A review: Typhoid fever

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Abstract

Typhoid fever is most prevalent in the Asian part of the world especially in the developing countries of Asia like Pakistan and India, caused by a gram-negative bacterium *Salmonella enterica* serval Typhi. It is an orally transmitted communicable disease caused by consuming contaminated food and impure water. The incubation period of the disease is 7 to 14 days. Symptoms include high fever, rash, weakness, abdominal pain constipation, headache, and poor appetite. Antibiotic resistance is a major problem to treat it effectively. Firstline drugs are mostly not used to treat typhoid and the resistance is emerging in fluoroquinolones. The only choice of drug remaining is ceftriaxone and azithromycin. A counteractive action of typhoid fever is chiefly by individual and household cleanliness. The provision of clean water and safe disposal of faeces should be implemented to eradicate *S. Typhi*. Good surveillance, better diagnostics, more sensible use of antibiotics and efficient vaccine will be significant to reduce the burden of disease caused by *S. Typhi*.

Keywords: Pakistan, Typhoid, *Salmonella Typhi*, Drug resistance, Food-borne illness, Proteomic approach

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Introduction

Typhoid is an extreme, infectious and dangerous malady related with fever. It is caused by Salmonella enterica serovars Typhi, Paratyphi A, Paratyphi B, and Paratyphi C can be collectively categorized as typhoidal Salmonella, though some are gathered as nontyphoidal Salmonella [NTS] [1]. Typhoid strains are human host-confined life forms that reason typhoid fever and paratyphoid fever, together alluded to as enteric fever. In some Asian nations, Salmonella serovar Paratyphi A has represented a developing extent of enteric fever [2,3].

Typhoidal Salmonella transmit dominatingly via water or sustenance polluted with the feces of human [4]. The hazard of disease is high in underdeveloped nations where typhoidal Salmonella is endemic and there is poor hygiene and sanitation and non-availability of safe sustenance and water [5]. Enteric fever in high-pay nations is generally obtained abroad and is related with movement to territories of endemicity, in spite of the fact that bunches might be related with sustenance preparers who are interminable bearers of Salmonella serovar Typhi [6].

An ongoing report on worldwide weight of typhoid fever announced 27 million diseases and 200,000 to 600,000 passing every year because of typhoid fever [7]. The International Vaccine Institute reported 11.9 million typhoid fever ailments and 129,000 passings in low-and center pay nations in 2010 [8]. Typhoid is endemic in the greater part of the creating nations like Pakistan [9].

The most recent two decades have seen the development and spread of multidrug opposition against the ordinary antityphoid drugs (chloramphenicol, co-trimoxazole, fluoroquinolones and ampicillin) among the typhoid salmonellae, particularly in South and Southeast Asia, including Pakistan [10].

Episodes of MDRTF require expensive and generally inaccessible medications for successful treatment. This is an additional weight to the medicinal services area in creating nations. Accentuation should along these lines be put on sickness avoidance, which can incorporate both short and long-haul measures that must be taken after entirely. Here and now measures incorporate inoculation of the high-hazard populace in endemic zones and balanced and reasonable anti-microbial recommending hones by wellbeing experts [11]. These issues require the aggregate activity of governments, the pharmaceutical business, social insurance suppliers and shoppers. A typhoid inoculation program in schoolchildren alongside the school based organization of Td (typhoid and diphtheria) or, with the coming of new conjugate antibody VI immunization, as a component of the extended program of vaccination, ought to be considered. Other imperative preventive measures incorporate upgrades in sanitation, accessibility of clean drinking water, advancement of safe sustenance taking care of practices, and general wellbeing instruction [12].

Epidemiology

As indicated by the worldwide gauge, every year around 27 million new instances of typhoid happen with mortality in around 200,000. The most noteworthy dismalness and mortality are noted in South Central and Southeast Asia [7]. A planned populace based reconnaissance directed in five Asian nations including Pakistan uncovered that Pakistan has the second most noteworthy frequency of typhoid fever with the

assessed yearly rate of 412.9 for every 100,000 individuals. The International Vaccine Institute evaluated that there were 11.9 million typhoid fever sicknesses and 129,000 passing in low-and center salary nations in 2010 [13].

The study of disease transmission of typhoid fever is human host-confined and fundamentally includes individual to-individual spread in light of the fact that these creatures do not have a huge creature store. The hazard for disease is high in low-and center salary nations where typhoidal Salmonella is endemic and that have poor sanitation and absence of access to safe sustenance and water [14] as appeared in the investigation directed in rustic regions of Islamabad, Pakistan [15]. Sullying with human defecation is the significant method of spread, and the typical vehicle is defiled water, nourishment, crude organic products, vegetables, desserts, squeezes and contact with tainted patients or bearer of the infections [16]. Explorers, kids, the elderly and invulnerable traded off people are particularly in danger. The kids maturing 2-10 years [14,17] and youthful populace up to 25 years old independent of their genders experience the ill effects of enteric fever and are admitted to the healing centers in the endemic areas as we found in the investigation led in Karachi and furthermore in Gujarat, Pakistan, in which high predominance of typhoid was found in more youthful age [18].

Furthermore, climatic factors, for example, precipitation, vapor weight and temperature importantly affect the transmission and circulation of typhoid diseases in human populaces [18].

The pervasiveness rate of typhoid fever is higher amid summer. In Pakistan it is accounted for in Punjab [18,19], Sindh [16], Khyberpakhtunkhwa [20,21] and furthermore in Balochistan [22] that this ailment happens sporadically everywhere throughout the year, however with a pinnacle occurrence amid summer.

Aside from the ingestion of defiled sustenance and water numerous social and statistic factors have been found to interaction with the high frequency in endemic settings like poor sanitation, contact with typhoid positive case or a bearer, instructive status, packing, abiding close water bodies, flooding and poor cleanliness [18]. As per an orderly writing audit on frequency of typhoid fever in low and center pay nations, occurrence of typhoid in Pakistan was most noteworthy in the district [2]. An ongoing network based examination from Quetta, Pakistan indicated 14.63% serologically positive patients of typhoid fever with more cases from rustic zones [22]. Another cross-sectional investigation uncovered that among febrile cases 36% were sure for typhoid. Despite the fact that this was a cross sectional investigation however the objective populace was all utilizing private wellbeing offices for treatment. Pakistan additionally has high bearer rate which is accepted to be a central point in charge of high endemicity as portrayed in an investigation from Karachi where just about 9% of the nourishment handlers were conveying typhoid S. enterica serovars in their feces [23]. The catchment region of Federal General Hospital Islamabad incorporates mauza Chatta Bakhtawar (UC 22) and Terlai Kalan (UC 19) and an investigation from same zone beforehand revealed the occurrence of typhoid fever to be 63% among febrile patients [15]. In one of the investigation led in matta, swat predominance of enteric fever was discovered 13.5% [21]. A Serological Diagnosis of Salmonella Typhi in District Hospital Quarter of Charsadda was performed and indicated 22% of prevelance [20]. So also in another investigation the high predominance of typhoid fever in five surge influenced Districts (Bannu, Hangu, Karak, Kohat and Peshawar) of khyber Pakhtunkhwa territory of Pakistan amid 2010/11 was observed [24]. An examination directed in Pakistan in pediatric populace additionally announced 170/100,000 frequency of typhoid fever every year [25]. This high rate of typhoid fever in Pakistan is for the most part contributed by tireless neediness, poor individual cleanliness, and sterile condition [26].

Bacteriology

Salmonella enteric serovar typhi (S. typhi) is a facultative intracellular pathogen that causes typhoid fever in people. Salmonellae are individuals from the family Enterobacteriaceae. The organism is non-capsulated, non-sporulating, flagellated, Gram-negative anaerobic bacilli and external coat antigens. The bacterium is serologically positive for lipopolysaccharide antigens O9 and O12, protein flagellar antigen Hd, and polysaccharide capsular antigen Vi [27,28].

Pathogenesis

Typhoid fever is a noteworthy nourishment and waterborne infection spread through shellfish and dairy items, and less normally by coordinate contact with pee, excrement, or other body discharges [29]. Typhoid fever is nowadays not common in nations with appropriate system of sewage and drain supplies and safe water availability [7].

Following ingestion, bacilli should first survive gastric corrosive and then enters the villi in small intestine, attack the mucosal membrane instantly, and duplicate in the lumen for a few days before infiltrating the mucosa. Bacilli at that point go to the lymphoid follicles in digestive tract and the depleting mesenteric lymph hubs. A few creatures go into the fundamental course and are phagocytosed by the reticuloendothelial cells of liver and spleen. Bacilli attack and multiply facilitate inside the phagocytic cells of the intestinal lymphoid follicles, mesenteric lymph hubs, liver, and spleen [30]. Amid this underlying brooding period, in this way, the bacilli are basically sequestered in the intracellular natural surroundings of the intestinal and mesenteric lymphoid framework. In the long run the bacilli are discharged from the reticuloendothelial cells, go through the thoracic channel, enter the circulation system, and deliver an essential transient bacteremia and clinical side effects [31]. Amid this dynamic attack/bacteremic stage, bacilli disperse to and multiply in numerous organs, however are most various in organs that have critical phagocytic movement, in particular liver, spleen and bone marrow. The Peyer's patches of the terminal ileum and the bother bladder are additionally neighborly locales. Bacilli attack the irritate bladder from either blood or bile, after which they return in the digestive system, are discharged in the stool, or reinvade the mass of the digestive system [30-32].

Sign and Symptoms

When Salmonella is ingested serovar Typhi or Paratyphi A, an asymptomatic period lasts for 7 to 14 days. During this period the predominant symptom is the fever. The temperature rises and may reaches a high plateau of 39 to 40°C the following week. Fever and rashes are two main symptoms. Typhoid fever is particularly high, gradually increasing over several days up to 104 degrees Fahrenheit, or 39 to 40 degrees Celsius. The rash, which does not affect every patient, consists of rose-colored spots, particularly on the neck and abdomen [28]. Other symptoms can include: malaise, headache abdominal pain, abdominal distension and other constitutional symptoms. Constipation is an earlier symptom though many patients experiences diarrhea at some point. Physical findings are raised temperature, relative bradycardia, spleenomegaly, hepatomegaly, abdominal tenderness, meningism. Major complications comprises intestinal hemorrhage, intestinal perforation, urinary retention, pneumonia, thrombophlebitis, myocarditis, cholecystitis, nephritis, myocarditis, osteomyelitis and meningitis [28,33].

Diagnosis

The World Health Organization (WHO) assess for yearly worldwide rate of typhoid fever, around 21 million cases, is likely a disparage in view of poor diagnostics [2]. A few choices exist for diagnosing enteric fever: clinical signs and side effects; serological markers; bacterial culture; antigen discovery; and DNA intensification. None is totally acceptable. The clinical conclusion of typhoid fever is troublesome in light of the fact that the indications of the ailment are differing and there are numerous reasons for delayed fever in typhoid endemic areas [8].

Diagnosis by culture

The World Health Organization (WHO) appraise for yearly worldwide frequency of typhoid fever, around 21 million cases, is likely a disparage as a result of poor diagnostics. A few alternatives exist for diagnosing enteric fever: clinical signs and manifestations; serological markers; bacterial culture; antigen recognition; and DNA enhancement. None is totally palatable. The clinical determination of typhoid fever is troublesome in light of the fact that the indications of the sickness are different and there are numerous reasons for delayed fever in typhoid endemic areas. Lab determination of enteric fever in creating nations is essentially accomplished either by blood culture or bone marrow suction culture which are highest quality level for diagnosis [34].

In creating nations affectability of blood culture is brought due down to silly utilization of anti-infection agents. Bone marrow culture is touchier at that point blood culture in view of high bacterial focus in bone marrow and are generally unaffected by anti-toxins [35]. Stool culture is likewise an essential aide for finding; it might be certain when blood culture is negative and it is additionally vital for the observing of carriage of S. Typhi after clear clinical fix, a hazard factor for the groups of cases [36]. Advancement media containing selenite are utilized to disconnect S. Typhi from stool due to expansive quantities of contending microorganisms, particularly Escherichia coli [37]. Different destinations have been refined yet are not utilized routinely as demonstrative examples: culture of the upper gastrointestinal tract utilizing a duodenal string can be important yet the procedure is ineffectively endured by youthful youngsters. S. Typhi can be developed from rose spots however climbed spots are regularly hard to see and may just be available in 4% of cases. S. Typhi can likewise be developed from pee however might be related with urinary tract disease as opposed to typhoid fever [38].

Serological Diagnosis

Because of obtrusiveness and specialized trouble of the technique, one needs to depend on serological finding.

The Widal test

Agglutinating antibodies are measured against LPS (O) and flagellar (H) antigens of Salmonella serovar typhi in the sera of people with suspected enteric fever. Albeit normally disheartened because of error, it is basic and cheap to perform is still broadly utilized as a part of a few nations [39,40].

Tubex TF

Tubex TF depends on a restraint response between tolerant antibodies (IgM) and monoclonal antibodies incorporated into the test that predicament to a Salmonella typhi particular O9 lipopolysaccharide. A perceptibly noticeable de-colorization of serum of patient in test reagent arrangement via attractive molecule detachment demonstrates a positive outcome [41]. Execution of TUBEX® TF in the analysis of enteric fever in private tertiary care Hospital Peshawar, Pakistan was checked and affectability of TUBEX® TF was discovered 41.86% while specificity was 95.97% [42].

Typhidot

Conversely the typhidot depends on a subjective dab smudge catalyst connected immunosorbent measure that independently identifies the nearness of IgM and IgG in persistent sera against a Salmonella Typhi particular 50 kD external film protein. Despite the fact that Typhidot is quick, simple and reasonable, its utilization ought to be demoralized because of low affectability and specificity and immaterial relationship to the illness [43] as found in the examination led in Pakistan in which they found that affectability of Typhidot was 26.7% and the specificity was 61.5% [44].

IgM dipstick test

The typhoid IgM dipstick measure is intended for the serodiagnosis of typhoid fever through identifying S. typhi-particular IgM antibodies in serum or entire blood tests. The measure comprises of a dipstick, a lyophilized non-enzymatic recognition reagent, fluid to reconstitute the identification reagent, fluid to wet the test segment of the dipstick before hatching with serum and location reagent, and test tubes. The segments are steady for a long time if put away in the temperature run 4-25°C of a dry place and shielded from guide presentation to sunlight. The examiner depends on the

authoritative of S. typhi-particular IgM antibodies to S. typhi LPS antigen and the recoloring of bound antibodies by an against human IgM counter acting agent conjugated to colloidal color particles. The white test piece of the dipstick contains the antigen immobilized in a particular line. The strip additionally has a control line with hostile to human IgM antibodies [35,45].

In spite of the fact that Tubex and Typhidot M tests are being accessible and broadly utilized as a part of the clinical research facilities, there is a requirement for a quick and reasonable lab test for right on time and precise finding of patients with typhoid fever has incited the investigation of an assortment of serologic and antigen recognition techniques. The tests like counter immuno-electrophoresis, Enzyme-Linked Immunosorbent test (ELISA), spot immunoassay, hemagglutination and coagglutination are not simple to perform, not fast, require unique gear or abilities, or rely upon power and on refrigeration for capacity of parts [41].

Shockingly, neither the Widal test, nor any of the serodiagnostic tests that have since been produced have demonstrated adequately touchy, particular and down to earth to be of significant worth in zones where this illness is endemic [35].

Molecular diagnosis

The sub-atomic technique for conclusion of typhoid fever has been advanced to conquer the impediments of societies and serologic tests. Numerous creators have investigated the utilization of polymerase chain response (PCR) for distinguishing particular DNA succession of the creatures introduces in clinical examples. The PCR as an indicative methodology for typhoid fever was first assessed in 1993, Song et al., effectively intensified the flagellin quality of S. typhi in all instances of culture demonstrated typhoid fever and from none of the solid controls. By utilizing two sets of preliminaries assessed in the examination by Song et al, enhancement of the flagellin quality of S. typhi affirmed the nearness of the life form in the patient's blood [46,47].

In Pakistan, 55 instances of suspected typhoid fever and a control gathering of 20 sound people were analyzed by PCR from blood tests and blood culture. The PCR and blood culture gave 58.2% and 14.5% energy, individually demonstrating fundamentally better outcomes by PCR [48]. Again in Pakistan, a multiplex PCR focusing on five unique qualities for differential conclusion of typhoidal pathogens has been created for utilize specifically on clinical blood tests. Of 42 multiplex PCR-positive blood tests, 35 were sure for S. typhi [49].

In view of the absence of the accessibility of good symptomatic apparatuses, especially that are field based, rectify analysis of typhoid fevers remains a hazy area. So the analysts in the creating nations should accentuation the exploration on the advancement of more current and simple indicative.

Treatment

Typhoid fever is a noteworthy wellbeing worry in the creating World. Most recently in last two decades there is development and spread of multidrug obstruction against customary antityphoid drugs (chloramphenicol, co-trimoxazole, and ampicillin) among the typhoid salmonellae, particularly in South and Southeast Asia, including Pakistan [50].

The rise of medication safe typhoid has been another stressing improvement. After sporadic flare-ups of chloramphenicol safe typhoid in the vicinity of 1970 and 1985, numerous strains of S typhi created plasmid interceded multidrug protection from the three essential antimicrobials utilized (ampicillin, chloramphenicol, and Co-trimoxazole) [51]. This was countered by the coming of oral quinolones, yet chromosomally procured quinolone obstruction in S typhi and S paratyphi has been as of late depicted in different parts of Asia, perhaps identified with the broad and aimless utilization of quinolones [52,53].

In Pakistan Antimicrobial powerlessness, dictated by Kirby-Bauer plate dispersion strategy, demonstrated that 54% of the Salmonella Typhi separates were completely defenseless to ciprofloxacin/ofloxacin. Already, a few emotional changing patterns in anti-infection agent's opposition are examined for typhoid salmonellae in Islamabad [54]. From 1996 to 2000, no confines were observed to be impervious to fluoroquinolones like ciprofloxacin in an examination led in Armed Forces Institute of Pathology, Rawalpindi however in session 2001-2003, a portion of the ciprofloxacin safe detaches were achieved from local populace [55].

In the 1980s, ciprofloxacin turned into main line medication for treatment S. typhi diseases after the majority of the customary medications ended up inadequate [51]. Notwithstanding, protection from ciprofloxacin was seen in the Clinical disconnects of S. Typhi disconnected from Faisalabad district are demonstrating expanding ciprofloxacin opposition as showed by increment in nalidixic corrosive safe confines. In any case, more up to date fluoroquinolones like ofloxacin and gatifloxacin are still extremely viable. Among third era cephalosporins, ceftriaxone demonstrated promising outcomes yet rising obstruction was apparent [55].

In one examination it was reasoned that cefipime and third era cephalosporin like ceftriaxone are appropriate medications to be endorsed rather than fluoroquinolones in Islamabad, the capital region of Pakistan [54]. In 2011, an investigation was directed in NIBGE, Pakistan to check antibiograms of S. typhi. 30% and 10% separates were impervious to nalidixic corrosive and ciprofloxacin individually. In the interim, protection from cefixime and ceftriaxone were seen in 13.3% and 3.3% confines individually [56].

The development and spread of Salmonella segregates showing protection from a few anti-infection agents is matter of concern in light of the fact that these drugs are essential to the effective treatment of obtrusive diseases. Since protection from more seasoned anti-toxins (e.g. chloramphenicol ampicillin, and sulfamethoxazole trimethoprim-) has been expanding for a

long time, suggested treatment alternatives for salmonellosis included fluoroquinolones (ciprofloxacin) and broadened range cephalosporins [28,57]. Be that as it may, protection from those 'fundamentally essential anti-toxins for human wellbeing' is developing, prompting expanded seriousness, dreariness and mortality of maladies and the requirement for the utilization of last-line antimicrobials in treatment [58].

Azithromycin is administered for typhoid fever and may be used as an elective oral medication in regions where fluoroquinolone obstruction is normal. Recently settled CLSI rules for azithromycin circle dispersion and MIC interpretive criteria for Salmonella serovar Typhi were distributed in CLSI report M100 in 2015 [59].

Prevention

Since the early acknowledgment of the part of water in the transmission of typhoid fever, it has been shown that upgrades in access to clean water and enhanced sanitation result in emotional decreases in typhoid fever-related passing rates in numerous settings [60]. Moreover, safe drinking water and sanitation have been announced a human rights issue by the worldwide network, because of their significance in human wellbeing. Unmistakably as access to safe water and enhanced sanitation are being produced, this ought to drastically decrease the introduction to S. Typhi and S. Paratyphi microorganisms in nature and, accordingly, enteric fever ailment. Be that as it may, worldwide advance toward widespread access to both safe water and enhanced sanitation at the family unit level where the medical advantages are ideal are lacking, and are likely aggravated by a few variables incorporating disparity in scope, where the most defenseless populaces have the poorest access; expanding urbanization; and expanding water shortage in numerous districts [61].

There has been enthusiasm for typhoid fever immunization for a very long while, and despite the fact that there has likewise been advance in creating control answers for typhoid, this advance has been to some degree stilted in numerous locales. The main antibody, an inactivated entire cell immunization, was being used for >100 years, for the most part in British and US military populaces, yet was esteemed too reactogenic for proceeded with utilize [62]. Presently, 2 typhoid antibodies are universally authorized and have been appeared to be sheltered and adequate in people >2 years old. The first is an oral antibody in view of a live weakened S. typhi Ty21a strain. The second is a solitary measurements injectable Vi capsular polysaccharide (Vi-PS) antibody, which has been created by a few makers, and no less than 1 of which is prequalified by the WHO for use in subjects >2 years old [61].

Neither one of the products has been generally utilized, especially in exceptionally endemic, low-asset settings, given the difficulties related with organization regimens and moderately brief length of security, which would require intermittent boosting.

Typhoid conjugate immunizations (TCVs) are required to beat a considerable lot of the difficulties related with these past antibodies, giving higher adequacy, prior organization to newborn children and youthful youngsters in danger, and a more drawn out length of assurance. A 2-measurement Vi-rEPA conjugate antibody was produced by the US National Institutes of Health, where Vi-PS is conjugated to a novel bearer protein comprising of recombinant exotoxin of Pseudomonas aeruginosa [63] and showed 91.5% defensive viability among preschool youngsters matured 2-5 years in Vietnam; however this immunization has not yet been authorized universally [64].

Conclusion

Typhoid fever is exceptionally basic disease in Pakistan caused by Salmonella typhi which is trans-mitted among people through faeco-oral course. Sickness can be controlled by anti-toxins like fluo-roquinolones as well as by quiet training, change in cleanliness and sanitation, safe supply of clean drinking water and prophylactic immunization also. Be that as it may, opportune conclusion and fitting administration with appropriate anti-toxins is the way to dodge the intense intricacies and chronicity of the sickness. Huge battles ought to be started to control the ailment. Arrangement of good quality life isn't better for the nation yet in addition critical for the world network. In spite of the fact that, arrangement of value instruction and destitution lightening programs are government needs, it is vital to keep constant watchfulness in remote territories where individuals still live under heartless conditions and give them essential necessities of life. Reach and experience of nearby NGOs to such territories can be exceptionally useful to raise solid and supported wellbeing changes.

References

1. Gal-Mor O, Boyle EC, Grassl GA, et al. Same Species, Different Diseases: How and Why Typhoidal and Non-Typhoidal Salmonella Enterica Serovars Differ. Front Microbiol 2014;5:391.
2. Crump JA, Luby SP, Mintz ED, et al. The global burden of typhoid fever. Bull World Health Organ 2004;82:346-353.
3. Eng SK, Pusparajah P, Ab Mutalib NS, et al. Salmonella: a review on pathogenesis, epidemiology and antibiotic resistance. Front Life Sci 2015;8:284-293.
4. Penakalapati G, Swarthout J, Delahoy MJ, et al. Exposure to animal feces and human health: a systematic review and proposed research priorities. Environ. Sci. Technol 2017;9:11537-11552.
5. Antillón M, Warren JL, Crawford FW, et al. The burden of typhoid fever in low-and middle-income countries: A meta-regression approach. PLoS Negl. Trop. Dis 2017;11:e0005376.
6. Gunn JS, Marshall JM, Baker S, et al. Salmonella chronic carriage: epidemiology, diagnosis, and gallbladder persistence. Trends in microbiology 2014;22:648-655.
7. Buckle GC, Walker CLF, Black RE, et al. Typhoid fever and paratyphoid fever: Systematic review to estimate global morbidity and mortality for 2010. J. Glob. Health 2012;2:10401.

8. Ayub U, Khattak AA, Saleem A, et al. Incidence of typhoid fever in Islamabad, Pakistan. American-Eurasian Journal of Toxicological Sciences 2015;7:220-223.
9. Butt T, Ahmad RN, Mahmood A, et al. Ciprofloxacin treatment failure in typhoid fever case, Pakistan. Emerging infectious diseases 2003;9:1621.
10. Zaki SA, Karande S. Multidrug-resistant typhoid fever: a review. J Infect Dev Ctries 2011; 5: 324-337.
11. Mara D, Lane J, Scott B, et al. Sanitation and health. PLoS medicine 2010;7:e1000363.
12. Ochiai RL, Acosta CJ, Danovaro-Holliday M, et al. study of typhoid fever in five Asian countries: disease burden and implications for controls. Bulletin of the world health organization 2008;86:260-268.
13. Javed N, Abbasi S, Tahir M, et al. Identifying the Risk Factors for Typhoid Fever among the Residents of Rural Islamabad. Pak J Med Res 2017;56:48.
14. Luby SP, Faizan MK, Fisher-Hoch SP, et al. Risk factors for typhoid fever in an endemic setting, Karachi, Pakistan. Epidemiol Infect 1998;120:129-138.
15. Owais A, Sultana S, Zaman U, et al. Incidence of typhoid bacteremia in infants and young children in southern coastal Pakistan. Pediatr Infect Dis J 2010;29:1035.
16. Rasul F, Sughra K, Mushtaq A, et al. Surveillance report on typhoid fever epidemiology and risk factor assessment in district Gujrat, Punjab, Pakistan. Biomedical Research 2017;28:6921-6926.
17. Bukhari N, Saleem A, Jabbar A, et al. Frequency of typhoid fever and its association with seasonal variations in Taxila, Pakistan. Asian Pac J Trop Dis 2016;6:608-610.
18. Siraj U, Shams WA, Rehman G, et al. Serological Diagnosis of Salmonella typhi in DHQ (District Head Quarter Hospital) of Charsadda, City of Kp Pakistan 2015-2016. Computational Biology and Bioinformatics 2018;6:21-24.
19. Khan AA, Ahmad S, haq I, et al. Prevalence and Epidemiological Findings of MDR (Multi-Drug Resistant) Typhoid bacillus in District Swat KPK, Pakistan. J Lung Pulm Respir Res 2017;4.
20. Tareen AM, Qasim M, Akhtar Y, et al. Prevalence of Typhoid Fever in General Population of District Quetta, Balochistan, Pakistan J. App. Em. Sc 2014;5.
21. Siddiqui TR, Bibi S, Mustufa MA, et al. High prevalence of typhoidal Salmonella enterica serovars excreting food handlers in Karachi-Pakistan: a probable factor for regional typhoid endemicity. Journal of Health, Population and Nutrition 2015;33:27.
22. Kalsoom, Akbar F, Younas M, et al. Prevalence of typhoid fever in five Southern districts of Khyber Pakhtunkhwa, Pakistan: A preliminary study. International Journal of Biosciences 2014;4:325-330.
23. Siddiqui FJ, Rabbani F, Hasan R, et al. Typhoid fever in children: some epidemiological considerations from Karachi, Pakistan. Int J infectious dis 2006;10:215-222.
24. Arif A, Naheed R. Socio-economic determinants of diarrhoea morbidity in Pakistan. Academic Research International 2012;2:490.
25. Fàbrega A, Vila J. Salmonella enterica serovar Typhimurium skills to succeed in the host: virulence and regulation. Clinical microbiology reviews 2013;26:308-341.
26. Parry CM, Hien TT, Dougan G, et al. Typhoid fever. N Engl J Med 2002;347:1770-1782.
27. Baker S, Holt KE, Clements AC, et al. Combined high-resolution genotyping and geospatial analysis reveals modes of endemic urban typhoid fever transmission. Open Biol 2011;1:110008.
28. Raffatellu M, Wilson RP, Winter SE, et al. Clinical pathogenesis of typhoid fever. J Infect Developing Countries 2008;2:260-266.
29. House D, Bishop A, Parry C, et al. Typhoid fever: pathogenesis and disease. Curr Opin Infect Dis 2001;14:573-578.
30. Everest P, Wain J, Roberts M, et al. The molecular mechanisms of severe typhoid fever. Trends Microbiol 2001;9:316-320.
31. Ahasan HA, Rafiqueddin AKM, Chowdhury MAJ, et al. An Unusual Presentation of Typhoid Fever : Report of Four Cases. Bangladesh J Med 1993;11:101-103.
32. Crump JA, Sjölund-Karlsson M, Gordon MA, et al. Epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance, and antimicrobial management of invasive Salmonella infections. Clinical microbiology reviews 2015;28:901-937.
33. Sultana S, Al Maruf MA, Sultana R, et al. Laboratory Diagnosis of Enteric Fever: A Review Update. Bangladesh Journal of Infectious Diseases 2016;3:43-51.
34. Escamilla J, Santiago LT, Sangalang RP, et al. Comparative study of three blood culture systems for isolation of enteric fever Salmonella. Southeast Asian J Trop Med Public Health 1984;15:161-166.
35. Morinigo MA, Muñoz MA, Martinez Manzanares E, et al. Laboratory study of several enrichment broths for the detection of Salmonella spp. particularly in relation to water samples. J Appl Bacteriol 1993;74:330-335.
36. Mathai E, John TJ, Rani M, et al. Significance of Salmonella typhi bacteriuria. J Clin Microbiol 1995; 33:1791-1792.
37. Parry CM, Hien TT, Dougan G, et al. Typhoid fever. Clin Infect Dis 2010;50:241-6.
38. Bhutta ZA. Current concepts in the diagnosis and treatment of typhoid fever. BMJ 2006;333:78-82.
39. Fadeel MA, House BL, Wasfy MM, et al. Evaluation of a newly developed ELISA against Widal, TUBEX-TF and Typhidot for typhoid fever surveillance. J Infect Dev Ctries 2011;5:169-75.
40. Khan K, Khalid L, Wahid K, et al. Performance of TUBEX® TF in the diagnosis of enteric fever in private tertiary care Hospital Peshawar, Pakistan. J Pak Med Assoc 2017;67:661-664.

41. Bhutta ZA, Mansur AN. Rapid serologic diagnosis of pediatric typhoid fever in an endemic area: a prospective comparative evaluation of two dot-enzyme immunoassays and the Widal test. Am J Trop Med Hyg 1999;61:654-7.
42. Mehmood K, Sundus A, Naqvi IH, et al. Typhidot - A blessing or a menace. Pak J Med Sci 2015; 31:439-443.
43. Hatta M, Goris MG, Heerkens E, et al. Simple dipstick assay for the detection of Salmonella typhi-specific IgM antibodies and the evolution of the immune response in patients with typhoid fever. Am J Trop Med Hyg 2002;66:416-21.
44. John W, Salih H. The laboratory diagnosis of enteric fever. J Infect Dev Ctries 2008;2:421-425.
45. Song JH, Cho H, Park MY, et al. Detection of Salmonella typhi in the blood of patients with typhoid fever by polymerase chain reaction. JCM 1993;31:1439-1443.
46. Zhou L, Pollard AJ. A fast and highly sensitive blood culture PCR method for clinical detection of Salmonella enterica serovar Typhi. Ann Clin Microbiol Antimicrob 2010;9:14.
47. Ali A, Haque A, Sarwar Y. Multiplex PCR for differential diagnosis of emerging typhoidal pathogens directly from blood samples. Epidemiol Infect 2009; 137:102-107.
48. Haque A, Ahmed N, Peerzada A, et al. Utility of PCR in diagnosis of problematic cases of typhoid. Jpn J Infect Dis 2001;54:237-9.
49. Butt T, Ahmad RN, Mahmood A, et al. Ciprofloxacin Treatment Failure in Typhoid Fever Case, Pakistan. Emerging Infectious Diseases. 2003;9:1621-1622.
50. Yan M, Li X, Liao Q, et al. "The emergence and outbreak of multidrug-resistant typhoid fever in China. Emerg Microbes Infect 2016;5:62.
51. Renuka K, Sood S, Das BK, et al. High-level ciprofloxacin resistance in Salmonella enterica serotype Typhi in India. J Med Microbiol 2005;54:999-1000.
52. Shirakawa T, Acharya B, Kinoshita S, et al. Decreased susceptibility to fluoroquinolones and gyrA gene mutation in the Salmonella enterica serovar Typhi and Paratyphi A isolated in Kathmandu, Nepal, in 2003. Diagn Microbiol Infect Dis 2006;54:299-303.
53. Butt T, Ahmad RN, Salman M, et al. Changing trends in drug resistance among typhoid salmonellae in Rawalpindi, Pakistan EMHJ 2005;11:1038-1044.
54. Saleem MZ, Arshad A, Qayyum M, et al. Changing Trends in Antibiogram and Molecular Analysis of Quinolone Resistant Salmonella typhi Isolates in Pakistan. J Infec Dis Treat 2017; 3:1.
55. Afzal A, Sarwar Y, Ali A, et al. Current status of fluoroquinolone and cephalosporin resistance in Salmonella enteric serovar Typhi isolates from Faisalabad, Pakistan. Pak J Med Sci 28:602-607.
56. Parry CM, Threlfall EJ. Antimicrobial resistance in typhoidal and nontyphoidal salmonellae. Curr Opin Infect Dis 2008;21:531-8.
57. Chen HM, Wang Y, Su LH, et al. Nontyphoid Salmonella infection: microbiology, clinical features, and antimicrobial therapy. Pediatr Neonatol 2013;54:147-52.
58. WHO World Health Organization. Critically important antimicrobials for human medicine, 3rd revision. 2012.
59. Misra R, Prasad KN Antimicrobial susceptibility to azithromycin among Salmonella enterica Typhi and Paratyphi A isolates from India. J Med Microbiol 2016;65:1536-1539.
60. Moorhead R. William Budd and typhoid fever. J R Soc Med 2002;95:561-4.
61. Cumming O, Elliot M, Overbo A, et al. Does global progress on sanitation really lag behind water? An analysis of global progress on community and household level access to safe water and sanitation. PLoS One 2014;9:e114699.
62. Garmory HS, Brown KA, Titball KA, et al. Salmonella vaccines for use in humans: present and future perspectives. FEMS Microbiol Rev 2002;26:339-53.
63. Szu SC. Development of Vi conjugate. A new generation of typhoid vaccine. Exp Rev Vaccines 2013;12:1273-86.
64. Lin FY, Ho Va, Khiem HB, et al. The efficacy of a Salmonella Typhi Vi conjugate vaccine in two-to-five-year-old children. N Engl J Med 2001;344:1263-9.

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