Typhoid

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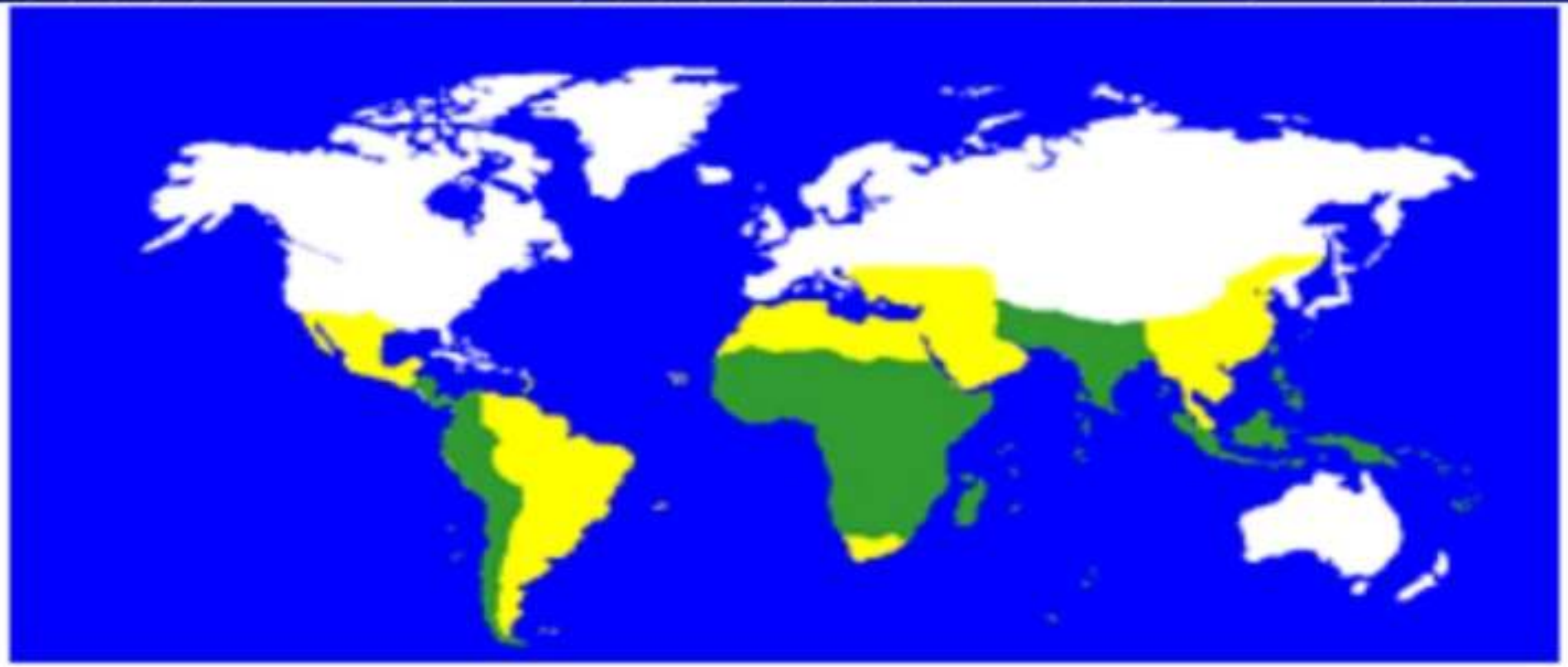
https://thebiologynotes.com/pathogenicity-clinical-manifestation-salmonella-typhi/

Typhoid fevers are prevalent in many regions in the World



High endemicity

Medium endemicity

Sporadic outbreaks

Enteric Fevers

- The syndrome associated with enteric fevers are produced only by a few of the Salmonella
- Salmonella typhi most important
- Salmonella paratyphi A, B,C

Historical landmarks in Typhoid

- In 1880s, the typhoid bacillus was first observed by Eberth in spleen sections and mesenteric lymph nodes from a patient who died from typhoid. Robert Koch confirmed a related finding by Gaffky and succeeded in cultivating the bacterium in 1881. But due to the lack of differential characters, separation of the typhoid bacillus from other enteric bacteria was uncertain.

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History of Sero Diagnosis

- In 1896, it was demonstrated that the serum from an animal immunized with the typhoid bacillus agglutinated (clumped) the typhoid bacterial cells, and it was shown that the serum of patients afflicted with typhoid likewise agglutinated the typhoid bacillus. Serodiagnosis of typhoid was thus made possible by 1896.

Typhoid Mary

- A famous example is "Typhoid" Mary Mallon, who was a food handler responsible for infecting at least 78 people, killing 5. These highly infectious carriers pose a great risk to public health.

Typhoid Mary

- "Typhoid Mary," real name Mary Mallon, worked as a cook in New York City in the early 1900s. Public health pioneer Sara Josephine Baker, MD, PhD tracked her down after discovering that she was the common link among many people who had become ill from typhoid fever She was traced to typhoid outbreaks a second time so she was put in prison again where she lived until she died.

Etiology of Typhoid fever

- Typhoid fever is a bacterial disease, caused by *Salmonella typhi*. It is transmitted through the ingestion of food or drink contaminated by the faeces or urine of infected people.
- Para typhoid fevers are produced by other species named

  Paratyphi A, B, C

Changing taxonomy of Salmonella species

- Salmonella are Gram-negative bacteria which cause intestinal infections. The taxonomy of *Salmonella* species is complicated. Formally, there are only two species within this genus: *S. bongori* and *S. enterica* (formerly called *S. choleraesuis*), which are divided into six subspecies:

Different types of Salmonella

I - *enterica*
II - *salamae*
IIIa -*arizonae*
IIIb -*diarizonae*
IV - *houtenae*
V - *bongori*
VI - *indica*

Bacteriology –Typhoid fever

- The Genus Salmonella belong to Enterobactericiae
- Facultative anaerobe
- Gram negative bacilli
- Distinguished from other bacteria by Biochemical and antigen structure

Antigenic structure of Salmonella

- Two sets of antigens
- Detection by serotyping
- 1 ***Somatic or 0 Antigens*** contain long chain polysaccharides (LPS) comprises of heat stable polysaccharide commonly.

- ***2 Flagellar or H Antigens*** are strongly immunogenic and induces antibody formation rapidly and in high titers following infection or immunization. The flagellar antigen is of a dual nature, occurring in one of the two phases.

Paratyphoid fevers on rise

- Paratyphoid fever can be caused by any of three serotypes of S. paratyphi A, B and C. It is similar in its symptoms to typhoid fever, but tends to be milder, with a lower fatality rate.

How a Typhoid fever spreads

- *Salmonella* Typhi lives only in humans. Persons with typhoid fever carry the bacteria in their bloodstream and intestinal tract. In addition, a small number of persons, called carriers , recover from typhoid fever but continue to carry the bacteria. Both ill persons and carriers shed *S.* Typhi in their feces (stool).

Clinical features

Typhoid fever (enteric fever) is a septicemia, illness characterized initially by fever, bradycardia, splenomegaly, abdominal symptoms and 'rose spots' which are clusters of pink mauls on the skin.

Complications such as intestinal hemorrhage or perforation can develop in untreated patients or when treatment is delayed.

Pathology and Pathogenesis of Enteric fever

- Caused by

  S. typhi

  S.paratyphi

  A B C

The organisms penetrate ileal mucosa reach mesentric lymph nodes via Lymphatics , Multiply,

Invade Blood stream via thoracic duct

In 7 – 10 days through blood stream infect

Liver, Gall Bladder,, spleen, Kidney, Bone marrow.

After multiplication bacilli pass into blood causing secondary and heavier bactermia

Fever

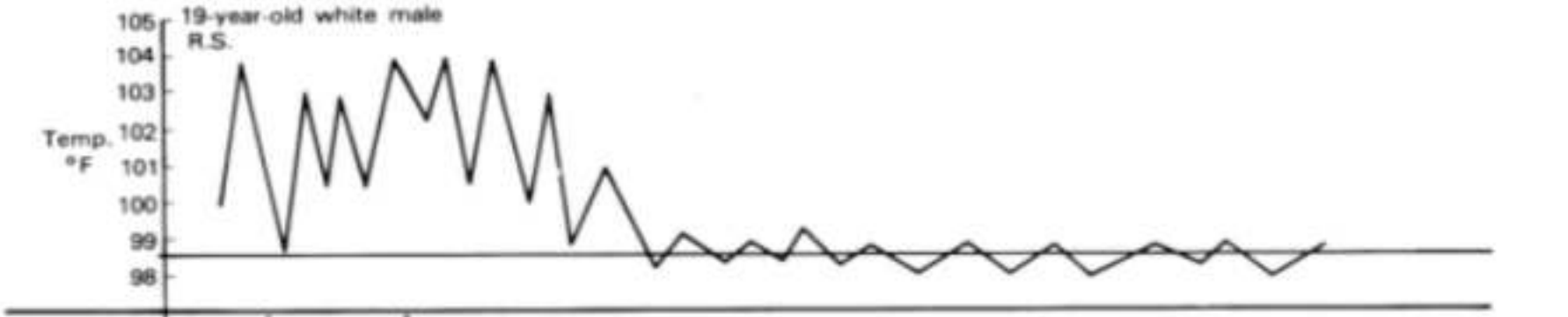
- All the events coincides with Fever and other signs of clinical illness
- From Gall bladder further invasion occurs in intestines
- Involvement of peyr's patches, gut lymphoid tissue
- Lead to inflammatory reaction, and infiltration with monocular cells
- Leads to Necrosis, Sloughing and formation of chacterstic typhoid ulcers

Clinical presentation

- Ingestion to onset of fever varies from 3 – 50 days. (2 weeks)
- Insidious start, early symptoms are vague
- Dull continuous head ache
- Abdominal tenderness discomfort may present with constipation.
- May progress and present with step ladder pattern temperature
- Temperature fall by crisis in 3 – 4th week

Events in a Typical typhoid Fever

CHART 23.—Course of typhoid fever of a previously immunized American patient in Vietnam



Cultures			C.S.F. negative		*S. typhosa* cultured from blood and stool								Blood-stool negative			
Hospital day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Antibiotic treatment				1 gram chloramphenicol Q6H			.5 gram Q6H									Total chloramphenicol treatment 2 weeks
Widal O				> 160								< 40				
Widal H				< 40								< 40				
WBC		6,200		4,200	4,300	7,400	6,600	5,600			7,400	8,000				
PMNS		50		58	65	60	50	52			49	52				

Source: Records of patients treated by Lt. Col. Kenneth W. Hedlund, MC, 85th Evacuation Hospital, Vietnam.

Other manifestations

- Relative bradycardia
- Hepatomegaly
- Splenomegaly

Complication in Typhoid

- Severe intestinal hemorrhage and intestinal perforation
- If not diagnosed can lead to fatal complications.

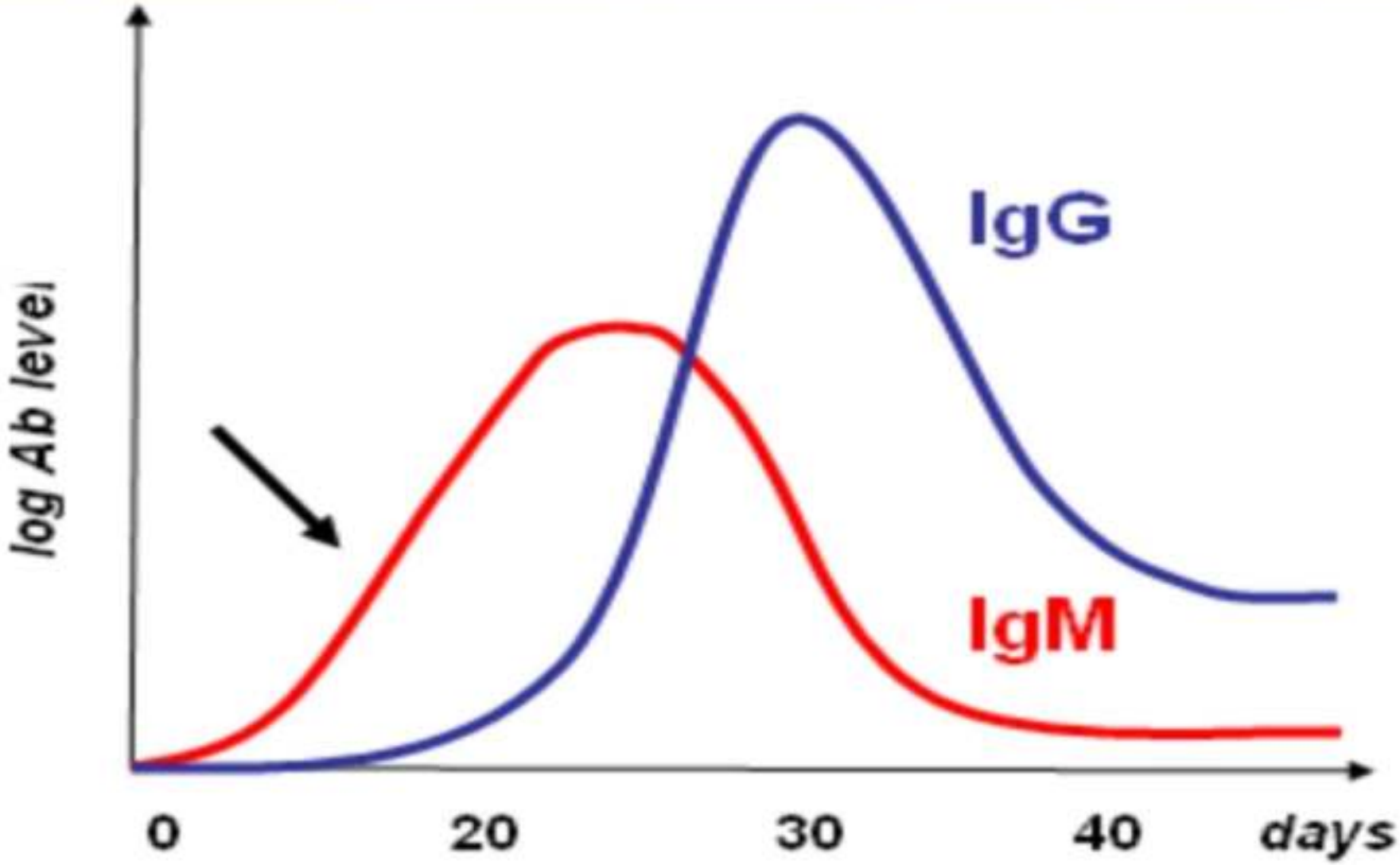
Rashes in Typhoid

- May present with rash, rose spots 2 -4 mm in diameter raised discrete irregular blanching pink maculae's found in front of chest
- Appear in crops of upto a dozen at a time
- Fade after 3 – 4 days

Relapse

- Apparent recovery can be followed by relapse in 5 – 10 % of untreated patients
- On few occasions relapses can be severe and may be fatal.

Immune Response in Typhoid



Morbidity and Mortality

- In untreated patients mortality can be up to 20 %
- Occasionally present with diarrhea may mimic other infections, which is particularly common in paratyphoid fever.
- Patient may present as gastro enteritis no different from that caused by other S.enterica serotypes.

Typhoid carriers

- *Salmonella enterica* causes approximately 16 million cases of typhoid fever worldwide, killing around 500,000 per year. One in thirty of the survivors, however, become carriers. In carriers the bacteria remain hidden inside cells and the gall bladder, causing new infections as they are shed from an apparently healthy host.

Academic progress on carrier state in Typhoid

- The factors that enable the bacteria to establish chronic infection were unclear. However, in a paper published this week in the Proceedings of the National Academy of Science, researchers at the Institute of Food Research in Norwich and the Karolinska Institute in Sweden found that the change of a single base pair in one *Salmonella* gene can determine if the bacteria cause short-term illness or a long-term carrier state.

Diagnosis of Enteric Fever

Blood cultures in Typhoid fever

- In Adults 5- 10 ml of Blood is collected by venepuncture inoculated into 50 – 100 ml of Bile broth (0.5 %)
- Several other media are available used as per the availability of medium to suit their laboratory conditions.

Blood Cultures in Typhoid Fevers

- Bacteremia occurs early in the disease
- Blood Cultures are positive in

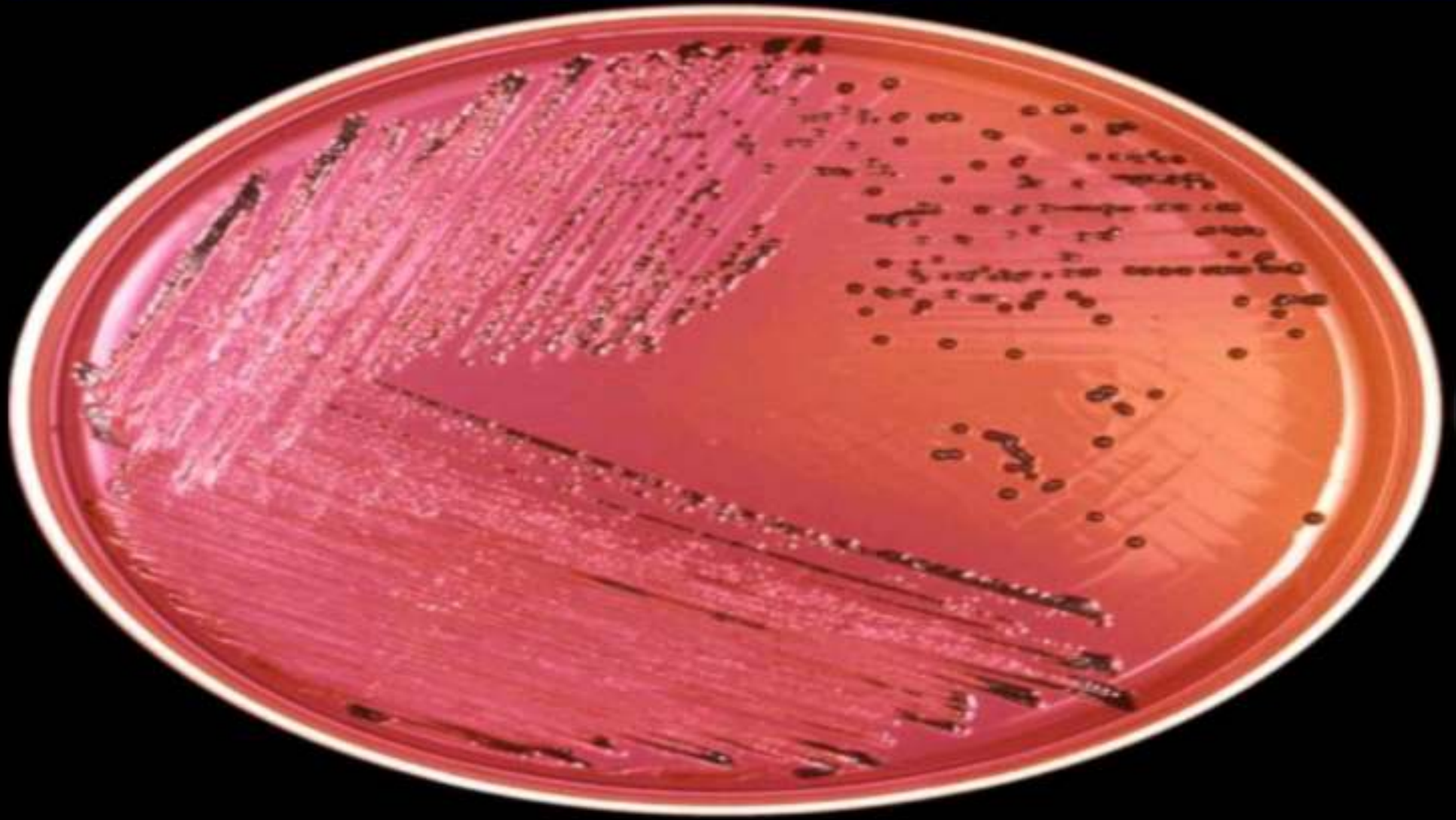
1st week in 90%
2nd week in 75%
3rd week in 60%
4th week and later in 25%

Identification of Salmonella

- Sub cultures are done after overnight incubation at 37^0c,and subcultures are done on Mac Conkey's agar
- Subcultures are repeated upto 10 days after futher incubation.

Salmonella on Mac Conkey's agar

Salmonella on XLD agar



Identifying Enteric Organisms

- Isolates which are Non lactose fermenting
- Motile, Indole positive
- Urease negative
- Ferment Glucose,Mannitol,Maltose
- Donot ferment Lactose, Sucrose
- Typhoid bacilli are anaerogenic
- Some of the Paratyphoid form acid and gas
- Further identification done by slide agglutination tests

Slide agglutination tests

- In slide agglutination tests a known serum and unknown culture isolate is mixed, clumping occurs within few minutes
- Commercial sera are available for detection of A, B, C_1, C_2, D, and E.

Clot culture

- Clot cultures are more productive in yielding better results in isolation.
- A blood after clotting, the clot is lysed with Streptokinase ,but expensive to perform in developing countries.

Bactek and Radiometric based methods are in recent use

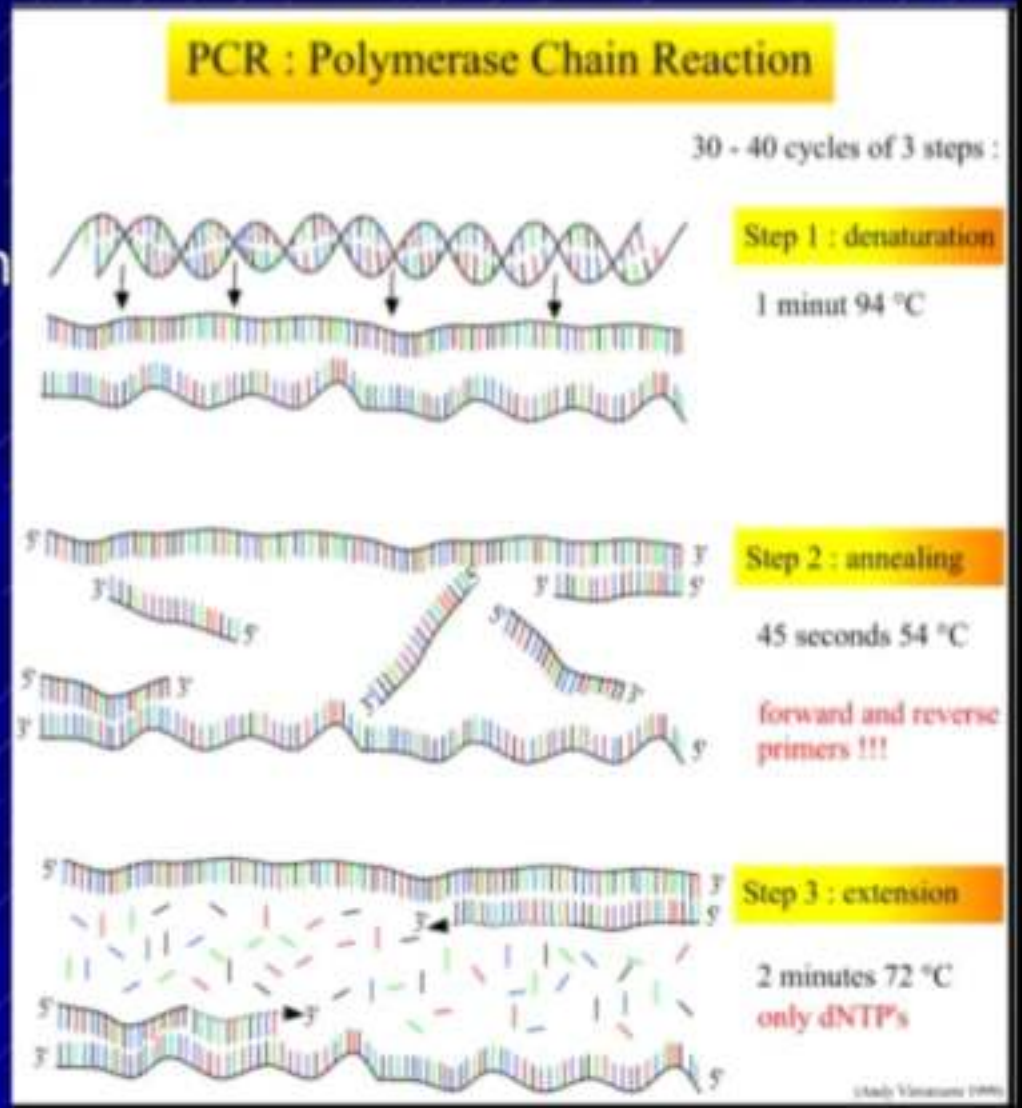
- Bactek methods in isolation of Salmonella is a rapid and sensitive method in early diagnosis of Enteric fever.
- Many Microbiology Diagnostic Laboratories are upgrading to Bactek methods

Other methods in Isolation of Enteric Pathogens

- Feces Culture
- Urine Culture
- Bone marrow cultures (Highly Sensitive)

Emerging Methods in Diagnosis of Enteric fevers.

- Detection of circulating antigen by Co - agglutination methods with use of Cowan's strain Staphylococcus coated with antibodies
- PCR. The advent of PCR technology has provided unparalleled sensitivity and specificity for the diagnosis of typhoid



Diagnosis of Carriers

- Useful in public health purpose.
- Useful in screening food handlers, cooks, to detect carrier state
- Typhoid bacilli can be isolated from feces or from bile aspirates
- Detection of Vi agglutinins in the Blood can be determinant of carrier state.

Widal Test

- In 1896 Widal A professor of pathology and internal medicine at the University of Paris (1911–29), he developed a procedure for diagnosing typhoid fever based on the fact that antibodies in the blood of an infected individual cause the bacteria to bind together into clumps (the Widal reaction).

Diagnosis of Enteric Fever

Widal test

- Serum agglutinins raise abruptly during the 2nd or 3rd week
- The widal test detects antibodies against O and H antigens
- Two serum specimens obtained at intervals of 7 – 10 days to read the raise of antibodies.
- Serial dilutions on unknown sera are tested against the antigens for respective Salmonella
- False positives and False negative limits the utility of the test
- The interpretative criteria when single serum specimens are tested vary
- Cross reactions limits the specificity

Significant Titers helps in Diagnosis

- Following Titers of antibodies against the antigens are significant when single sample is tested

  O > 1 in 160

  H > 1 in 320

  Testing a paired sample for raise of antibodies carries a greater significance

Widal test – Still a popular test

- The Widal test (Widal's agglutination reaction) is routinely practised for the serodiagnosis of typhoid fever by most of the laboratories. Several workers have expressed doubt regarding the reliability of the test. Several factors have contributed to this uncertainty. These include poorly standardised antigens, the sharing of antigenic determinants with other Salmonellae and the effects of immunisation with TAB vaccine. Another major problem relates to the difficulty of interpreting Widal test results in areas where Salmonella typhi is endemic and where the antibody titres of the normal population are often not known.

Limitations of Widal test

- Classically, a four-fold rise of antibody in paired sera Widal test is considered diagnostic of typhoid fever. However, paired sera are often difficult to obtain and specific chemotherapy has to be instituted on the basis of a single Widal test. Furthermore, in areas where fever due to infectious causes is a common occurrence the possibility exists that false positive reactions may occur as a result of non-typhoid

Antimicrobial Therapy in Typhoid

- With prompt antibiotic therapy, more than 99% of the people with typhoid fever are cured, although convalescence may last several months. The antibiotic chloramphenicolSome Trade Names
  CHLOROMYCETIN
  is used worldwide, but increasing resistance to it has prompted the use of other antibiotics (such as trimethoprim-sulfamethoxazole
  BACTRIM
  SEPTRA
  or ciprofloxacin

Drug resitance an Emerging concern

- Previously Choramphenicol was the drug of choice for the treatment of typhoid fever. However, with the development more safer and more effective drugs the use of Choramphenicol has declined these days. 3rd generation cephalosporins, like Ceftriaxone, and Flouroquinolones, like ciprofloxacin and levofloxacin are the drugs of choice for treatment of typhoid fever .Once again many strains are sensitive to Choramphenicol

Vaccines for Typhoid Prevention

- Two types of vaccines are available
- Oral and Inject able
- Oral – A live oral vaccine (typhoral) is a stable mutant of S.typhi strain Ty 21a lacking the enzyme UDP Galactose -4-epimerase.

  One capsule given orally taken before food, with glass of water or milk, on 1, 3, 5 days (three doses)

  No antibiotics should be taken during the period of administration of vaccine

Vaccine - injectable

- The inject able vaccine, (typhim –vi) contains purified Vi polysaccharide antigen derived from S.typhi strain ty21
- Given as single subcutaneous or intramuscular injection
- Single dose is adequate.

Vaccines for Typhoid

Both vaccines are given to only > 5 years of age.

Immunity lasts for 3 years

Need a booster

Vaccines are not effective in prevention of Paratyphoid fevers

Simple hand hygiene and washing can reduce several cases of Typhoid