disease.

The vaccines used are not fully effective. Some have low efficiency while other exhibit high efficiency as concluded from literature survey. More over the

vaccine so far constructed has got side effects. A number of vaccines with their affectivity and drawback have been discussed in the Table 3.

Table 3. Efficacy and drawbacks of vaccine against typhoid

Vaccines so far used	Effect	Draw backs	References
Vi polysaccharide vaccine	65% (55-75%)		Cook et al., 2008.
Ty21a vaccine	51%	Local swelling, Vomiting, Diarrhea.	
Vi polysaccharide vaccine	55%,	Local swelling, Local erythema.	Fraser *et al.,* 2007.
Vi-rEPA vaccine	89%		
Whole cell vaccine	51-88%	Fever (6–30%), Headache (10%), Severe local pain (35%)	
Vi vaccine	64-72%	Most common side effects are pain, redness and induration at the injection site, and fever. Inability to stimulate mucosal immunity and revaccination does not elicit any booster effect.	Guzman *et al.,* 2006.
Ty21a vaccine	60-80%		
M01ZH09 vaccine	Efficacy testing of this single-dose oral typhoid vaccine has not been done.	The most common symptoms shown was headache and flatulence.Diarrhoea and low gread fever were also reported.	Lyon *et al.,* 2010.
Porins		Pain, Redness,Induration, Malaise,Headache and Fatigue.	Salazar-González *et al.,* 2004.

Salmonella and herbal drugs

Medicinal plants are the back bone of traditional medicine. A number of infectious diseases are caused by different microorganisms. In Indian system of medicine, a large number of drugs of either herbal or mineral origin have been implicated in various diseases and other pathological conditions in humans. The plant extracts have been used as it lacks side effects. A number of plants has been screened for antisalmonella activities and listed in the Table 4.

The corresponding author studied *Emblica officinalis* and *Terminalia chebula* and found to exhibit full protection a gainst *S. typhimurium* (Khan and Jain, 2009; Khan 2010a). Immunomodulatory activity of *Terminalia chebula* against *S. typhimurium* in mice was also reported by this corresponding author (Khan 2009a). Moreover the same author reported the activity of the same extract against the oxidative stress induced by *S. typhimurium* in Swiss albino mice (Khan, 2009b; Khan 2009c). He further reported the protective effect of *Emblica officinalis* against *S.typhimurium* through its antioxidant activity (Khan 2010a).

Table 4. Medicinal plants having anti-salmonellae activity.

Medicinal plants	Microorganisms	References
Syzygium cumini (L.) (Myrtaceae)	*Salmonella enteritidis, S. typhi, S. typhi A, S. paratyphi A, S. paratyphi B*	Gowri and Vasantha, 2010.
Phyllanthus niruri	*S. typhi*	Sumathi and Parvathi, 2010.
Unripe Carica papaya fruit *Citrus aurantifolia* *Gossypium spp leaves* *Cocus nucifera chaffs* *Unripe Ananas sativus* *Unripe Citrus Paradisi* *Cymbopogon citratus* *Carica papaya brown leaves* *Euphorbia heterophylla*	*S. typhi*	Anthonia and Olumide, 2010.
Anarcadium occidentale *Anthocleista vogelii Planch* *Alchornea cordifolia* *Cassia sieberiana* *Daniela oliveri* *Mamgifera indica* *Nauclea latifolia* *Triplochyton scleroxylon*	*S. typhi*	Musa *et al.,* 2010.
Andrographis paniculata	*S. typhi*	Vinothkumara *et al.,* 2010.
Terminalia chebula	*S. typhimurium*	Khan and Jain, 2009.
Emblica officinalis	*S. typhimurium*	Khan 2010; Khan 2010.

Conclusion

It is concluded from the study that the author carefully reviewed typhoid fever and presented this article in the terms of its epidemiology, symptoms. Moreover the clinical aspect of this disease was explained in condensed form by surveying the causative agents of typhoid on various organs of the body. The author also gave stress on vaccination, antibiotics and the application of herbal drugs against the microorganisms. It is concluded from the study that more stress should be given by the researchers to find out new antimicrobial drugs to fight typhoid as the bacteria is getting resistant to new drugs. Moreover continues efforts have to be made to discover new vaccine against typhoid that must be fully safe and hundred percent effective. In addition to this, work has to be done to explore medicinal plants at molecular level to make drug that should prevent typhoid. It is beyond doubt that due to the emergence of tools and technologies of molecular biology and biotechnology the researchers in future will be able to synthesize new drugs that will eradicate typhoid from the globe.

References

Abdoel TH, Pastoor R, Smits HL, Hatta M. 2007. Laboratory evaluation of a simple and rapid latex agglutination assay for the serodiagnosis of

typhoid fever. Trans R Soc Trop Med Hyg **101(10),** 1032-1038.

Akinyemi KO, Mendie UE, Smith ST, Oyefolu AO, Coker AO. 2005a. Screening of some medicinal plants used in south-west Nigerian traditional medicine for anti-*Salmonella typhi* activity. J Herb Pharmacother **5(1),** 45-60.

Akinyemi KO, Smith SI, Bola Oyefolu AO, Coker AO. 2005b. Multidrug resistance in Salmonella enterica serovar typhi isolated from patients with typhoid fever complications in Lagos, Nigeria. Public Health **119 (4),** 321-327.

Anthonia O, Olumide O. 2010. *In Vitro* Antibacterial Potentials and Synergistic Effect of South- Western Nigerian Plant Parts Used in Folklore Remedy for *Salmonella typhi* infection. Nature and Science **8(9),** 52-59.

Bajracharya BL, Baral MR, Shakya S, Tuladhar P, Paudel M, Acharya B. 2006. Clinical profile and antibiotics response in typhoid fever. Kathmandu Univ Med J **4 (1),** 25-29.

Chowdhury AN, Azam MS, Aktaruzzaman M, Rahim A. 2009. Oxidative and antibacterial activity of Mn3O4. J Hazard Mater **172(2-3),** 1229-1235.

Chowta MN, Chowta NK. 2005. Study of Clinical Profile And Antibiotic Response In Typhoid Fever. Indian J Med Microbiol **23(2),** 125-127.

Clark TW, Daneshvar C, Pareek M, Perera N, Stephenson I. 2010. Enteric fever in a UK regional infectious diseases unit: A 10 year retrospective review. J Infect **60 (2),** 91-98.

Cook J, Jeuland M, Whittington D, Poulos C, Clemens J, Sur D, Anh DD, Agtini M, Bhutta Z. 2008. The cost-effectiveness of typhoid Vi vaccination programs: Calculations for four urban sites in four Asian countries. Vaccine **26 (50),** 6305-3616.

Crawford RW, Rosales RR, Ramírez-Aguilar Mde L, Chapa AO, Alpuche AC, Gunn GS. 2010. Gallstones play a significant role in Salmonella spp. gallbladder colonization and carriage. Proc Natl Acad Sci U S A **107(9),** 4353-4358.

Daigle F. 2008. Typhi genes expressed during infection or involved in pathogenesis. J Infect Dev Ctries **2(6),** 431-437.

D'Cruz S, Kochhar S, Chauhan S, Gupta V. 2009. Isolation of Salmonella paratyphi A from renal abscess. Indian J Pathol Microbiol **52(1),** 117-119.

Dong BQ, Yang J, Wang XY, Gong J, Seidlein, L.von, Wang ML, Lin M, Liao HZ, Ochiai RL, Xu ZY, Jodar L, Clemens JD. 2010. Trends and disease burden of enteric fever in Guangxi province, China, 1994-2004. Bull World Health Organ **88 (9),** 689-696.

Dutta S, Sur D, Manna B, Sena B, Deba A, Deen JL, Wainc J, Seidlein LV, Ochiai L, Clemens JD, Bhattacharya S. 2006. Evaluation of new-generation serologic tests for the diagnosis of typhoid fever: data from a community-based surveillance in Calcutta, India. Diagn Microbiol Infect Dis **56 (4),** 359-365.

Fae Farrer. 2010. Antibiotic Prescriptions. SA Pharmaceutical Journal **77 (3),** 17-24.

Faucher SP, Porwollik S, Dozois CM, McClelland M, Daigle F. 2006. Transcriptome of Salmonella enterica serovar Typhi within macrophages revealed through the selective capture of transcribed sequences. Proc Natl Acad Sci U S A. **103(6),** 1906-1911.

Forest CG, Ferraro E, Sabbagh SC, Daigle F. 2010. Intracellular survival of Salmonella enterica serovar Typhi in human macrophages is independent of Salmonella pathogenicity island (SPI)-2. Microbiology. **156(Pt 12),** 3689-3698.

Fraser A, Paul M, Goldberg E, Acosta CJ, Leibovici L. 2007. Typhoid fever vaccines: Systematic review and meta-analysis of randomised controlled trials. Vaccine **25(45),** 7848-7857.

Gowri SS, Vasantha K. 2010. Phytochemical Screening and Antibacterial Activity of *Syzygium cumini* (L.) (Myrtaceae) Leaves Extracts. International Journal of PharmTech Research **2 (2),** 1569-1573.

Guzman CA, Borsutzky S, Griot-Wenk M, Metcalfe IC, Pearman J, Collioud A. 2006. Didier Favre and Guido Dietrich, Vaccines against typhoid fever. Vaccine **24 (18),** 3804-3811.

Holt KE, Dolecek C, Chau TT, Duy PT, La TT, Hoang NV, Nga TV, Campbell JI, Manh BH, Vinu Chau NV, Hien TT, Farrar J, Dougan G, Baker S. 2011. Temporal fluctuation of multidrug resistant salmonella typhi haplotypes in the mekong river delta region of Vietnam. PLoS Negl Trop Dis **5 (1),** e929.

Jackson AA, Ismail A, Ibrahim TA, Kadar ZS, Nawi NM. 1995. Retrospective review of dot enzyme immunoassay test for typhoid fever in an endemic area. Sotheast Asian J Trop Med Public Health **26(4),** 625-630.

Jhawar M, George P, Pawar B. 2010. Salmonella typhi sepsis and rhabdomyolysis with acute renal failure: a rare presentation of a common disease. Saudi J Kidney Dis Transpl **21(4),** 732-734.

Khan KH. 2010a. *Emblica officinalis* Reduces the Initiation of Oxidative Stress by *Salmonella typhimurium* in Mice and Can be Used in Typhoid. Lat. Am. J. Pharm **29 (2),** 171-177.

Khan KH. 2010b. Protective effect of *Emblica officinalis* against *S.typhimurium* through its antioxidant activity. Recent Research in Science and Technology **2(4),** 29-36.

Khan KH. 2009a. Immunomodulatory activity of *Terminalia chebula* against *Salmonella typhimurium* in mice. Recent Research in Science and Technologies **1(5),** 211-216.

Khan KH. 2009b. The effect of regular intake of Terminalia chebula on oxidative stress in mice originated from Salmonella typhimurium. Eur Asia J Bio Sci **3 (15),** 113-121.

Khan KH. 2009c. *Terminalia chebula* reduces the oxidative stress induced by *salmonella typhimurium* in mice and may reduce the risk of getting typhoid. Advances in Biological Research **3 (1-2),** 1-8.

Khan KH, Ganjewala D, Rao KVB. 2008. Recent advancement in typhoid research- a review. Advanced BioTech **7 (4),** 35-41.

Khan KH, Jain SK. 2009. Regular intake of *Terminalia chebula* can reduce the risk of getting typhoid fever. Advanced Biotech **8(9),** 10-15.

Krishnan P, Stalin M, Balasubramanian S. 2009. Changing trends in antimicrobial resistance of Salmonella enterica serovar typhi and salmonella enterica serovar paratyphi A in Chennai. Indian J Pathol Microbiol **52(4),** 505-508.

Lauria DT, Maskery B, Poulos C, Whittington D. 2009. An optimization model for reducing typhoid cases in developing countries without increasing public spending. Vaccine **27 (10),** 1609-1621.

Lyon CE, Sadigh KS, Carmolli MP, Harro C, Sheldon E, Lindow JC, Larsson CJ, Martinez T, Feller A, Ventrone CH, Sack DA, DeNearing B, Fingar A, Pierce K, Dill EA, Schwartz HI, Beardsworth EE, Kilonzo B, May JP, Lam W, Upton A, Budhram R, Kirkpatrick BD. 2010. In a randomized,double-blined,placebo-controlled trial,the single oral dose typhoid vaccine,M01ZH09,is and immunogenic at doses up to 1.7×1010 Colony-forming units.Vaccine **28 (20),** 3602-3608.

Mège JL, Mehraj V, Capo C. 2011. Macrophage polarization and bacterial infections. Curr Opin Infect Dis **24(3),** 230-234.

Mohammadi G, Valizadeh H, Barzegar-Jalali M, Lotfipour F.,Adibakia K, Milani M, Azhdarzadeh M., Kiafar F., Nokhodchi. A. 2010. Development of azithromycin–PLGA nanoparticles: Physicochemical characterization and antibacterial effect against *Salmonella typhi*. Colloids Surf B Biointerfaces **80 (1),** 34-39.

Musa AD, Yusuf GO, Ojogbane EB, Nwodo OFC. 2010. Screening of Eight Plants Used In Folkloric Medicine for the Treatment of Typhoid Fever. J. Chem. Pharm. Res **2(4),** 7-15.

Naheed A, Ram PK, Brooks WA, Hossain MA, Parsons MB, Talukder KA, Mintz E, Luby S, Breiman RF. 2010. Burden of typhoid and paratyphoid fever in a densely populated urban community, Dhaka, Bangladesh. Int J Infect Dis **14 (3),** 93-99.

Nath G, Gulati AK, Shukla VK. 2010. Role of bacteria in carcinogenesis, with special reference to carcinoma of the gallbladder. World J Gastroenterol **16(43),** 5395-5404.

Osifo OD, Ogiemwonyi SO. 2010. Typhoid ileal perforation in children in Benin city. Afr J Paediatr Surg **7(2),** 96-100.

Parkhill J, Dougan G, James KD, Thomson NR, Pickard D, Wain J, Churcher C, Mungall KL, Bentley SD, Holden MT, Sebaihia SM, Baker S, Basham D, Brooks K, Chillingworth T, Connerton P, Cronin A, Davis P, Davies RM, Dowd L, White N, Farrar J, Feltwell T, Hamlin N, Haque A, Hien TT, Holroyd S, Jagels K, Krogh A, Larsen TS., Leather S, Moule S, O'Gaora P, Parry C, Quail M, Rutherford K, Simmonds M, Skelton J, Stevens K, Whitehead S, Barrel BG. 2001. Complete genome sequence of a multiple drug resistant Salmonella enterica serovar Typhi CT18. Nature **413 (6858),** 848-852.

Pastoor R, Hatta M, Abdoel TH, Smits HL. 2008. Simple, rapid, and affordable point-of-care test for the serodiagnosis of typhoid fever. Diagn Microbiol Infect Dis **61(2),** 129-134.

Pinto-Alphandary H, Andremont A, Couvreur P. 2000. Targeted delivery of antibiotics using liposomes and nanoparticles: research and applications-Review. Int J Antimicrob Agents **13 (3),** 155-168.

Salazar-González RM, Maldonado-Bernal C, Ram´ırez-Cruz NE, Rios-Sarabia N, Beltrán-Nava J, Castañón-González J, Castillo-Torres N, Palma-Aguirre JA, Carrera-Camargo M, López-Mac´ıas C, Isibasi A. 2004. Induction of cellular immune response and anti-*Salmonella enteric* serovar *typhi* bactericidal antibodies in healthy volunteers by immunization with a vaccine candidate against typhoid fever. Immunology Letters **93 (2-3),** 115-122.

Schwan W, Huang X, Hu L, Kopecko D. 2000. Differential bacterial survival, replication, and

apoptosis-inducing ability of Salmonella serovars within human and murine macrophages. Infect Immun **68 (3),** 1005-1013.

Shetty AK, Mital SR, Bahrainwala AH, Khubchandani RP, Kumta NB. 1999. Typhoid hepatitis in children. J Trop Pediatr **45(5),** 287-290.

Sulaiman K, Sarwari AR. 2007. Culture-confirmed typhoid fever and pregnancy. Int J Infect Dis **11 (4),** 337-341.

Sumathi P, Parvathi A. 2010. Antimicrobial activity of some traditional medicinal plants Journal of Medicinal Plants Research **4 (4),** 316-321.

Trivedi ND, Trivedi UN. 2010. Case Report and Pathological Result Based Study On Typhoid Patients. International Journal of Pharmaceutical Sciences Review and Research **2(2),** 22-23.

Van Wolfswinkel ME, Lahri H, Wismans PJ, Petit PLC, van Genderen PJJ. 2009. Early small bowel perforation and cochleovestibular impairment as rare complications of typhoid fever. Travel Med Infect Dis **7 (5),** 265-268.

Villarreal JM, Hernández-Lucas I, Gil F, Calderón IL, Calva E, Saavedra CP. 2011. The cAMP-Receptor Protein (CRP) positively regulates the yihU-yshA operon in Salmonella enterica serovar Typhi. Microbiology **157(Pt 3),** 636-47.

Vinothkumara P, Sivaraja A, Syed ZA, Sivamani P, Devi K, Senthilkumar, B. 2010. Evaluation of antibacterial activities of *Andrographis paniculata* leaf extract against selective gram positive and gram negative species by *in vitro* methods. Journal of Pharmacy Research **3(7),** 1513-1515.

Wang S, Singh AK, Senapati D, Neely A, Yu H, Ray PC. 2010. Rapid colorimetric identification and targeted photothermal lysis of Salmonella bacteria by using bioconjugated oval-shaped gold nanoparticles. Chemistry **16(19),** 5600-5606.

Watson KG, Holden DW. 2010. Dynamics of growth and dissemination of Salmonella in vivo. Cell Microbiol **12(10),** 1389-1397.

Widal F. 1896. Serodiagnostique de la fievre typhoide. Bull. Mem. Soc. Med. Hop. Paris 13:561-565.

Yang Y, Chen J, Li H, Wang Y, Xie Z, Wu M, Zhang H, Zhao Z, Chen Q, Fu M, Wu K, Chi C, Wang H, Gao R. 2007. Porcine interleukin-2 gene encapsulated in chitosan nanoparticles enhances immune response of mice to piglet paratyphoid vaccine. Comp Immunol Microbiol Infect Dis. **30(1),** 19-32.

Zaki SA, Karande S. 2011. Multidrug-resistant typhoid fever: a review. J Infect Dev Ctries **5(5),** 324-337.

Zhou L, Pollard AJ. 2010. A fast and highly sensitive blood culture PCR method for clinical detection of Salmonella enterica serovar Typhi. Ann Clin Microbiol Antimicrob **19,** 9:14.