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REVIEW ON - TO STUDY THE PATHOPHYSIOLOGY OF TYPHOID

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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 enteric 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. First line 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.

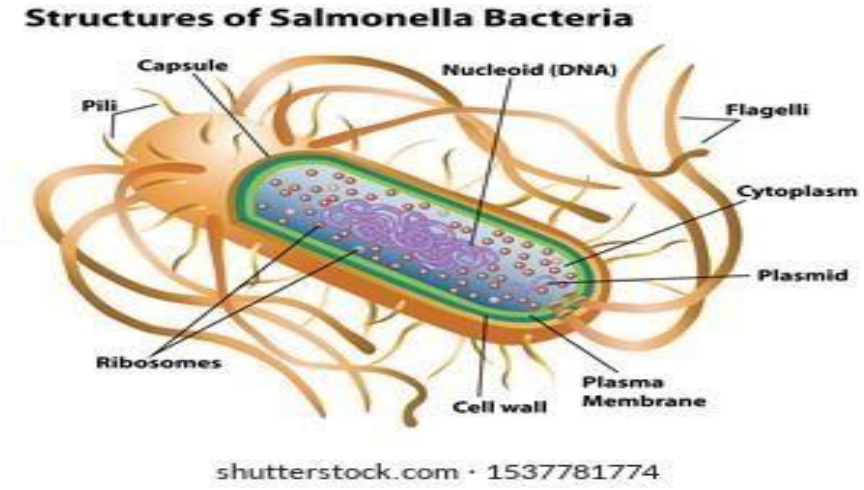
Objectives:

- Describe the structure of S.typhi, mechanism, etiology and epidemiology of typhoid fever.
- Describe the pathophysiology and evaluation typhoid fever.
- Describe the causes, transmission, sign and symptoms of typhoid fever and procedure of Widal test for detecting the typhoid fever.
- Describe the diagnosis, treatment and prevention of typhoid fever

1. INTRODUCTION

Typhoid is an extreme, infectious and dangerous malady related with fever. It is caused by Salmonella enterica servers Typhi,Paratyphi A, Paratyphi B, and Paratyphi C can be collectively categorized as typhoidal Salmonella, though some are gathered as non typhoidal 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 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] The most recent two decades have seen the development and spread of multidrug opposition against the ordinary antityphoiddrugs (chloramphenicol, cotrimoxazole, fluoroquinolones andampicillin) among the typhoid salmonellae, particularly in South and Southeast Asia, including Pakistan.[7]

STRUCTURE OF S.TYPHI:



ETIOLOGY:

The main causative agent of typhoid fever is Salmonella typhi and Salmonella paratyphi, both are members of the Enterobacteriaceae family. Salmonella is a genus that has two species Salmonella enteric serovar and enteritidis classified through extensive analysis by multiplex quantitative polymerase chain reaction (PCR). Both Salmonella typhi and Salmonella paratyphi (A, B, C) are Salmonella enteric serotypes. Nontyphoidal salmonella (NTS) is more typical in children and is mostly limited to gastroenteritis.

Salmonella is transmitted by the fecal-oral route through contaminated water, undercooked foods, fomites of infected patients, and is more common in areas with overcrowding, social chaos, and poor sanitation. It is only transmitted from an infected person to another person, as humans are its only host. Major sources of salmonella are poultry, eggs, and rarely turtles. In one study done on the distribution of salmonella isolates by whole-genome sequencing in chicken slaughterhouses in China, 57% of samples were positive.[8]

Normal flora of the gut is protective against the infection. The use of antibiotics such as streptomycin destroys the normal flora, which heightens its invasion. Malnutrition decreases normal gut flora and thus increases the susceptibility to this infection as well. Hence, the use of broad spectrum antibiotics and poor nutrition amplify the incidence of typhoid fever.[9]

EPIDEMIOLOGY:

While the United States reports only about 350 culture-confirmed cases of typhoid fever and fewer than 100 paratyphi A cases each year since 2008, enteric fever remains an important cause of illness worldwide. Approximately 215,000 deaths result from over 26 million cases of typhoid fever and 5 million cases of paratyphoid infection each year worldwide. The incidence of typhoid is more common in low and middle-income countries of south-central Asia and southern Africa than in developed countries. Most cases in developed countries are carried by travelers returning from endemic areas and travelers visiting relatives and friends that are at heightened risk due to their likelihood to be less cautious with sources of food and water. Those less likely to seek vaccination and pretravel consultation are also at heightened risk. Typhoid fever is more prevalent in temperate and tropical climates. It is directly associated with sanitation, sewage, and water treatment system. [10]Salmonella typhi is more common than Salmonella paratyphi, and Salmonella paratyphi A is more prevalent than Salmonella paratyphi B infections. The number of new cases of typhoid fever has been increasing worldwide due to rapid increases in population, pollution, and shortages of pure drinking water. Still, death rates have decreased due to extensive research, changes in treatment modalities, and the invention of new drugs despite growing multidrug-resistance. In the era of routine antibiotics, classic presentations are not always seen. In the United States, splenomegaly and rose spots may be seen in only 10% and 1.5% of the cases, respectively.

Up to 4% of patients with typhoid fever go on to become chronic carriers. These patients remain asymptomatic after their acute treatment, but they may excrete Salmonella for up to 1 year in their stool, or less frequently their urine. It is more commonly seen in women and those with biliary abnormalities, including cholelithiasis. Blood group antigens may also be linked to susceptibility to S. typhi chronic carriage.[11]

PATHOPHYSIOLOGY:

The pathogenesis of typhoid fever depends upon a number of factors, including infectious species, virulence, host's immunity, and infectious dose. The larger the infectious dose, the shorter the incubation period, and the higher the attack rate. Typhoid fever is more severe in debilitated and immunocompromised patients such as those with HIV (mainly paratyphi), those on glucocorticoid therapy, and those with altered phagocyte function (i.e., patients with malaria and sickle cell anemia). Salmonella is an acid-sensitive bacteria except for a few resistant strains, so typically it is destroyed in the stomach by gastric acid unless a large dose is ingested. In patients with achlorhydria, intake of antacids and antihistamines, colonization of Salmonella occurs even with smaller doses. Food and beverages also act as buffers against gastric acid that facilitates bacteria reaching the small gut. [12]

The virulence of Salmonella is determined by typhoid toxin, Vi antigen (polysaccharide capsule), liposaccharide O antigen, and flagellar H antigen. Strains positive for Vi antigen have an attack rate twice that of Vi negative strains, even for the same dose of micro-organisms. One of the main differences between Salmonella typhi and non-typhoidal salmonella (NTS) is the presence of Vi antigen in Salmonella typhi but absent in NTS. The main role of the Vi antigen is to act as an antiphagocytic agent preventing the action of macrophages, thus shielding the O antigen from antibodies that confer the serum resistance. The flagellar H antigen provides bacterial mobility and adherence upon the gut wall mucosa. Invasion of the gut wall is assisted by flagella, and the type III secretion system is capable of transferring bacterial protein into enterocytes and M cells (specialized epithelial cells that serve as antigen-presenting cells in gut mucosa or lymphoid tissue) or by direct penetration of mucosa. Bacteria attached to M cells are absorbed by pinched off cytoplasm containing bacteria and extruded into the luminal space. In this process, M cells are damaged, and the basal lamina is exposed. It provides easy access to pathogens for the invasion, which worsens the condition. The cystic fibrosis transmembrane conductance regulator (CFTR) is said to be important in the uptake of Salmonella; so, patients with abnormal CFTR protein are resistant to typhoid. The transferred proteins activate the host cell Rho GTPases, which trigger the actin rearrangement so that bacterial protein uptake takes place in the phagosomes where the bacteria can grow. This special characteristic of the bacteria helps them to remain viable in a pool of host immunity. Salmonella also produces a molecule that stimulates the epithelial release of chemo attractant eicosanoid, which sequesters neutrophils into the lumen and potentiates mucosal damage.

Bacteria induce proliferation of Payer patches via recruitment of lymphocytes and mononuclear cells and induce necrosis and eventually, ulceration that complicates the symptoms. Pathogens reach the reticuloendothelial system via both lymphatic system and bloodstream, including other multiple organs, most commonly gallbladder in almost all cases. The early bacteremic phase (24 hours to 72 hours) is asymptomatic and transient as these bacteria are phagocytosed by macrophages and monocytes in the reticuloendothelial system called primary bacteremia. The capacity of pathogens to grow in these immune cells makes them characteristic, and intracellular multiplication of bacteria in the reticuloendothelial system enforces them to re-enter the bloodstream causing continuous bacteremia for several days and weeks known as secondary bacteremia. Secondary bacteremia is the phase in which disease symptoms manifest. Like in other gram-negative bacteria, an endotoxin has an important role in the pathogenesis. The lipopolysaccharide induces the shock-like reaction, and endotoxemia leads to vascular hyperactivity and catecholamine release, which causes focal necrosis and hemorrhage.[13]

EVALUATION

The approach to typhoid patients should be clinical. Patients residing in areas with poor sanitation or impure drinking water or history of travel from endemic areas presenting with febrile illness for more than three days along with gastrointestinal manifestations (pain, constipation, or diarrhea) are highly suspicious. Diagnosis in the first week is difficult, but a variety of laboratory studies assist in making the diagnosis.

- **Blood Culture:**

Blood culture remains the primary mechanism of confirmation of a typhoid fever diagnosis. It is widely available and the most commonly performed test, as it is not expensive or technically difficult. The efficacy of the blood culture is increased when high volume samples are taken. Blood cultures done during secondary bacteremia (i.e., clinical manifestations) are more reliable though 30% to 50% of cultures may be falsely negative depending on the technique and time series.

- **Stool Culture:**

Stool culture is less effective in the bacteremic phase of the disease. Stool culture is diagnostic in the second and third weeks. It was estimated to yield a positive result in only 37% of patients with antibiotic therapy. The sensitivity of stool culture depends upon the amount of stool sample taken and the duration of illness. Chronic carriers intermittently pass pathogens in the fecal matter for a long time so, several samples should be taken. Additional metabolite biomarkers are under investigation.[14]

- **Bone Marrow:**

Bone marrow culture is the gold standard for typhoid diagnosis. The aspirated bone marrow sample is cultured in specific agar media. It is more sensitive than blood cultures due to the larger number of micro-organisms present in the bone marrow. Bone marrow culture is highly sensitive (around 90%) and even remains positive in more than 50% of cases despite several days of antibiotic therapy. However, the test is highly invasive and expensive, so it is not routinely used for the diagnosis and treatment of typhoid. [15]

CAUSES:

1. It can spread by contaminated of food and water.
2. Direct contacted with someone who is infected?
3. Poor sanitation and poor hygiene.
4. Lack of personal hygiene.[16]

TRANSMISSION:

Humans are the only natural host and reservoir. The infection is transmitted by ingestion of food or water contaminated with faeces. Ice cream is recognized as a significant risk factor for the transmission of typhoid fever. Shellfish taken from contaminated water,and raw fruit and vegetables fertilized with sewage, have been sources of past outbreaks. The highest incidence occurs where water supplies serving large populations are

contaminated with faeces. Epidemiological data suggest that waterborne transmission of S. typhi usually involves small inocula, whereas foodborne transmission is associated with large inocula and high attack rates over short periods. The inoculum size and the type of vehicle in which the organisms are ingested greatly influence both the attack rate and the incubation period. In volunteers who ingested 109 and 108 pathogenic S. typhi in 45 ml of skimmed milk, clinical illness appeared in 98% and 89% respectively.Doses of 105 caused typhoid fever in 28% to 55% of volunteers, whereas none of 14 persons who ingested 103 organisms developed clinical illness. Although it is widely believed that Salmonella is transmitted via the oral route, the transmission of S. typhimurium via the respiratory route has been demonstrated in a mousemodel Family studies were conducted in Santiago, Chile, during an era of high typhoid endemicity in order to as certain whether chronic carriers were significantly more frequent in households where there were index cases of children with typhoid fever than in matched control households. Other epidemiological studies investigated whether risk factors could be identified for persons with typhoid fever in comparison with uninfected household members. It was concluded that chronic carriers in householdsdid not play an important role in transmission. Subsequently, it was shown that theirrigation of salad with wastewater contaminated with sewage was the key factorresponsible for maintaining the high endemicity of typhoid in Santiago. In developed countries, on the other hand, typhoid is transmitted when chronic carriers contaminate food as a consequence of unsatisfactory food-related hygiene practices. [17] [18]

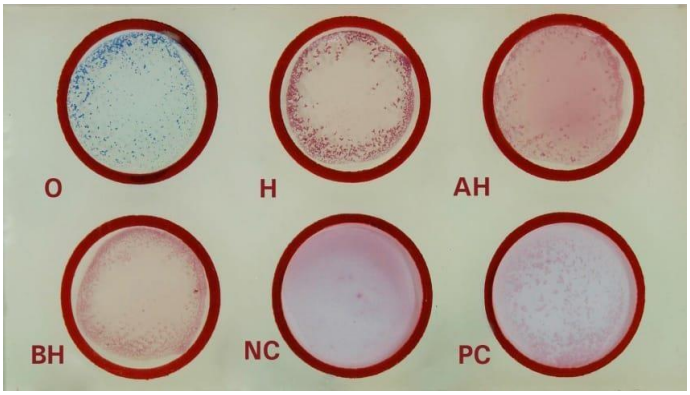
SIGNS AND SYMPTOMS INCLUDE:

1.Headache	6.Loss of appetite and weight loss
2.Weakness and fatigue	7.Stomuch pain
3.Muscle aches	8.Diarrhea or constipation
4.Sweating	9.Rash
5.Dry cough	10.Extremely swollen stomuch

PROCEDURE OF WIDAL TEST:

SLIDE TEST

1. Place one drop of positive control on one reaction circles of the slide.
2. Pipette one drop of Isotonic saline on the next reaction cirlcle. (-ve Control).
3. Pipette one drop of the patient serum to be tested onto the remaining four reaction circles.
4. Add one drop of Widal TEST antigen suspension ‘H’ to the first two reaction circles. (PC & NC).
5. Add one drop each of ‘O’, ‘H’, ‘AH’ and ‘BH’ antigens to the remaining four reaction circles.
6. Mix contents of each circle uniformly over the entire circle with separate mixing sticks.
7. Rock the slide, gently back and forth and observe for agglutination macroscopically within one minute.



DIAGNOSIS:

Body fluid or tissue culture:

For the culture, a small sample of your blood, stool, urine or bone marrow is placed on a special medium that encourages the growth of bacteria. The culture is checked under a microscope for the presence of typhoid bacteria. A bone marrow culture often is the most sensitive test for Salmonella typhi.[19]

Although performing a culture test is the most common diagnostic test, other testing may be used to confirm a suspected typhoid fever infection, such as a test to detect antibodies to typhoid bacteria in your blood, or a test that checks for typhoid DNA in your blood.

TREATMENT:

Antibiotic therapy is the only effective treatment for typhoid fever.

- **Ciprofloxacin (Cipro:** In the United States, doctors often prescribe this for adults who aren't pregnant. ...
- **Azithromycin (Zithromax):** This may be used if a person is unable to take ciprofloxacin or the bacteria are resistant to ciprofloxacin.[20]

PREVENTATION:

1. **Safe water:** Typhoid fever is a waterborne disease and the main preventive measure is to ensure access to safe water. The water needs to be of good quality and must be sufficient to supply all the community with enough drinking water as well as for all other domestic purposes such as cooking and washing.

2. **Food safety:** Contaminated food is another important vehicle for typhoid fever transmission. Appropriate food handling and processing is paramount and the following basic hygiene measures must be implemented or reinforced during epidemics:

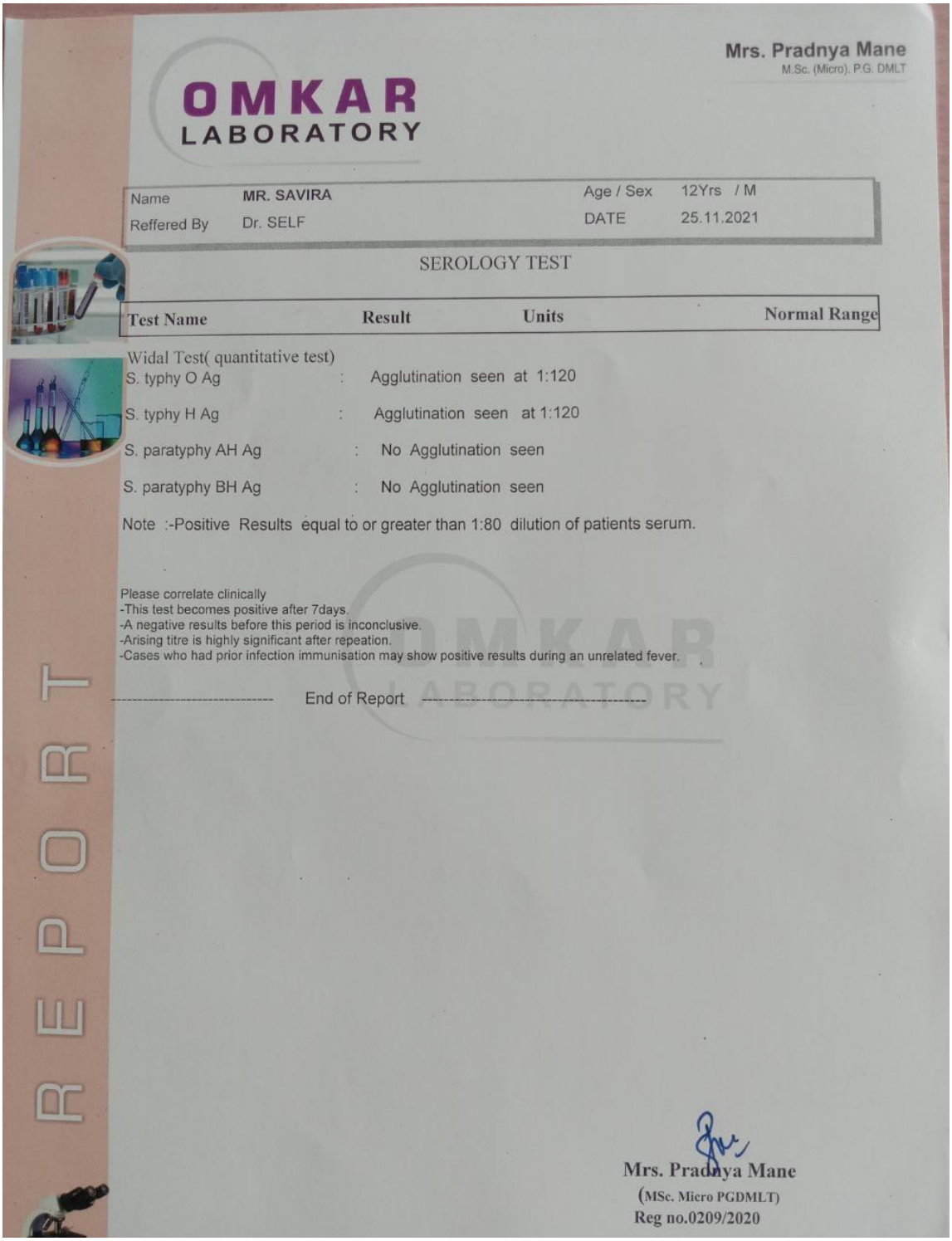
    - Washing hands with soap before preparing or eating food; avoiding raw food, shellfish, ice.
    - Eating only cooked and still hot food or re-heating it.

3. **Sanitation:** Proper sanitation contributes to reducing the risk of transmission of all diarrhoeal pathogens including Salmonella typhi.

    - Appropriate facilities for human waste disposal must be available for all the community. In an emergency, pit latrines can be quickly built.
    - Collection and treatment of sewage, especially during the rainy season, must be implemented
    - In areas where typhoid fever is known to be present, the use of human excreta as fertilisers must be discouraged.

4. **Vaccination:** Vaccination can help prevent typhoid fever. CDC recommends vaccination for people traveling to places where typhoid fever is common, such as South Asia, especially India, Pakistan, or Bangladesh.

    - Oral vaccine: Can be given to people at least 6 years old. It consists of four pills taken every other day and should be finished at least 1 week before travel.
    - Inject able vaccine: Can be given to people at least 2 years old and should be given at least 2 weeks before travel.[21][22]



Mrs. Pradnya Mane
M.Sc. (Micro). P.G. DMLT

OMKAR
LABORATORY

Name	MR. SAVIRA	Age / Sex	12Yrs / M
Reffered By	Dr. SELF	DATE	25.11.2021

SEROLOGY TEST

Test Name	Result	Units	Normal Range
Widal Test(quantitative test)			
S. typhy O Ag	: Agglutination seen at 1:120		
S. typhy H Ag	: Agglutination seen at 1:120		
S. paratyphy AH Ag	: No Agglutination seen		
S. paratyphy BH Ag	: No Agglutination seen		

Note :-Positive Results equal to or greater than 1:80 dilution of patients serum.

Please correlate clinically
-This test becomes positive after 7days.
-A negative results before this period is inconclusive.
-Arising titre is highly significant after repeation.
-Cases who had prior infection immunisation may show positive results during an unrelated fever.

---------- End of Report ----------

REPORT

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(MSc. Micro PGDMLT)
Reg no.0209/2020

Outcomes:

After the completion of report on Typhoid, I understood,

1. Understood the pathology of the typhoid.
2. Understood the information about typhoid fever.
3. Able to understand the different technique use to determine typhoid fever.
4. Understood the causes of fever and diagnosis the disease for further treatment of typhoid.

2. CONCLUSION

Project helps to understood transmission of disease with the different types of modes. From above report antigen H and O are seen, hence the widal test of this blood sample is positive.

From the above study it is concluded and analyzed cause of fever and diagnosis of disease for further treatment as per cause.

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MAPPING WITH POS:

Program Outcomes:

PO 1: Pharmacy Knowledge

PO 2: Planning Abilities

PO 3: Problem Analysis

PO 4: Modern tool usage

PO 5: Leadership skills

PO 6: Professional identity

PO7: Pharmacist ethics

PO 8: Communication

PO 9: Pharmacist & society

PO 10: Environment & sustainability

PO 11: Lifelong learning