Typhoid

Helena Rabie

Stellenbosch University

Tygerberg Academic Hospital Complex

When we saw her:

- Looks unwell
  - Abdominal pain
  - Loose stools
- Murmur with out cardiac failure
- Abdomen “uncomfortable”
- Splenomegaly

- Blood culture
- Salmonella typhi

https://medlineplus.gov/.

When we saw her:

- Looks unwell
  - Abdominal pain
  - Loose stools
- Murmur with out cardiac failure
- Abdomen “uncomfortable”
- Splenomegaly

- Long fever – sub-acute/chronic course
- Vague abdominal Sx
- Not “septic” looking
- “funny stare”
- “Geo-spacing”

Zimbabwe

- October 2017 to February 2018, 3000 suspected cases caused by a strain of *Salmonella enterica* subsp *enterica* serovar Typhi (*S* Typhi) resistant to ciprofloxacin

Vaccination

Zimbabwe tackles typhoid and cholera through vaccination

Lancet microbe 2021

Genus *Salmonella*

Species *Salmonella bongoi*

Species *Salmonella enterica*

Salmonella enterica subsp. *enterica*

subsp. *salamae*
subsp. *arizonae*
subsp. *diarizonae*
subsp. *houtenae*
subsp. *indica*

Typhoidal

Non- Typhoidal

Salmonella enterica subsp. *enterica* ser. Typhi

Salmonella enterica subsp. *enterica* serotype Paratyphi A, B, and C.

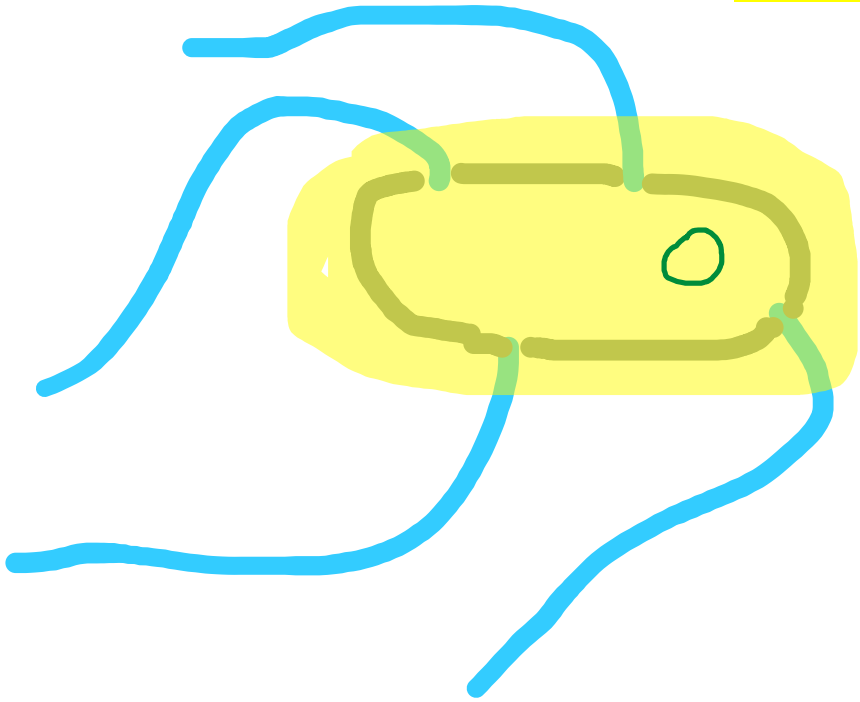
Intestinal
- Invasive
- Non-invasive

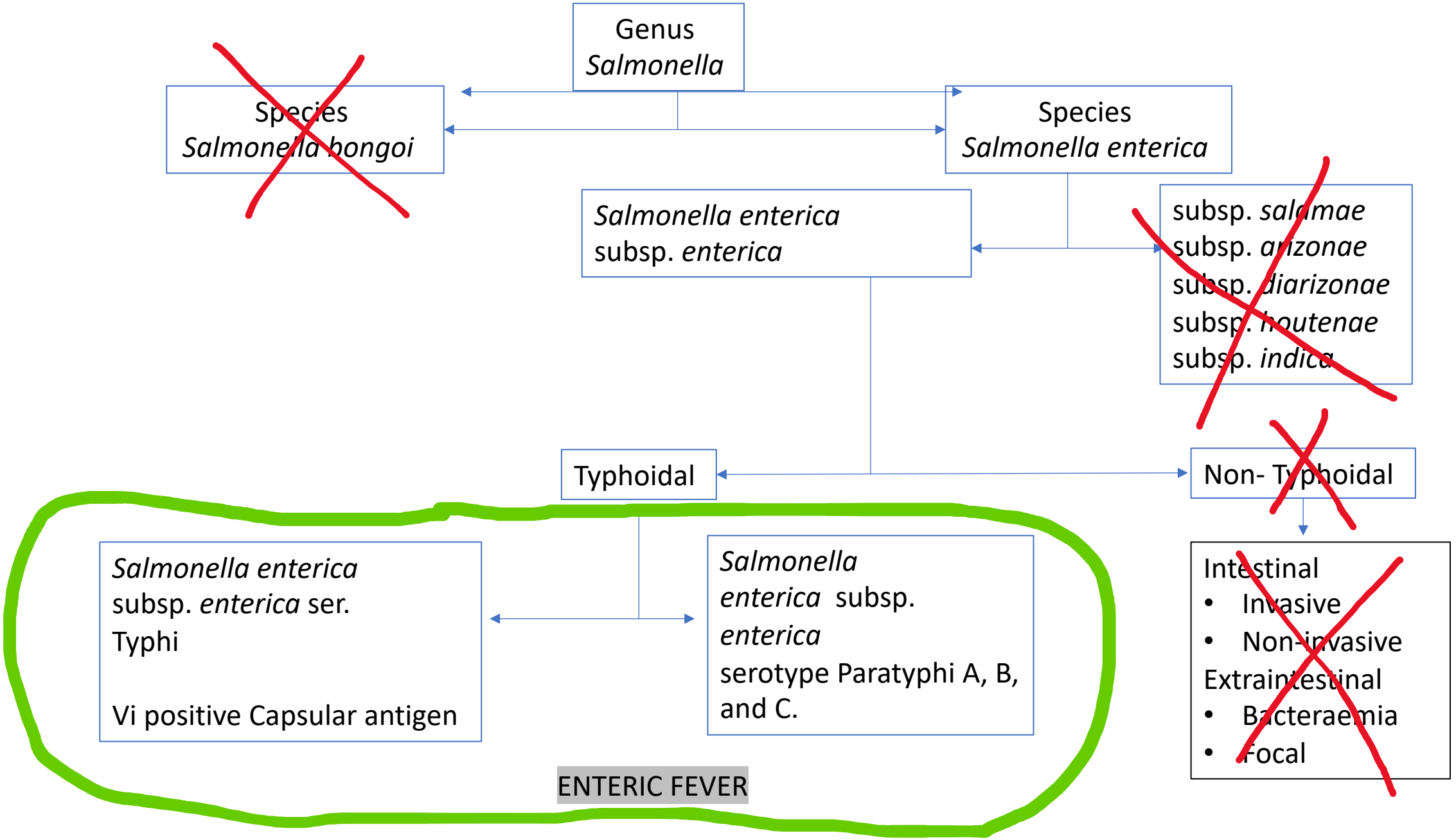
Extraintestinal
- Bacteraemia
- Focal

Flagella – H antigen

Somatic O antigen – Cell wall

Surface antigen




Genus
Salmonella
Species
Salmonella bongoi
Species
Salmonella enterica
Salmonella enterica
subsp. enterica
subsp. salamae
subsp. arizonae
subsp. diarizonae
subsp. houtenae
subsp. indica
Typhoidal
Non- Typhoidal
Salmonella enterica
subsp. enterica ser.
Typhi
Vi positive Capsular antigen
Salmonella
enterica subsp.
enterica
serotype Paratyphi A, B,
and C.
Intestinal
• Invasive
• Non-invasive
Extraintestinal
• Bacteraemia
• Focal
ENTERIC FEVER

1829: Pierre Louis, a French pathologist. Used the word “ typhoid” -described in detail post-mortem finding, especially the enlargement and ulceration of peyer’s patches.

1868: Carl Wunderlich, a German clinician. Used a new technology – thermometer to show differences typhoid and typhus fever patterns

1873: William Budd from Bristol described the contagious nature of the disease and link to sewers

1880: Karl Eberth Identified *S. enterica* in the abdominal nodes

- 1884 Robert Koch “comma virus” Vibrio cholera

1884:Georg Gaffky Cultured

1896-1911: Heat killed phenol preserved whole cell vaccine

1903-1906 – German Festchrift – the role of health cariers

1948 Antibiotics

“Bodentheorie” – Von Plettenkofer
X+Y= Z
One and only drinking water faith” “Does not hold water”

Ruhr valley Outbreak of typhoid fever 3000 victims, 8% dies

- Water supply inadequate
  - An emergency pipe was opened to admit untreated water from the Ruhr river.
  - There was also a ruptured pipe
- Robert Koch
  - Explosive nature of the epidemic
  - Distribution of cases in a particular area among people who had not been in contact with each other, and the exact correspondence of the affected area with the piped water supply.
  - Koch was relying essentially on the arguments put forward by John Snow in regard to cholera half a century before.

- Is water a food stuff?
- Act of God.
- *Ignoramus*?
  - School of thought may change

"liquidate the drinking water theories
- 1912 Stickler "

BMJ 1973

Could some individuals spread the disease without showing any symptoms?

1906 Long Island, summer home of Charles Warren

- 27 August 3 September, 6 /11 suffering from typhoid fever
- Civil engineer George Soper
  - Fresh water clams
  - “Stalking Mary Mallon”
  - Mary was then frequently accused of being the source of contact for hundreds of the ill.

THE WORK OF A CHRONIC TYPHOID GERM DISTRIBUTOR.*

GEORGE A SOPER, PH.D

NEW YORK CITY.

In the winter of 1906 I was called on to investigate a household epidemic of typhoid fever which had broken out in the latter part of August at Oyster Bay, N. Y. The epidemic had been studied carefully immediately after it took place, but its cause had not been ascertained with as much certainty as seemed desirable to the owner of the property.

The essential facts concerning the investigation follow:

THE CURIOUS CAREER OF TYPHOID MARY*

GEORGE A. SOPER

JAMA 1907
Bull NY Acad Med

Salmonella enterica Subs *enterica* serotype Typhi

- Gram negative enteric bacillus
- Non-spore forming non-capsulated
- Can survive for several months in water
- Oral ingestion food or water
- *S. enterica* serotype Typhi – Only cause disease in humans
- Intracellular
- 204 pseudogenes encoded inactivated by a stop codon
- *Salmonella* pathogenicity island
  - Vi- higher attack rate – prohibits cellular response
  - LPS
  - AB5-toxin – if intracellular
  - Fagella

Enteric fever

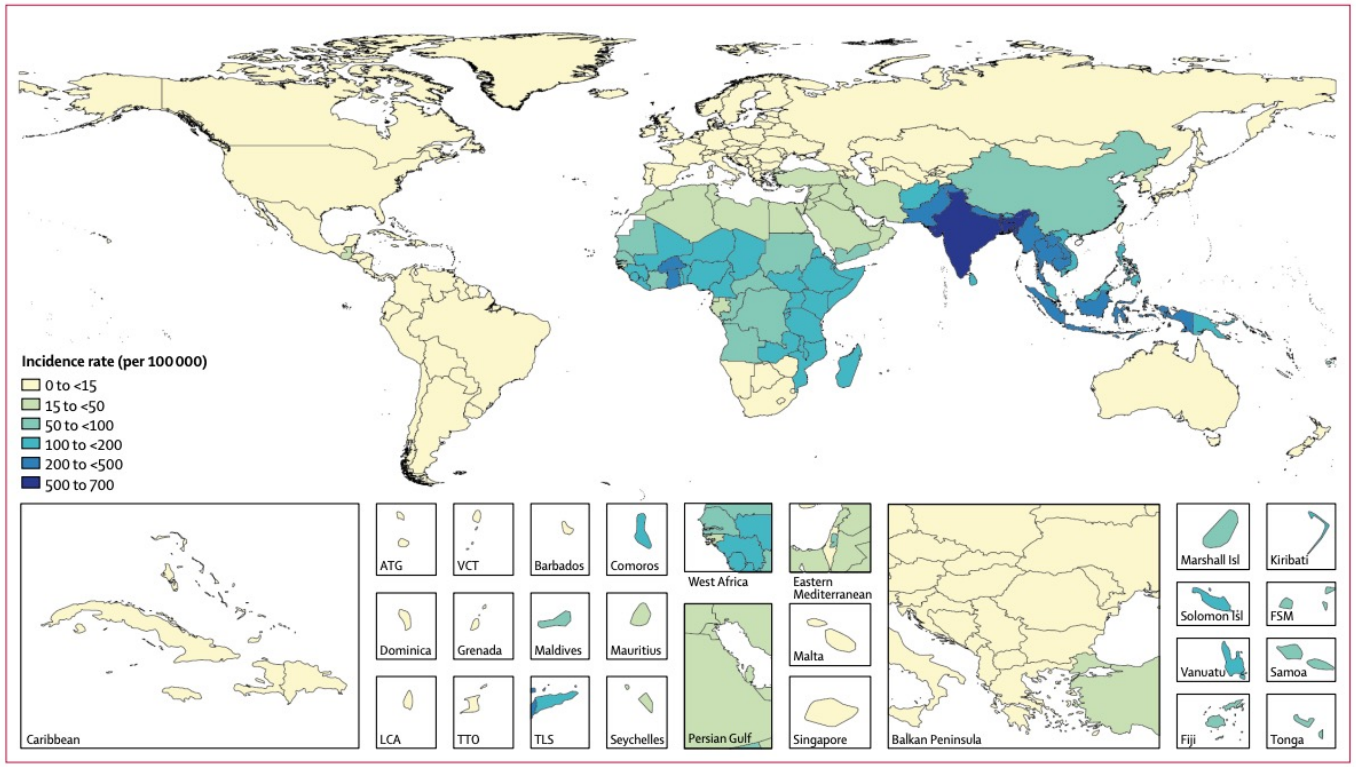
Caused by:

- *Salmonella enterica* serotype Typhi
- *Salmonella enterica* serotype Paratyphi A, B, and C.

Typhoid and paratyphoid fever clinically similar acute febrile illnesses and accurate diagnosis relies on laboratory confirmation

Global epidemiology

- 2017 14·3 million cases of typhoid and paratyphoid fevers in 2017, a 44·6% decline from 25·9 million cases in 1990
- Africa –south of the Sahara 12·1% of all cases



Lancet 2019

	Cases (thousands)	Incidence (per 100 000)	Proportion of cases attributable to HIV
Year			
1990	342·0 (264·8 to 451·2)	5·9 (4·6 to 7·7)	5·2 (2·6 to 8·5)
1995	410·5 (319·7 to 535·9)	6·8 (5·3 to 8·8)	8·9 (4·8 to 14·2)
2000	521·2 (410·4 to 669·4)	8·3 (6·6 to 10·7)	11·0 (6·0 to 17·5)
2005	690·7 (552·2 to 873·6)	10·7 (8·5 to 13·6)	10·4 (5·5 to 16·9)
2010	622·0 (490·1 to 800·0)	9·2 (7·3 to 12·0)	8·5 (4·3 to 14·0)
2017	534·6 (409·0 to 705·0)	7·5 (5·7 to 10·0)	8·2 (4·4 to 13·2)
GBD super-region			
Southeast Asia, east Asia, and Oceania	21·5 (15·7 to 28·3)	1·2 (0·9 to 1·6)	2·0 (1·1 to 3·3)
Central Europe, eastern Europe, and central Asia	4·8 (3·6 to 6·1)	1·3 (1·0 to 1·7)	5·3 (3·2 to 8·2)
High-income	10·9 (8·1 to 13·7)	1·1 (0·8 to 1·4)	19·1 (9·0 to 32·6)
Latin America and Caribbean	11·2 (8·4 to 14·4)	2·0 (1·5 to 2·6)	5·5 (3·1 to 8·9)
North Africa and Middle East	15·8 (12·3 to 20·3)	2·5 (2·0 to 3·2)	0·5 (0·2 to 0·9)
South Asia	48·9 (35·8 to 64·6)	2·7 (2·0 to 3·5)	0·9 (0·5 to 1·7)
Sub-Saharan Africa	421·6 (316·0 to 574·1)	34·5 (26·6 to 45·0)	9·5 (5·0 to 15·7)
Age group			
<5 years	233·4 (158·2 to 372·4)	34·3 (23·2 to 54·7)	0·5 (0·0 to 1·3)
5–14 years	120·8 (68·7 to 183·2)	9·3 (5·3 to 14·1)	1·6 (0·7 to 3·1)
15–49 years	146·9 (107·4 to 201·2)	3·8 (2·7 to 5·1)	22·3 (13·7 to 32·7)
50–69 years	26·8 (16·6 to 39·6)	2·0 (1·3 to 3·0)	25·4 (13·9 to 38·4)
≥70 years	6·6 (4·5 to 9·8)	1·5 (1·0 to 2·3)	15·5 (7·2 to 26·6)
Sex			
Male	278·2 (212·8 to 370·3)	7·7 (5·8 to 10·3)	7·6 (4·0 to 12·4)
Female	256·4 (196·1 to 340·8)	7·4 (5·6 to 9·9)	8·9 (4·9 to 14·3)

Age matters

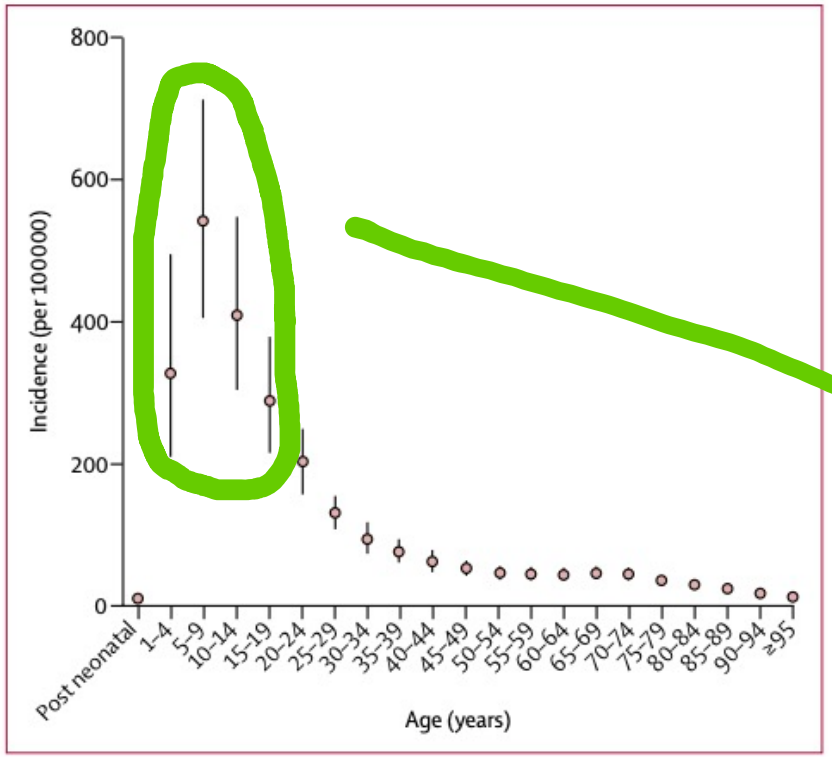
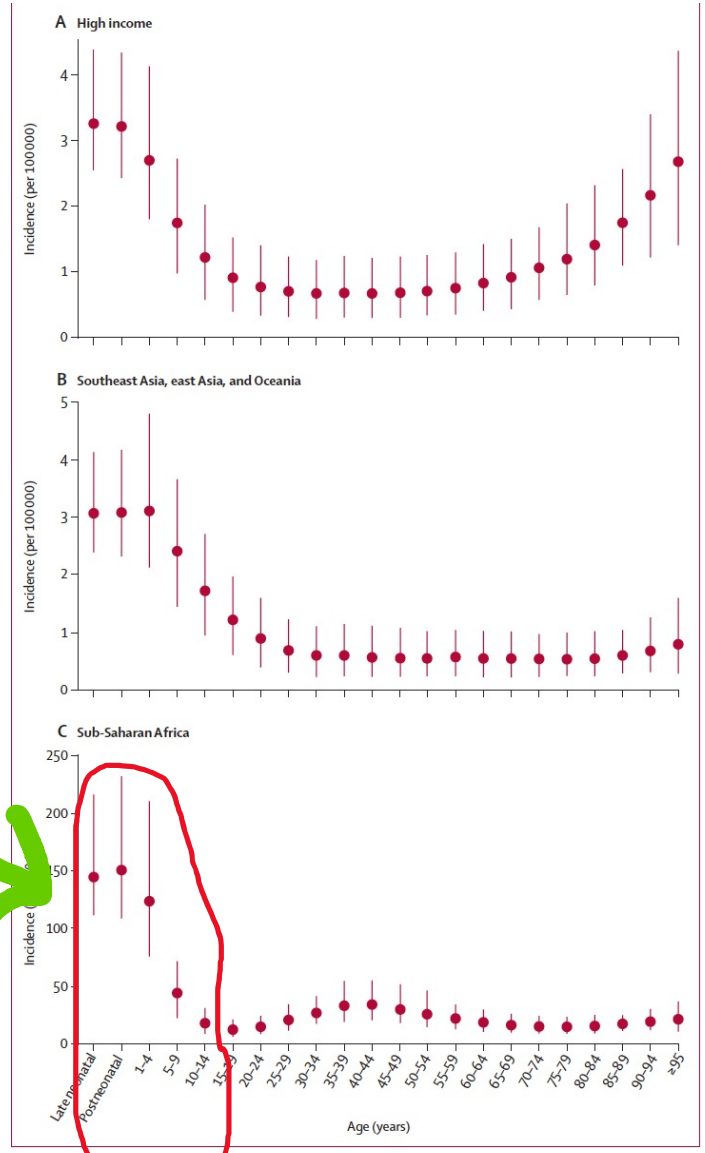
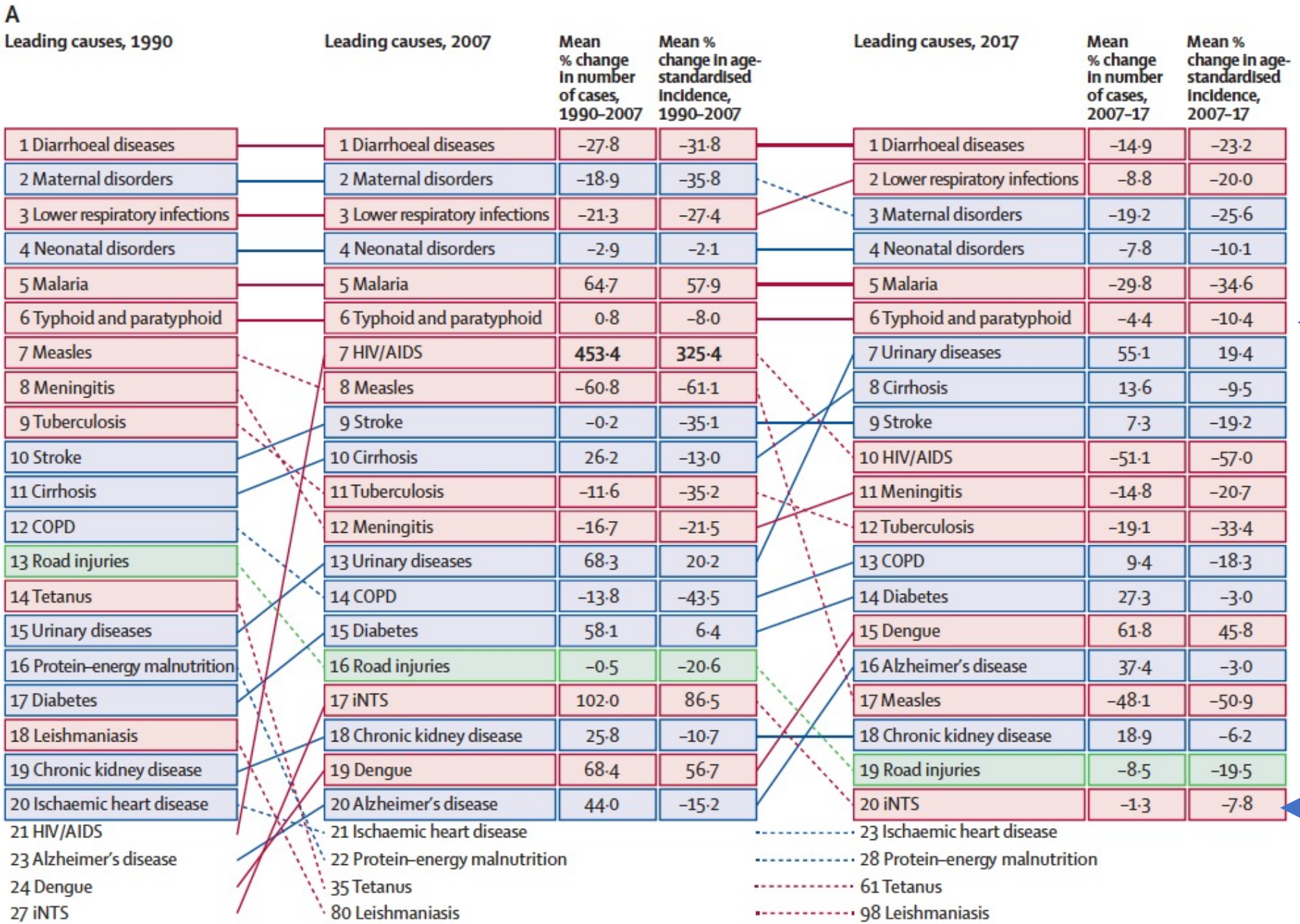


Figure 2: **Global age-specific incidence rates (per 100 000) of typhoid and paratyphoid fevers in 2017**



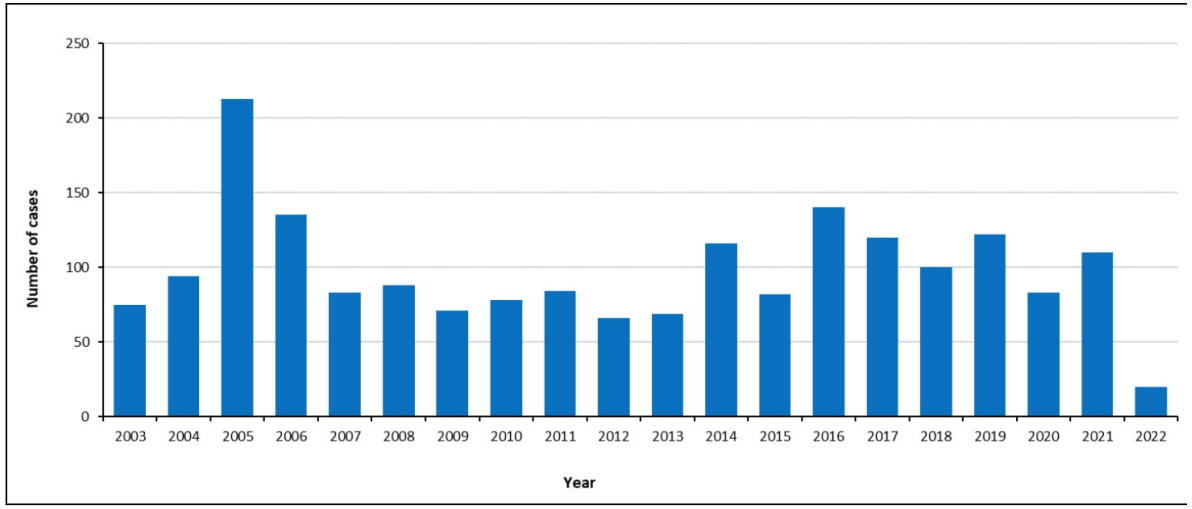
Lancet 2019

Sepsis



Lancet 2020

South Africa Endemic *Salmonella enterica* serotype Typhi



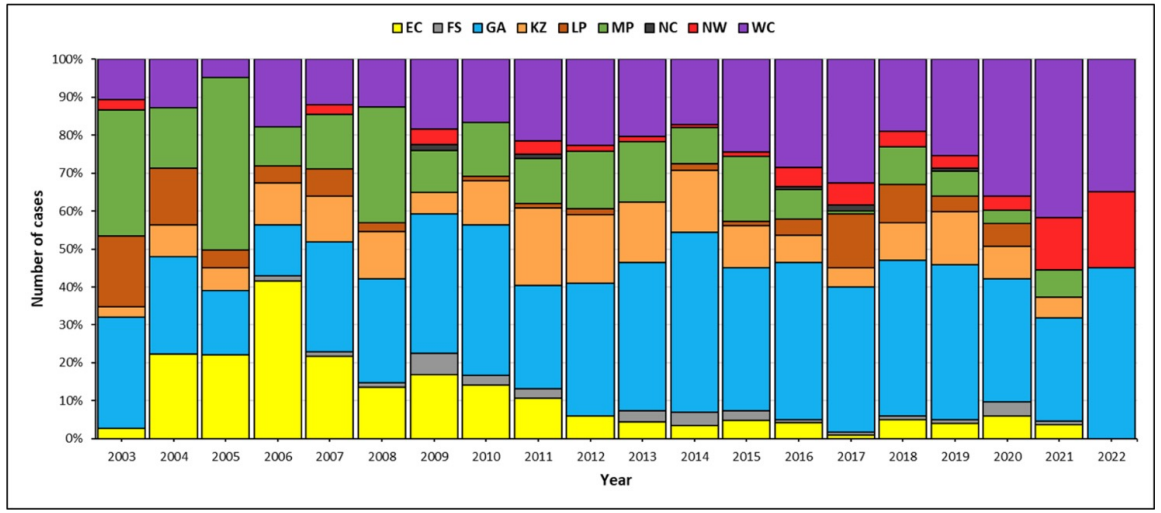


Figure 1. Enteric fever cases, South Africa, 1 January 2003 – 14 February 2022

0.1 cases per 100,000 population of culture-confirmed typhoid fever

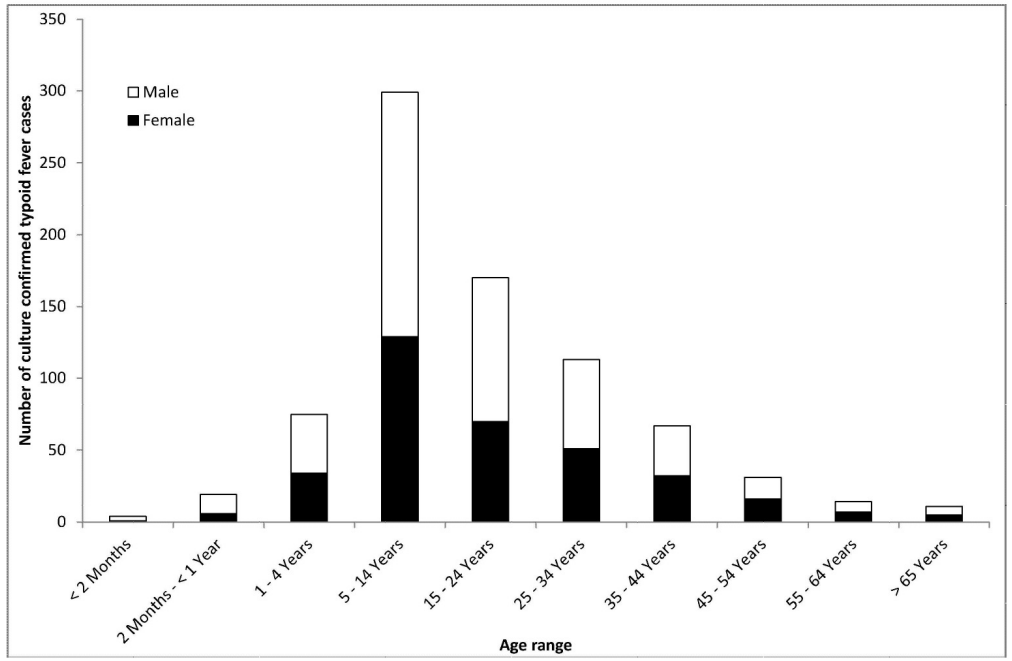


Fig 1. Number of culture-confirmed typhoid fever cases (N = 803) by age range and sex in South Africa, 2003–2013.

- Incidence unchanged
- Severity predicts mortality
- Incidence disease not related to HIV seroprevalence

Plos 2016

Clusters of cases

Prov	District	#	Start
WC	CT	14	11/2020
WC	Winelands	11	7/2020
WC	Garden route	12	08/2020
NW	Dr Kenneth Kaunda	16	11/2020

- Reservoirs
- Untreated cases

https://www.nicd.ac.za/update-on-enteric-fever-in-south-africa-18-feb-2022/

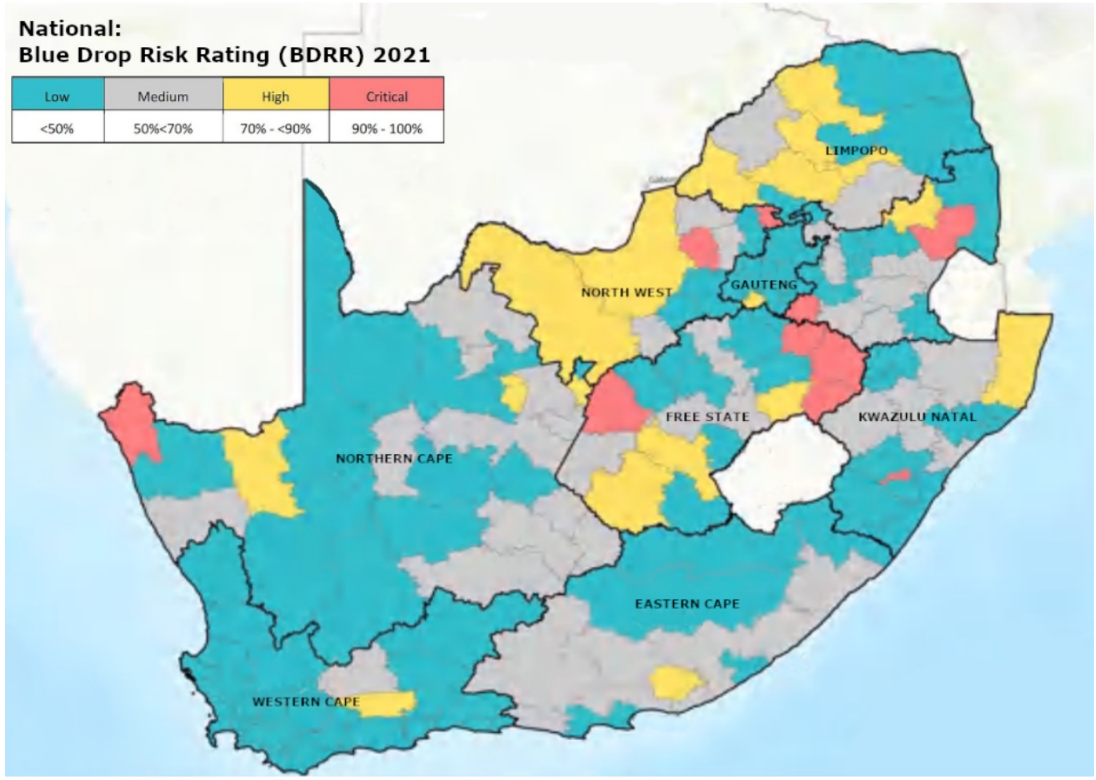
Government to issue ‘boil water notices’ as South Africa’s tap water quality tanks

Staff Writer 29 April 2022

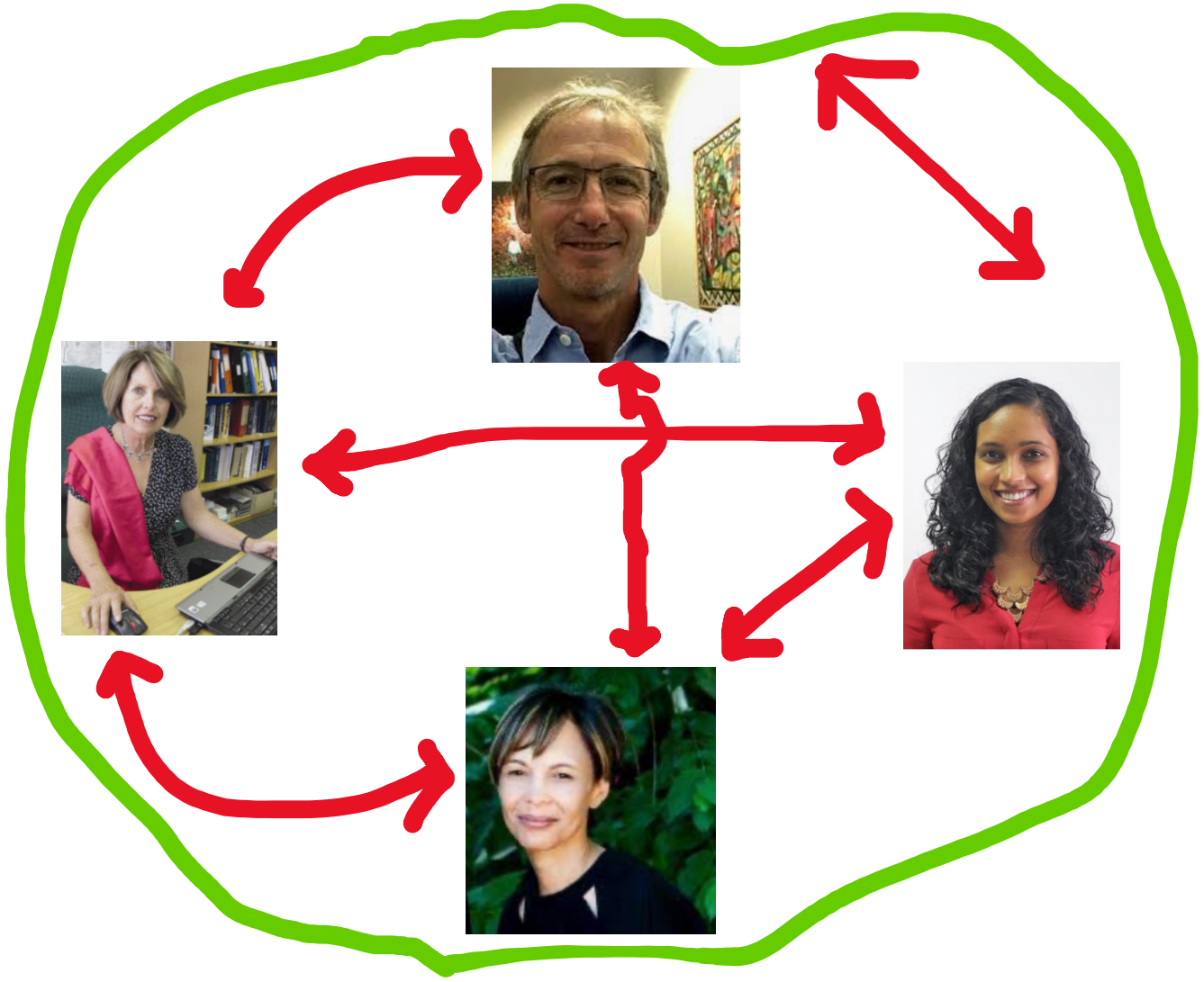
NO EVIDENCE THAT RECENT CASES OF TYPHOID FEVER ARE LINKED TO CONTAMINATED MUNICIPAL WATER IN ANY PART OF THE COUNTRY

21 February , 2022

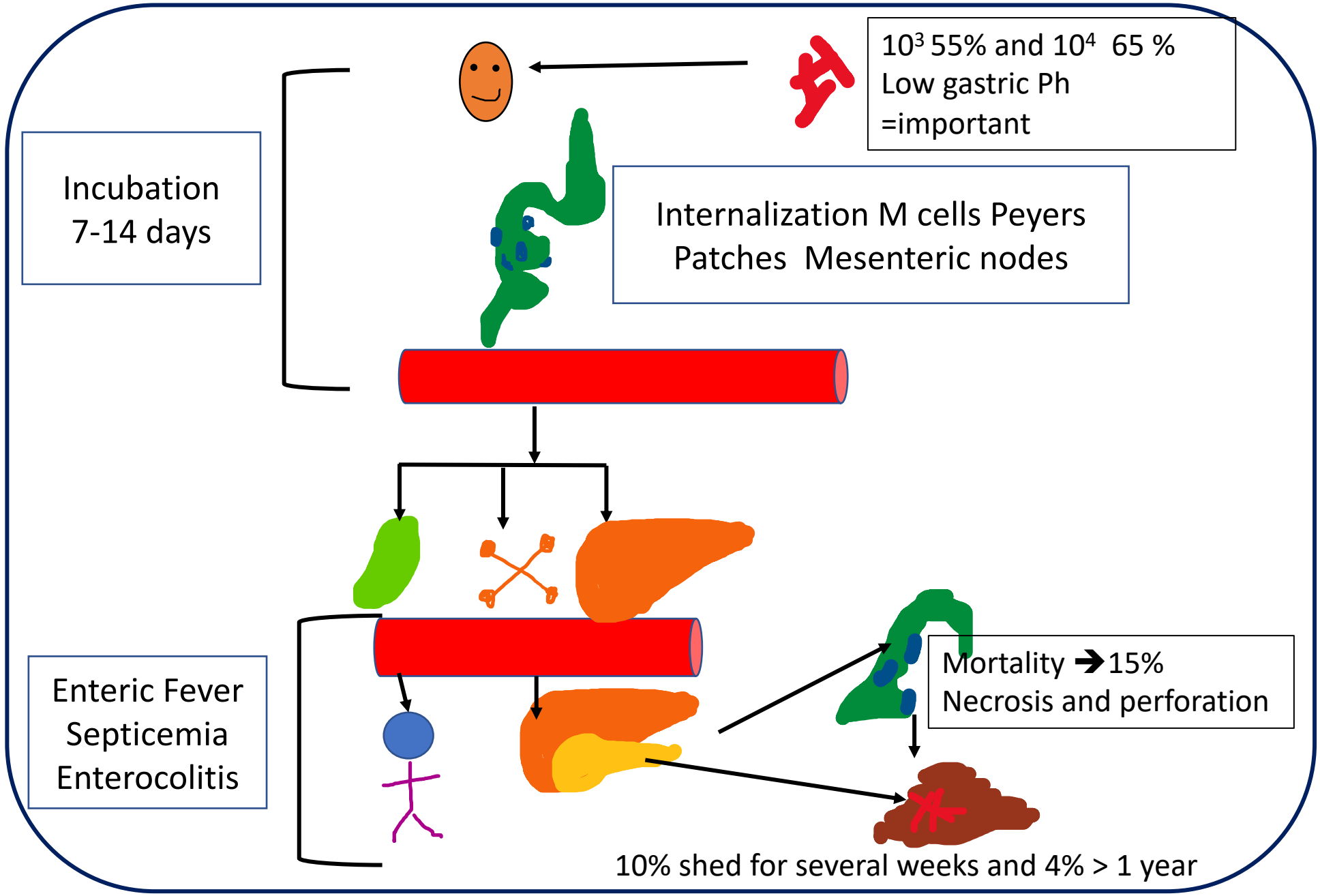
- 48% of supply systems are in the low risk category,
- 18% are in the medium risk category,
- 11% are in the high risk category, and
- 23% are in the critical risk category.



https://ws.dws.gov.za/IRIS/releases/2021_BD_PAT_report_final-28Mar22_MN_web.pdf



Survive and multiply within the mononuclear phagocytic cells



Classic presentation - **Week 1**

- Rising ("stepwise") fever with chills
- Relative bradycardia or pulse-temperature dissociation

Plato around end of week 1: 39-40°C

Classic presentation - Week 2

- High-grade fever >3 days with no clear focus of infection.
- "rose spots"
- Dull frontal headache, malaise, anorexia, nausea, poorly localized abdominal discomfort, a dry cough, and myalgia

Classic presentation - Week 3

- Hepatosplenomegaly
- Intestinal bleeding
- Secondary bacteremia and peritonitis.
- Septic shock or an altered level of consciousness

- Complications of enteric fever occur in 10% to 15% of patients.
- <5 years old only fever, and the diagnosis may be missed unless they have complications

	< 5	5-10	>10
Rose spot	< 7 -19%		
Abdominal pain	20%	70%	54%
Nausea or vomiting	32%	45%	50%
Diarrhoea	2.5x more (50-78%)		46%
Constipation			24-30% Pre-antibiotic
Headache			63-96%%
Seizures	Febrile		
Hepatomegaly	44-85%		30%
Splenomegaly	26-90%		40%
Cough	30-72%Pneumonia mostly in children		41%

Other issues

GIT

- Intestinal perforation – ileum
  - Secondary infections with other bacteria
  - more in among adults
  - 15% mortality

CNS

- " with altered consciousness, delirium, and confusion” 17% Possibly prognostic
- Less common – meningitis and focal infections

Arthralgias and myalgias 20%

- hepatobiliary, cardiovascular, respiratory, genitourinary, musculoskeletal

Labs

- Frequently have anemia and either leukopenia or leukocytosis
  - Later leucocytosis – consider perforation
- Abnormal liver enzymes common but lower peak than viral hepatitis
- CRP
- Cerebrospinal fluid -usually normal or reveal a mild pleocytosis (<35 cells/mm^3), even in patients with neuropsychiatric symptoms

	< 5	5-10	Adult
Anaemia	70%		30%
Leucopenia		21%	36%
Leucocytosis		47%	13%
Thrombocytopenia	<20%		53%
Hepatitis	36%	26%	28%

Risk factors for infection / severe disease

- Low gastric acid
- HIV
- Glucocorticoid therapy
- Altered phagocyte function
- Malaria
- Sickle cell anaemia
- Very young age

South African Children

Clinical

- Fever -57% >°40C
- Rose spots ONLY 1
- Headache 77%
- 50% apathetic
- 11% stupor
- Tummy pain 40%
- Loose stools 64%
- Hepato/ splenomegaly 33%
- Coughing and respiratory features 37%

Time to fever free 7 days Amoxil

2.5% mortality , but mortality in children < 1 year 15%

Table I Typhoid fever; other laboratory results

	Number abnormal	*Number studied*	*% of patients*
Haemoglobin <10 g/dl	157	441	36
Platelets $<150 \times 10^9$/l	60	147	30
ESR >100 mm/h	11	51	22
Serum sodium $\leqslant 130$ mmol/l	173	428	40
Serum potassium $\leqslant 3$ mmol/l	94	428	22
Serum bicarbonate $\leqslant 20$ mmol/l	197	428	46
Serum protein $\leqslant 60$ g/l	65	261	25
Serum alanine aminotransferase $\geqslant 1.5 \times$ upper limit of normal together with a normal bilirubin	65	145	45

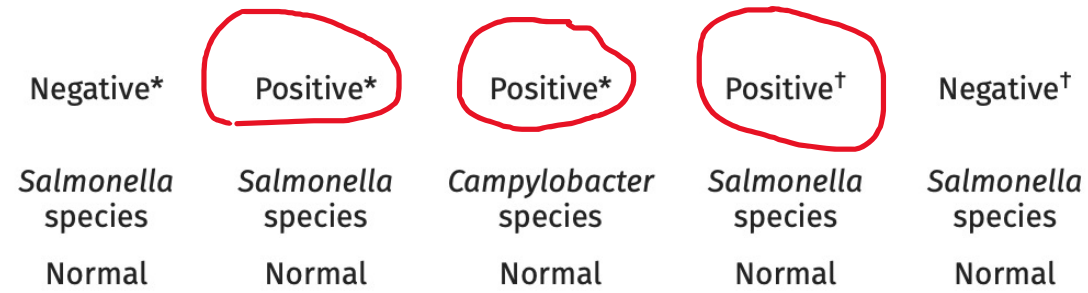
Postgrad Med J 1990

Mistaken MIS-C: A Case Series of Bacterial Enteritis Mimicking MIS-C

Dworsky, Zephyr D. MD[*,†]; Roberts, Jordan E. MD[‡,§]; Son, Mary Beth F. MD[‡,§]; Tremoulet, Adriana H. MD, MAS[*,†]; Newburger, Jane W. MD, MPH[‡,¶]; Burns, Jane C. MD[*,†]

Author Information

The Pediatric Infectious Disease Journal: April 2021 - Volume 40 - Issue 4 - p e159-e161
doi: 10.1097/INF.0000000000003050



PIDJ 2021

Diagnosis - culture

- Bone marrow culture is the most sensitive diagnostic modality +>90% (can stay postive many days of antibiotic)
- Blood cultures +50-70% (maximal bacteria in the first week)
  - Timing
  - Antibiotics
  - Volume
- Stool -30-40%
  - Interperate stool with the clincal features
- Urine
- Duodenum content

50% of patients with typhoid fever whose blood cultures are positive have less than 1 CFU/ml of blood,

- Blood culture 61 % (95 % CI 52–70 %) and
- Bone marrow 96 % (95 % CI 93–99 %) were detected by blood
- Blood culture sensitivity was 66 % (95 % CI 56–75 %) when compared with bone marrow culture results.

Ann Clin Microbiol Antimicrob (2016)

South African Case definitions

	Definition
Suspected case	A person presenting with fever for at least three out of seven consecutive days and symptoms compatible with enteric fever
Confirmed case	Isolation of Salmonella Typhi or Salmonella Paratyphi A,B or C from a clinical sample
Probable case (relevant only in outbreaks)	A clinically compatible case that is epidemiologically linked to a confirmed case

Other testing

- Widal test
  - Widal test detects anti-*S*. Typhi antibodies, and the minimal titers defined as positive for the O (surface polysaccharide) antigens and H (flagellar) antigens must be determined for individual geographic areas
- Rapid antibody-based diagnostic tests have only moderate diagnostic accuracy can not replace blood culture
- Polymerase chain reaction-based diagnostics have had limited sensitivity in most studies given the low concentration of bacteria during bacteremia

Carriage

- Feces
  - Gallstones
- Urine
  - Schistosoma
  - Stones

- Convalescent carrier:

  Evidence of shedding (positive stool culture) 1–12 months after finishing an appropriate course of antimicrobial treatment and the resolution of symptoms following a laboratory-confirmed episode of acute disease.

- Definitive carrier:

  Evidence of shedding (positive stool culture) at least 12 months after finishing an appropriate course of antimicrobial treatment and the resolution of symptoms following a laboratory-confirmed episode of acute disease OR two positive stool samples 12 months apart.

Treatment

	Children	U_Comp	Comp	Adults	U_Comp	Comp
Ciprofloxacin susceptible	Ciprofloxacin	7	10-14	Ciprofloxacin	7	10-14
Not susceptible to ciprofloxacin	Ceftriaxone	10-14	10-14	Ceftriaxone	10-14	10-14
	Azithromycin	7		Azithromycin	7	
XDR	Meropenem		10-14	Meropenem		10-14

Fluoroquinolone

- Bactiocidal intracellular and in bile
- Faster resolution
- Shorter duration of therapy

Cephalosporins – ceftriaxone better than cefotaxime and cefepime

- longer therapy 10-14 days

Azithromycin

- Quinelone resistance

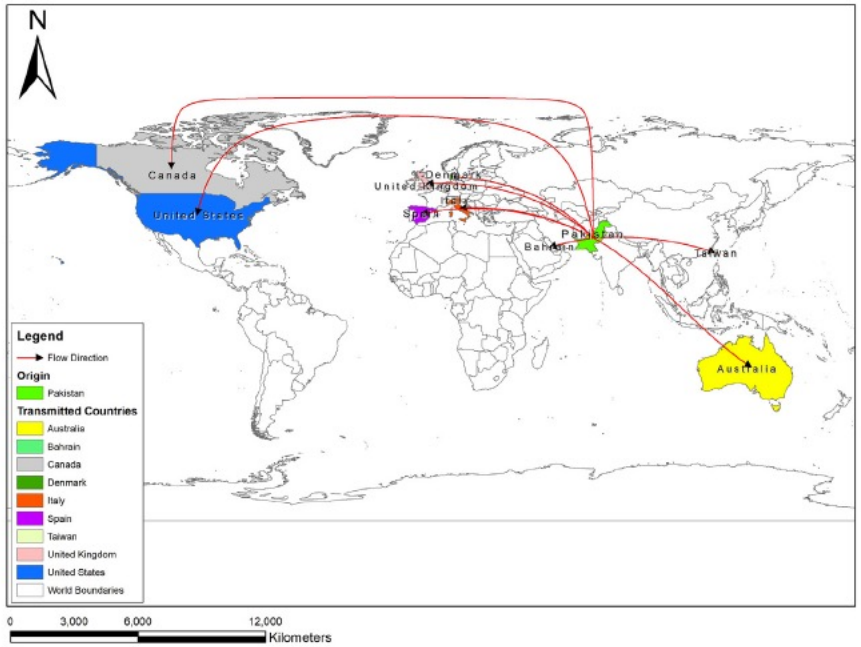


Fig. 1. Global spread of XDR- typhoid fever cases.

Epidemiol. Infect. (2010), **138**, 86–90.
doi:10.1017/S0950268809990331 Printed in the United Kingdom

SHORT REPORT
Quinolone-resistant *Salmonella* Typhi in South Africa, 2003–2007

A. M. SMITH[1,2*], N. GOVENDER[1], K. H. KEDDY[1,2] and the Group for Enteric, Respiratory and Meningeal Disease Surveillance in South Africa (GERMS-SA)

[1] *Enteric Diseases Reference Unit, National Institute for Communicable Diseases, Johannesburg, South Africa*
[2] *University of the Witwatersrand, Johannesburg, South Africa*

Adjunctive corticosteroids for severe infection

- Delirium, obtundation, stupor, coma, or shock
- Dexamethazome

Mortality

- With out antibiotic case fatality up to 20%
- Currently 2.5%
  - Hospitalized
  - Resistance
  - Perforation
  - Children<5yers of age

After therapy

- Stool
  - 1st one week after completion of antibiotics.
  - 2nd and 3rd 48 hours apart.
- Urine If case originally had a positive urine culture, a history of urinary tract infection and/or a history of schistosomiasis (bilharzia), collect urine samples for culture in addition to stool samples.
  - 1st one week after completion of antibiotics.
  - 2nd and 3rd 48 hours apart.

Any sample culture positive

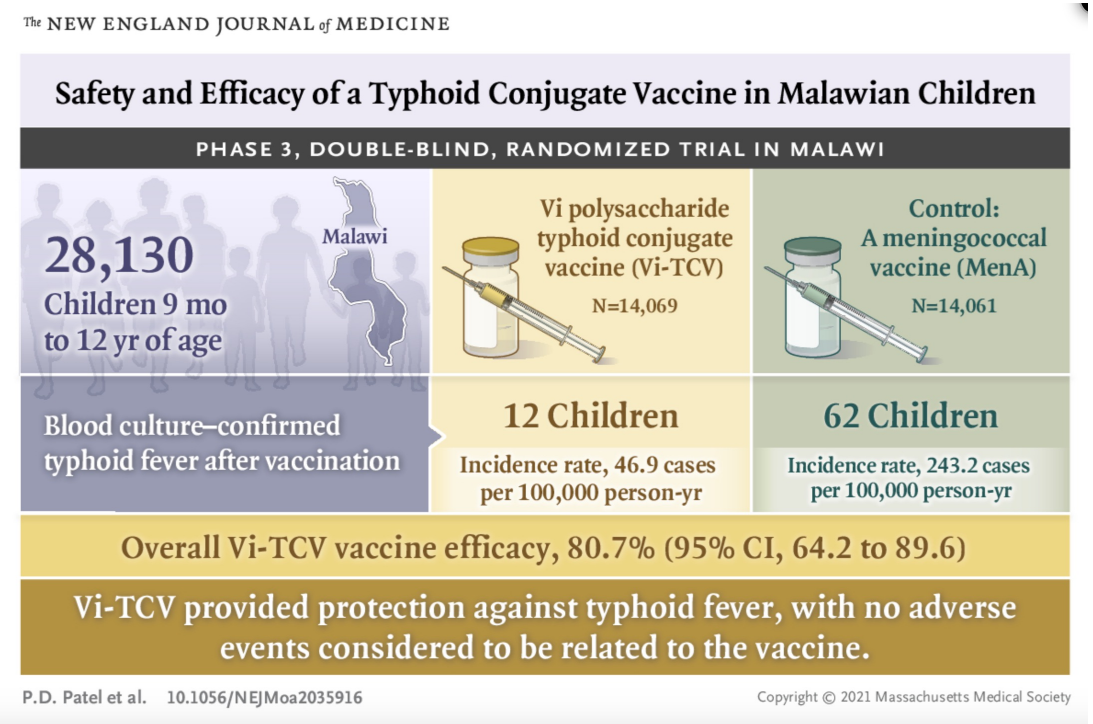
- Treat for 1 month
- Monthly stool samples
- If remains positive – investigate for the cause

- Ciprofloxacin 28 days
- Treat underling illnesses

Contact management:

- Household members, care givers of the case, and people who may have eaten the implicated food/water/beverages.
- Line list with interview
- Collect a stool/rectal swab sample culture.
  - culture positive, refer the person for antibiotic treatment
- Educate all contacts on enteric fever infection, transmission, prevention, and recognising symptoms and seeking medical care if these occur.

- Typhoid conjugate vaccine
  - Preferred by WHO
- **Unconjugated Vi polysaccharide vaccine**
  - **2 years and older**
  - **Single IMI dose 20-3 weeks before effective**
  - **Protects for 3 years**
  - **Not effected against para typhoid**
- Live attenuated Ty21a vaccine.



NEJM 2021

https://www.nicd.ac.za/diseases-a-z-index/typhoid-fever/