

# Specific infections/Typhoid fever

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# Typhoid Fever

Library



*Salmonella typhi*

# Typhoid Fever

- Gram negative bacilli
  - *Salmonella typhi*
  - *Salmonella paratyphi*
- Fecal-oral route
  - *Contaminated food or water*
- Incubation period 5-21 days

# Global epidemiology

- Endemic in almost all developing countries
- In 2000:
  - typhoid fever caused an estimated 21.7 million illnesses and 217,000 deaths
  - paratyphoid fever caused an estimated 5.4 million illnesses
- Many more subclinical cases

Crump JA, et al. The global burden of typhoid fever. Bull World Health Organ 2004

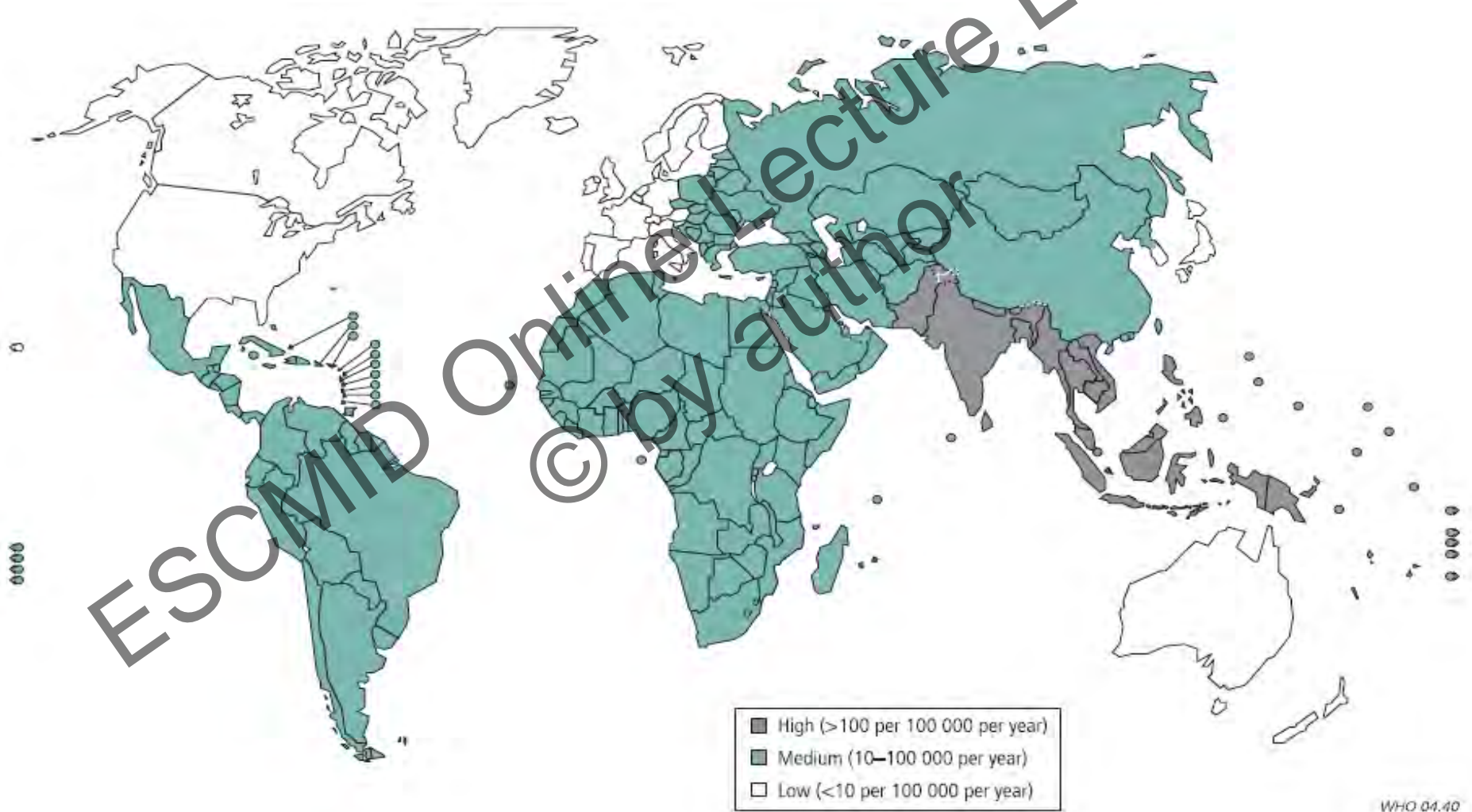
# Crude typhoid fever incidence rates by region, 2000

Area/Region	Typhoid cases	Population	Crude Incidence <sup>a</sup>	Incidence classification
<b>Africa</b>				
Eastern Africa <sup>b</sup>	98 560	255 500 000	39	Medium
Middle Africa <sup>b</sup>	36 857	95 385 000	39	Medium
Northern Africa	58 210	175 037 000	33	Medium
Southern Africa	123 473	52 887 000	233	High
Western Africa <sup>b</sup>	91 737	241 102 000	38	Medium
<b>Area total</b>	<b>408 837</b>	<b>819 911 000</b>	<b>50</b>	<b>Medium</b>
<b>Asia</b>				
Eastern Asia	182 927	1 483 111 000	12	Medium
South-central Asia	9 299 064	1 495 977 000	622	High
South-eastern Asia	575 407	521 983 000	110	High
Western Asia <sup>b</sup>	61 481	187 463 000	33	Medium
<b>Area total</b>	<b>10 118 879</b>	<b>3 688 534 000</b>	<b>274</b>	<b>High</b>
<b>Europe</b>				
Eastern Europe	15 940	306 654 000	5	Low
Northern Europe	143	93 736 000	<1	Low
Southern Europe	2785	144 861 000	2	Low
Western Europe	276	184 077 000	<1	Low
<b>Area total</b>	<b>19 144</b>	<b>729 328 000</b>	<b>3</b>	<b>Low</b>
<b>Latin America/Caribbean</b>				
Caribbean <sup>b</sup>	19 889	37 757 000	53	Medium
Central America <sup>b</sup>	79 164	135 497 000	58	Medium
South America	174 465	341 434 000	51	Medium
<b>Area total</b>	<b>273 518</b>	<b>514 688 000</b>	<b>53</b>	<b>Medium</b>
<b>Northern America</b>				
Northern America	453	308 636 000	<1	Low
<b>Area total</b>	<b>453</b>	<b>308 636 000</b>	<b>&lt;1</b>	<b>Low</b>
<b>Oceania</b>				
Australia/New Zealand	62	22 598 000	<1	Low
Melanesia <sup>b</sup>	3897	6 489 000	60	Medium
Micronesia <sup>b</sup>	326	539 000	60	Medium
Polynesia	371	626 000	59	Medium
<b>Area total</b>	<b>4656</b>	<b>30 252 000</b>	<b>15</b>	<b>Medium</b>
<b>Global</b>				
Crude total	10 825 487	6 091 349 000	178	High
Adjusted total	21 650 974	6 091 349 000	355	

<sup>a</sup> Per 100 000 persons per year.

<sup>b</sup> Region incidence estimate derived by extrapolation.

# Geographical distribution of typhoid fever



# Clinical Presentation

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# Patients without treatment

- Week 1
  - Fever
  - Bacteremia
- Week 2 and 3
  - Severe clinical picture
  - Abdominal pain
  - Rash (Rose spots)
  - Hepatosplenomegaly
- Week 4
  - Intestinal perforation / hemorrhage



# Early Phase

- Findings are not specific
- Fever
- Malaise
- Anorexia
- Headache
- Myalgia
- A flue like clinic?

<b>Symptoms</b>	<b>Frequency (%)</b>
Fever	89 - 99
Headache	48 - 83
Nausea	39 - 71
Vomiting	36 - 63
Stomachache	32 - 66
Diarrhea	37 - 60
Constipation	11 - 28
Coughing	14 - 41
Anorexia	63 - 81
Chilling-Shivering	33 - 74
Myalgia and arthralgia	27-35
Sore throat	9-20

**Table 1** Clinical Variables in 41 Cases of Enteric Fever Seen in a Parisian Hospital

	<i>Typhoid Fever</i> n = 22 (%)	<i>Paratyphoid Fever</i> n = 19 (%)
Symptoms		
Fever	22 (100)	17 (89)
Headache	18 (82)	15 (79)
Diarrhea	11 (50)	11 (58)
Chills	11 (50)	9 (47)
Anorexia	8 (36)	9 (47)
Fatigue	10 (45)	5 (26)
Abdominal pain	8 (36)	6 (31)
Myalgia	6 (27)	7 (37)
Nausea	5 (23)	7 (37)
Vomiting	5 (23)	3 (16)
Insomnia	8 (36)	3 (16)
Physical Signs		
Abdominal tenderness	9 (41)	6 (31.5)
Relative bradycardia	6 (27)	2 (10.5)
Rose spots	2 (9)	3 (16)
Splenomegaly	1 (4.5)	4 (21)
RLQ gurgling	3 (14)	2 (10.5)
Coated tongue	3 (14)	1 (5)

RLQ = right lower quadrant.

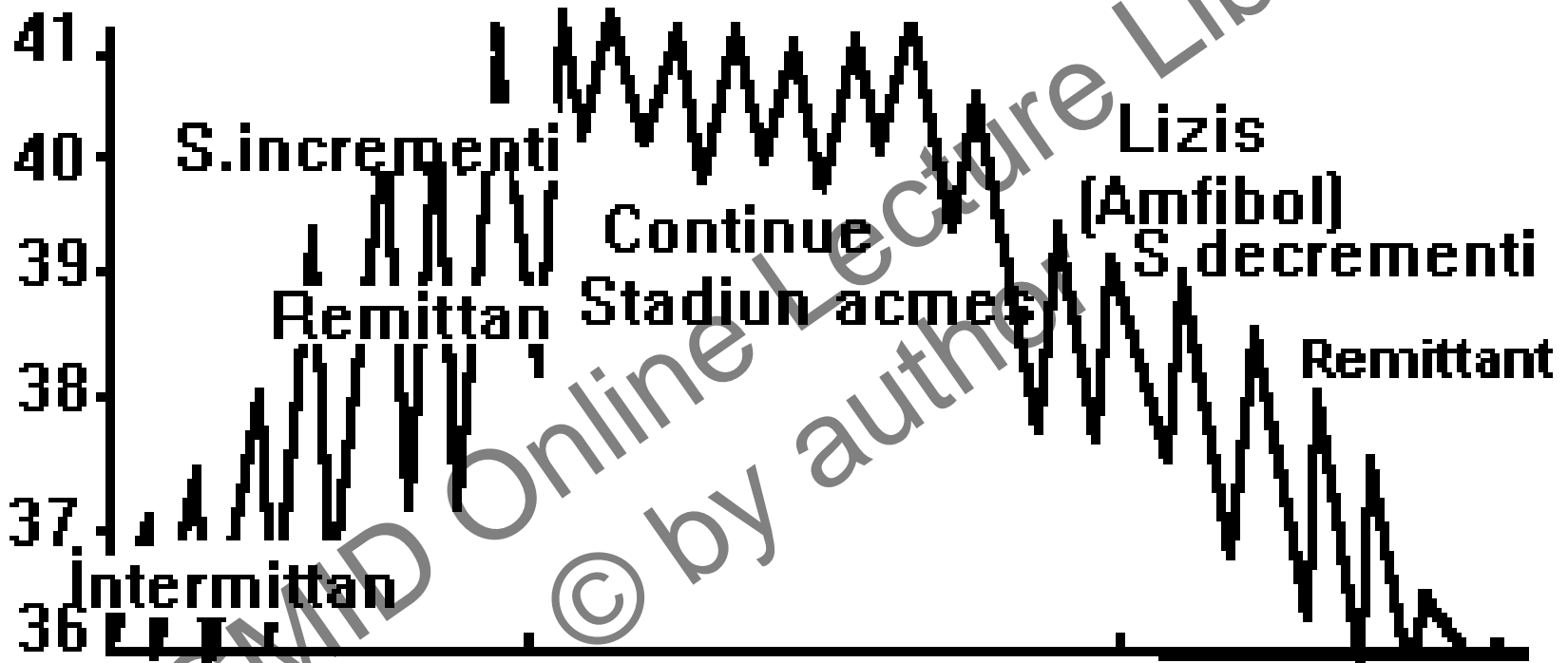
# Course of the disease

- Physical findings have diversity
- Clinical presentation is acute
- Fever (intermittent and remittent in the 1<sup>st</sup> week, then continued)
- Use of antipyretics or anti-inflammatory drugs lead chilling and sweating
- Chilling in 1/3 of the patients
- Lower abdomen is sensitive
- Peristaltism is low
- Cervical lymphadenopathy could be detected

# Findings

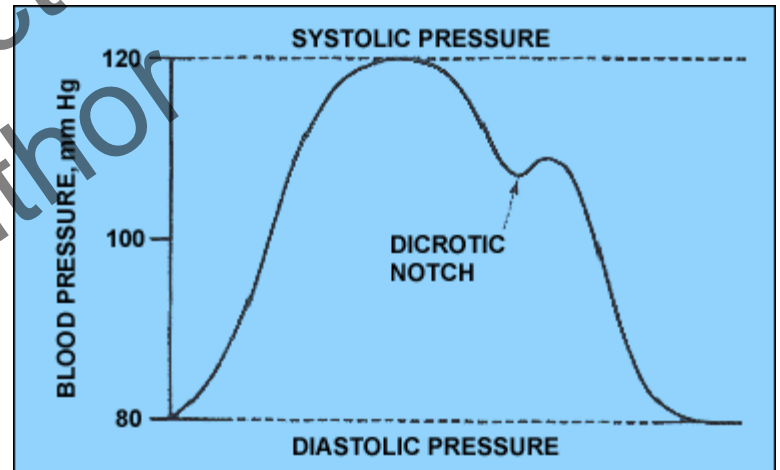
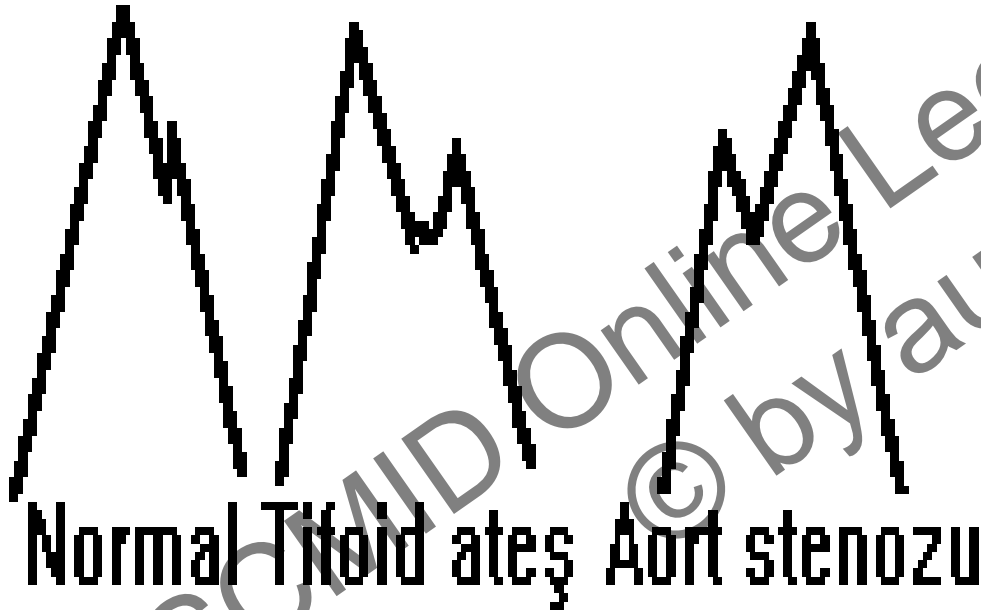
- The end of 1<sup>st</sup> week, fever could be 40°C
- Coated tongue
- Mental dullness % 10
- Discordance in pulsation (common)
- Dicrotic pulse (soft and double pulse)
- Tache rose
- Hepatomegalia % 25-50
- Splenomegalia % 40-60
- Lethargy, delirium and coma rare
- Rales could be available
- Distention is common

# Course of typhoid fever without treatment

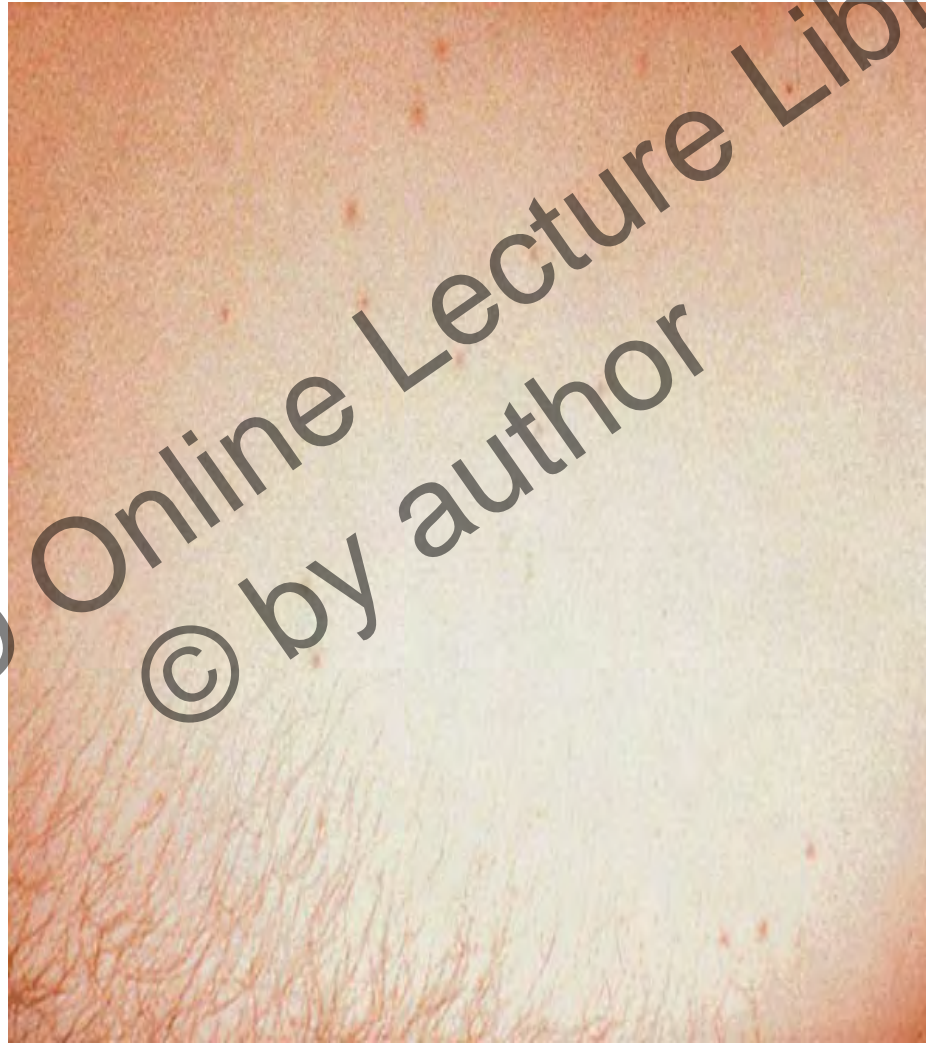


1 <sup>st</sup> week	2 <sup>nd</sup> -3 <sup>rd</sup> weeks	4 <sup>th</sup> week
Intermittent	Remittant	Remittant
Headache	Discordance	Convalescence
Constipation	Somnolence, drowsy	
Diarrhea	Coated tongue, HSM	
	Taches rose, Complications	

# Dicrotic Pulse



# ROSEOL



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# Diagnosis

- Anamnesis
  - Suspected food or drink in the last 2-3 weeks
  - Travel in the last 2-3 weeks
  - Fever (could be irregular at the beginning)
- Laboratory
  - Anemia
  - Leukocytosis / leukopenia
  - Abnormal Liver Function Tests
- Isolation of bacteria
  - Blood culture – positive in 40-80%
  - Stool culture – positive in 30-40%
  - Bone marrow – positive in 98%

# Key topics in diagnosis

- Diagnose sometimes is not easy
- Fever is almost exist
- In endemic area misdiagnosis is common
- In traveler, no suspect, diagnose is difficult
- The destination is important
- Antibiotic use makes the diagnose complex
- The symptoms and signs of uncomplicated typhoid fever are nonspecific
- The diagnosis is challenge

# Typhoid fever mimics

- Brucellosis
- Encephalitis
- Meningitis
  - Viral
  - Tuberculosis
  - Bacterial
- Pneumonia
- Leptospirosis
- Malaria
- Bacteremia/sepsis
- Tularemia
- Rickettsial diseases,
- Dengue fever
- Acute hepatitis
- EMN
- Leishmaniasis,
- Amebiasis
- Urinary tract infection
- Upper viral respiratory infection
- Adult-onset Still's disease
- Others

Yamaguchi M, 1992

- Culture positivity
  - Blood culture – 1<sup>st</sup> and 2<sup>nd</sup> weeks high
  - Stool culture – 3<sup>rd</sup> week better
  - Bone marrow – 1<sup>st</sup> and 2<sup>nd</sup> weeks high
    - The most sensitive
    - Difficult to perform and invasive
  - Other body sites
    - Stool
    - Urine
- Blood cultures are positive in 40-80%
- Cultures may be useless or less sensitive because of antibiotic use

Hoffman, S.L., 1984; Chart, H, 2000

# Other Laboratory Tests

- Leucopenia is common, not specific
- In infants leukocytosis is not rare
- Widal test is available in everywhere
- Nested PCR may be more sensitive than blood cultures
- PCR is becoming the "**gold-standard**" for diagnosis of typhoid fever
- Using monoclonal antibodies
  - *S. typhi*-specific antigens in the serum or *S. typhi* Vi antigen in the urine

# Widal test

- The most common test

More valuable!!!

OR

Useless!!!

- Classic Widal test in endemic areas
  - Low level sensitivity and specificity
- Many false-positive and false-negative results
- Widal test alone is not adequate
- Sensitivity estimated from 25% to 80%
- In developed countries, it is not exactly necessary

# Treatment

- Use culture and sensitivity results
- Fluoroquinolone
  - Ciprofloxacin 500 mg bid
  - Ofloxacin 400 mg bid
- Plus 3<sup>rd</sup> generation cephalosporin
  - High levels of resistance in some strains
  - Continue while sensitivities pending
  - Ceftriaxone 2-3 g od

# Treatment of typhoid fever in adults

Treatment type, antibiotic	Dosage (route)	Duration, days
Empirical treatment		
Ceftriaxone <sup>a</sup>	60 mg/kg/day (intravenous or intramuscular) <sup>b</sup>	7–14
Azithromycin	8–10 mg/kg/day (oral)	7
Treatment of fully drug-susceptible infection		
Ciprofloxacin (first-line treatment) <sup>c</sup>	15 mg/kg/day (oral or intravenous)	5–7
Amoxicillin (second-line treatment)	75–100 mg/kg/day (oral or intravenous)	14
Chloramphenicol	75 mg/kg/day (oral, intravenous, or intramuscular)	14–21
Trimethoprim-sulfamethoxazole	8/40 mg/kg/day (oral or intravenous)	14
Treatment of multidrug-resistant infection		
Ceftriaxone <sup>a</sup>	60 mg/kg/day (intravenous or intramuscular) <sup>b</sup>	5–7
Ciprofloxacin <sup>c</sup>	15 mg/kg/day (oral or intravenous)	7–14
Azithromycin	8–10 mg/kg/day (oral)	7
Treatment of fluoroquinolone-resistant infection		
Ceftriaxone <sup>a</sup>	60 mg/kg/day (intravenous or intramuscular) <sup>b</sup>	7–14
Azithromycin	8–10 mg/kg/day (oral)	7
High-dose ciprofloxacin <sup>c</sup>	20 mg/kg/day (oral or intravenous)	10–14

<sup>a</sup> Or other third-generation cephalosporins (e.g., cefotaxime and cefixime).

<sup>c</sup> Or ofloxacin

<sup>b</sup> Intramuscular administration with 1% lidocaine.



# Monitoring of treatment

- Fever may continue 5-6 days after treatment
- Be aware about intestinal bleeding and perforation during treatment
- Patient can spread the bacilli, prevent other patients and workers
- Fluid support is important for serious cases
- If not MDR strain, 7-10 days is enough

# Prevention

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# Hazardous behaviors

- Traveler should be aware about food and drink
- Hazardous foods
  - Uncooked foods
  - Vegetables (especially salads, lettuce etc.)
  - Local uncooked foods
  - Ice-cream
  - Unbottled drinks
  - Tap water
- Depends on the countries and destination
- Hand hygiene is important

# Vaccine

Vaccines against typhoid fever	Age of recipients, years	Regimen	Adverse effects and comments
Oral, live attenuated Ty 21 a vaccine (Vivotif Bernal) <sup>a</sup>	>6	Given on days 1, 3, 5, and 7; booster given every 5 years; in Europe, it is available as a 3-dose vaccine	Live, attenuated vaccine should not be given to immunocompromised persons or persons receiving antibiotics; vaccine is well tolerated (50%–80% effective); rare adverse effects include abdominal pain, nausea, and vomiting
Parenteral capsular polysaccharide vaccine (Typhim Vi, Aventis Pasteur SA) <sup>a</sup>	>2	Given in 1 dose with a booster every 2 years	Vaccine is well tolerated (50%–80% effective; adverse effects include headache (16%–20% of recipients) and fever (0%–1%))
Acetone-killed whole cell vaccine <sup>b</sup>	...	...	...
Modified Vi vaccine conjugated to nontoxic recombinant <i>Pseudomonas aeruginosa</i> exotoxin A	>2	Given in 2 parenteral doses	Vaccine was well tolerated and had the highest efficacy rate (90%); vaccine may even be immunogenic for infants aged <2 years; vaccine is not commercially available at present

<sup>a</sup> Not be administered to people with acute febrile illness.

<sup>b</sup> Available for use only by the US military.

# Trends in traveler typhoid fever

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Risk of Travel-Associated Typhoid and  
Paratyphoid Fevers in Various Regions

*Karl Ekdahl, Birgitta de Jong, and Yvonne Andersson*

*J Travel Med* 2005; 12:197–204.

# A Swedish Study

- All case records of travelers from 1997 to 2003 on typhoid and paratyphoid fevers
- 16,000 Swedish residents with recent overnight travel outside Sweden
- The overall risk after travel was 0.42 in 100,000 travelers for typhoid fever:
  - India and neighboring countries (41.7 in 100,000)
  - Middle East (5.91 in 100,000)
  - Central Africa (3.33 in 100,000),
  - East Asia (0.24 in 100,000)
- Almost the same risk areas stood out for paratyphoid fever:
  - India and neighbors (37.5 in 100,000)
  - Middle East (3.64 in 100,000)
  - East Africa (3.33 in 100,000).

# Incidence is decreasing



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## **Fecal-Orally Transmitted Diseases Among Travelers Are Decreasing Due to Better Hygienic Standards at Travel Destination**

**Gijs G. Baaten, MD,<sup>\*††</sup> Gerard J.B. Sonder, MD, PhD,<sup>\*††</sup> Maarten F. Schim van der Loeff, MD, PhD,<sup>\*†</sup> Roel A. Coutinho, MD, PhD,<sup>\*†§</sup> and Anneke van den Hoek, MD, PhD<sup>\*†</sup>**

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## Incidence is decreasing

- The incidence among travelers are decreasing due to better hygienic standards at travel destination
- A study from the Netherland
- All laboratory-confirmed cases of travel-related typhoid fever from 1995 to 2006
- Attack rates among Dutch travelers to developing regions declined for typhoid fever
- Declining attack rates of the disease correlated with improvements in socioeconomic, sanitary, and water supply conditions

Trends in attack rates for typhoid fever per 100,000 Dutch travelers to developing countries, from 1995 to 2006 (per region/country)

	Typhoid fever				
	Median	1995*	2006*	<i>p</i> Value	
<b>All regions</b>	1.9	5.6	1.0	<0.0001	↓
<b>Latin America<sup>†</sup></b>	0.4	1.2	0.3	0.55	=
Caribbean	0.0	0.0	0.0	0.24	=
<b>Sub-Saharan Africa<sup>‡</sup></b>	2.1	6.5	1.6	0.2609	=
Eastern/Southern	0.0	0.0	0.0	0.17	=
Western/Middle	8.3	18.2	8.3	0.93	=
<b>Arab region<sup>§</sup></b>	1.2	4.6	0.2	<0.0001	↓
Turkey	0.2	2.0	0.0	<0.0001	↓
Egypt	0.6	3.8	0.0	<0.0001	↓
<b>Asia<sup>  </sup></b>	5.2	7.5	3.2	0.0007	↓
Thailand/Malaysia	0.0	0.0	0.0	0.12	=
Indian subcontinent	19.7	39.0	15.3	0.71	=

# Conclusion

- Travelers need to be targeted for the prevention of enteric fever
- Especially going to the Indian subcontinent
- Travelers should be aware about typhoid fever risks
- The hazardous behaviors are eating raw vegetables and tap water, not obtain typhoid and other vaccines
- Non-typhoid fever is increasing because of lacking of vaccine