Typhoid Fever: Epidemiology and Beyond

Education Slideset

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

MODULE 1: TYPHOID EPIDEMIOLOGY

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

LEARNING OBJECTIVES

In this module, you will:

1. Learn the basics of typhoid epidemiology
2. Identify populations most at risk for typhoid
3. Recognize global disease trends and learn about existing knowledge gaps

INTRODUCTION TO ENTERIC FEVER

- Enteric fever collectively refers to typhoid and paratyphoid fevers
- Typhoid fever is a systemic infection caused by the bacteria *Salmonella enterica* serovar Typhi (*S*. Typhi)
  - Waterborne or foodborne transmission
  - Fecal-oral route of infection
  - Bacteria lives only in humans
- Paratyphoid fever is caused by the bacteria *Salmonella enterica* serovar Paratyphi A/B/C
  - Paratyphoid is less common and typically less severe than typhoid
- Typhoid can be prevented through access to clean water, improved sanitation and hygiene infrastructure, and vaccines

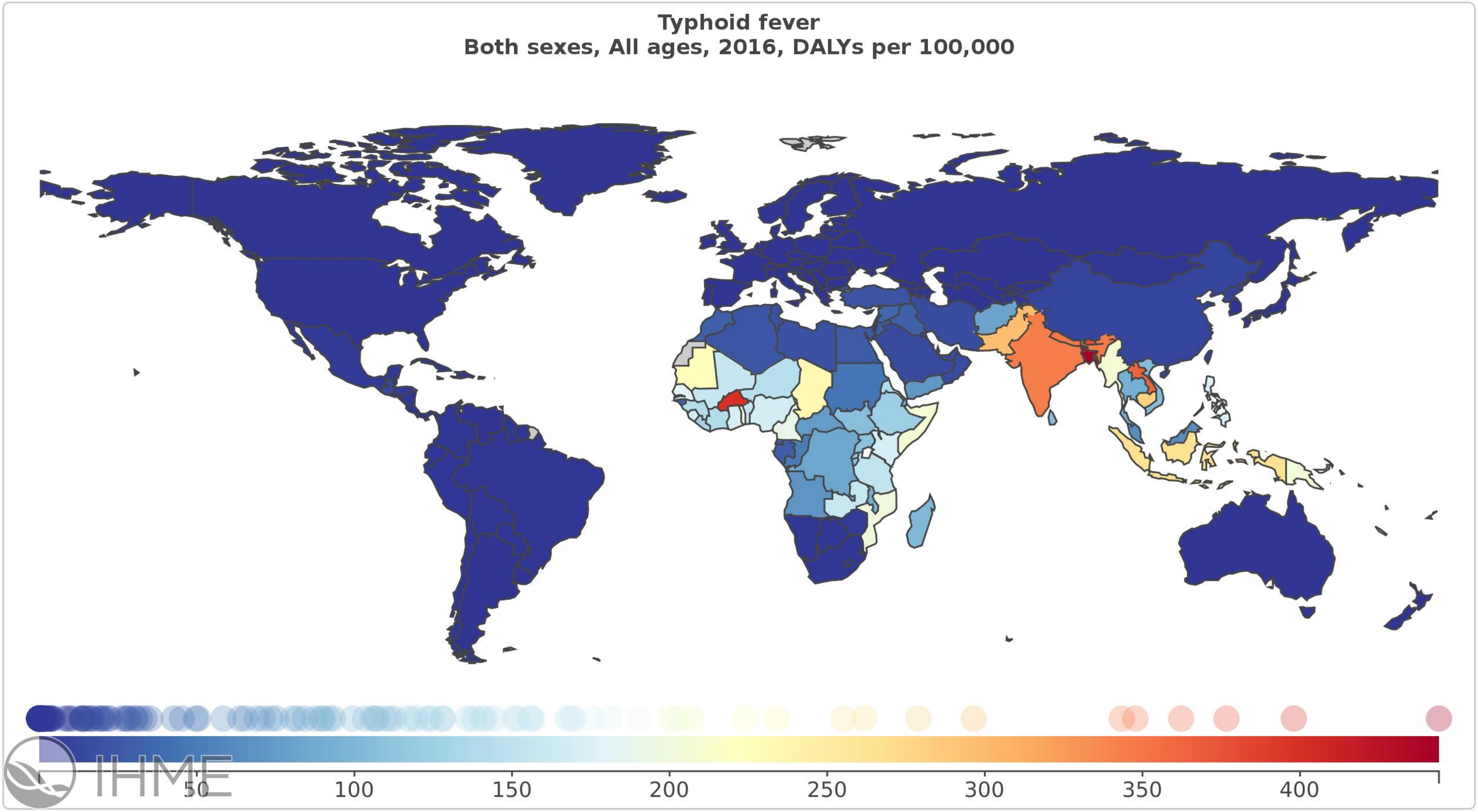
INCIDENCE OF TYPHOID

- Approximately 12 million cases per year
  - Multiple unreported subclinical and mild infections occur for each clinical case
- More than 128,000 deaths per year
  - 1-4% case fatality with treatment
  - 10-20% case fatality without treatment
- Complications arise in 10-15% of untreated patients
  - Intestinal perforation, hemorrhage of the intestine and septic shock
- These estimates are limited by the lack of reliable surveillance data

GEOGRAPHIC DISTRIBUTION OF TYPHOID

- Mainly restricted to low- and middle-income countries
  - Highest incidence is found in Southeast Asia and Indian subcontinent
    - Pakistan + India + Bangladesh = 85% of the world's cases
  - Also prevalent in Africa, although substantial knowledge gaps exist
    - Recent findings reveal incidence in some areas may be high as in Asia
  - Oceania has high incidence of typhoid except in high-income countries such as Australia and New Zealand
- Most typhoid cases in high-income countries occur among travelers returning from endemic countries

MAP OF GEOGRAPHIC DISTRIBUTION



GBD 2016. https://vizhub.healthdata.org/gbd-compare/

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

SUSCEPTIBILITY AND TRENDS

- **Age:** Children suffer the highest incidence of typhoid
  - Study conducted in Indonesia, India and Pakistan found annual incidence of 180-494/100,000 of blood-culture confirmed cases among children 5-15 years old
  - In Pakistan, children 2-4 years old had an incidence of 405/100,000, and children less than 2 years of age had an incidence of 443/100,000
- **Income:** Associated with low socioeconomic status
- **Location:** High incidence documented in overcrowded areas with poor access to improved water and sanitation
  - Examples: Urban slums, refugee camps

Ochiai, R. L., Acosta, C. J., Danovaro-Holliday, M. C., Baiqing, D., Bhattacharya, S. K., Agtini, M. D., … Domi Typhoid Study Group, the D. T. S. (2008). A study of typhoid fever in five Asian countries: disease burden and implications for controls. *Bulletin of the World Health Organization*, *86*(4), 260–8. http://doi.org/10.2471/blt.06.039818

Owais A, Sultana S, Zaman U, Rizvi A, Zaidi AKM. Incidence of Typhoid Bacteremia in Infants and Young Children in Southern Coastal Pakistan. The Pediatric infectious disease journal. 2010;29(11):1035-1039.

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

COSTS OF TYPHOID

Direct	Indirect
Medical Expenses	Lost Income/Productivity
• Physician fees • Diagnostic tests • Hospitalization • Emergency room • Medication	• Patient's lost income • Caretaker's lost income • Interrupted education • Long-term morbidity • Time lost from patient's other beneficial activities • Time lost from caretaker's other beneficial activities
Non-Medical Expenses	
• Transportation • Food & beverages to aid treatment • Lodging and meals for caretaker	

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

SNAPSHOT: TYPHOID IN INDIA

- Endemic in India, typhoid carries substantial morbidity and mortality in both pediatric and adult populations
  - Incidence estimate: 340 cases per 100,000 in children aged 2-5; 493 cases per 100,000 in children aged 5-15; 120 cases per 100,000 in adults older than 15
- Factors increasing the risk for typhoid:
  - 77 million people do not have access to safe water and 769 million people lack improved sanitation
  - Estimated slum population of 158.42 million people
  - 67% of households do not treat their drinking water
- Typhoid cases in India peak from July to October during the rainy season when the chance of water contamination is high

Divyashree, S., Nabarro, L. E. B., Veeraraghavan, B., & Rupali, P. (2016). Enteric fever in India: current scenario and future directions. *Tropical Medicine & International Health*, *21*(10), 1255–1262. http://doi.org/10.1111/tmi.12762

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

SNAPSHOT: TYPHOID OUTBREAK IN UGANDA

- Outbreak in Kampala from February-June 2015
- Main source: contaminated water and juice
  - 26% of patients consumed water and ~50% drank local passion-fruit juice from busy taxi park area
  - Most patients were men between 20-39 years old
  - Almost all worked in the market at the taxi park
- 10,230 suspected cases
- Ministry of Health launched communications campaign to encourage the public to avoid drinking water and juice from local markets and treat their drinking water at home

CDC Global Health - Stories - Uganda FETP Gets Crash Course in Disease Detection. (2015). Retrieved from https://www.cdc.gov/globalhealth/stories/uganda_disease_detection.htm

Kabwama, S. N., Bulage, L., Nsubuga, F., Pande, G., Oguttu, D. W., Mafigiri, R., … Zhu, B.-P. (2017). A large and persistent outbreak of typhoid fever caused by consuming contaminated water and street-vended beverages: Kampala, Uganda, January - June 2015. *BMC Public Health*, *17*(1), 23. https://doi.org/10.1186/s12889-016-4002-0

KNOWLEDGE GAPS

- There are gaps in our knowledge of the global distribution of typhoid due to:
    - Lack of resources: Facilities in endemic settings often do not have the capability for diagnostic tests
    - Lack of reliable diagnostics: The diagnostic tests commonly used are not highly accurate
    - Lack of reporting: Inadequate surveillance systems in place
- More data are needed to help governments prioritize health care resources and enact cost-effective means of reducing the burden of typhoid

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

TYPHOID AND SUSTAINABLE DEVELOPMENT

- Typhoid is linked to socioeconomic inequity and stands as an obstacle to ending poverty
- Typhoid control is important to reaching multiple Sustainable Development Goals, including:
  - Goal 3: Ensure healthy lives and promote well-being for all at all-ages
  - Goal 6: Ensure availability and sustainable management of water and sanitation for all
  - Goal 10: Reduce inequality within and among countries
- An estimated 1.8 billion people use a source of drinking water that is contaminated with fecal matter, putting them at risk of contracting typhoid fever

MODULE 1 KEY MESSAGES

1. Typhoid is a preventable bacterial infection spread through contaminated food and water, impacting millions of people in low- and middle-income countries
2. Typhoid is estimated to be most prevalent in school-age children, people of low socioeconomic status and those living in high-density areas, such as urban slums
3. Lack of resources, including diagnostic tools and surveillance networks, makes it difficult to know the real disease burden
4. Typhoid is an obstacle to sustainable development and reducing inequality

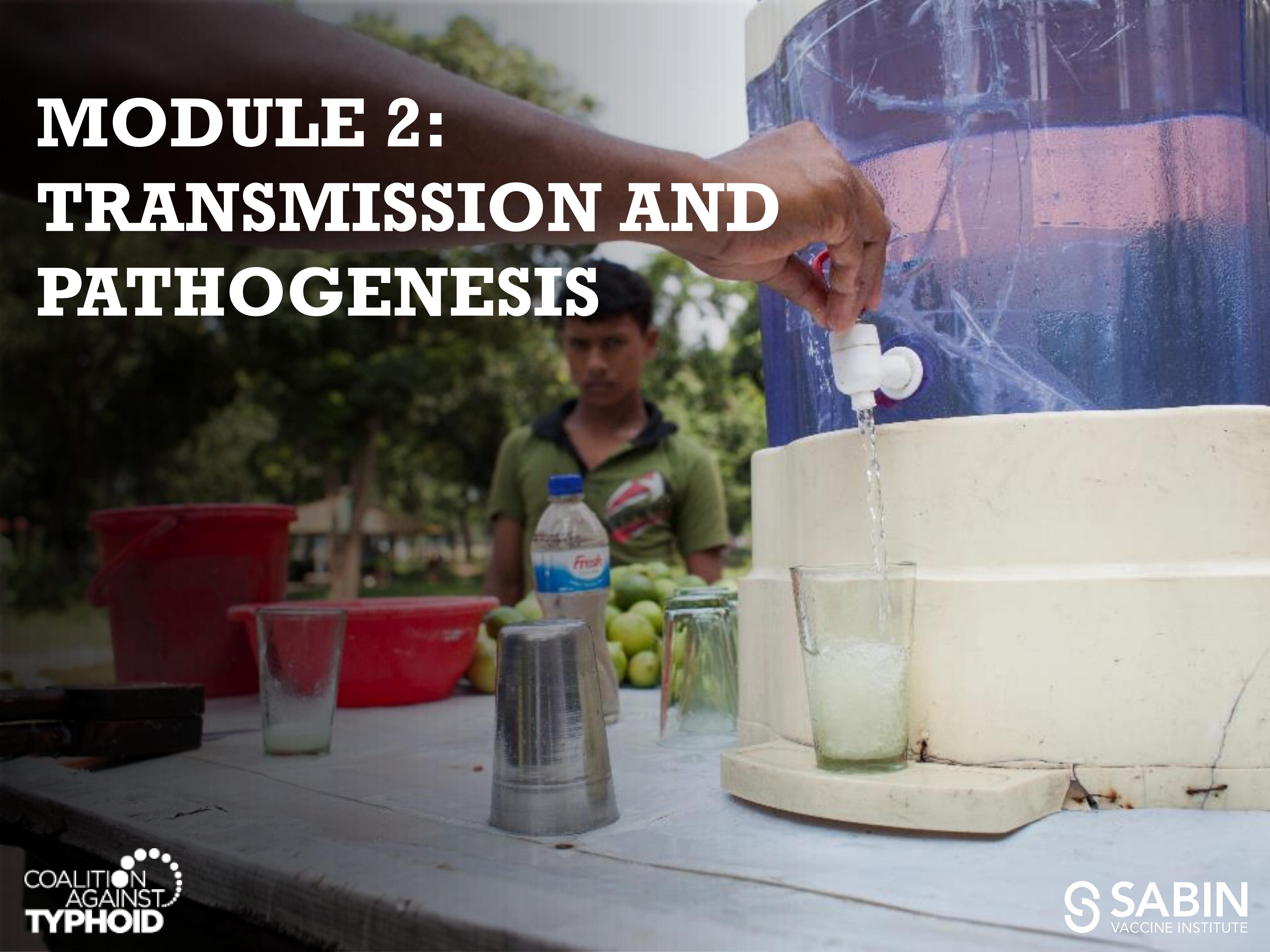
COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

REFERENCES

1. Luby, S. P., Saha, S., & Andrews, J. R. (2015). Towards sustainable public health surveillance for enteric fever. *Vaccine*, *33*, C3–C7. http://doi.org/10.1016/j.vaccine.2015.02.054
2. WHO | Typhoid fever – Uganda. (2015). *WHO*. Retrieved from http://www.who.int/csr/don/17-march-2015-uganda/en/
3. Buckle, G. C., Walker, C. L. F., & Black, R. E. (2012). Typhoid fever and paratyphoid fever: Systematic review to estimate global morbidity and mortality for 2010. *Journal of Global Health*, *2*(1), 10401. http://doi.org/10.7189/jogh.02.010401
4. Parry, C. M., Hien, T. T., Dougan, G., White, N. J., & Farrar, J. J. (2002). Typhoid Fever. *New England Journal of Medicine*, *347*(22), 1770–1782. http://doi.org/10.1056/NEJMra020201
5. Maurice, J. (2012). A first step in bringing typhoid fever out of the closet. *Lancet (London, England)*, *379*(9817), 699–700. https://doi.org/10.1016/S0140-6736(12)60294-3
6. Marks, F., von Kalckreuth, V., Aaby, P., Adu-Sarkodie, Y., El Tayeb, M. A., Ali, M., … Wierzba, T. F. (2017). Incidence of invasive salmonella disease in sub-Saharan Africa: a multicentre population-based surveillance study. *The Lancet Global Health*, *5*(3), e310–e323. https://doi.org/10.1016/S2214-109X(17)30022-0
7. Crump, J. A., Luby, S. P., & Mintz, E. D. (2004). The global burden of typhoid fever. *Bulletin of the World Health Organization*, *82*(5), 346–53. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15298225
8. Mogasale V, Maskery B, Ochiai RL, Lee JS, Mogasale VV, Ramani E, et al. Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment. The Lancet Global health. 2014;2(10):e570-80.
9. Ochiai, R. L., Acosta, C. J., Danovaro-Holliday, M. C., Baiqing, D., Bhattacharya, S. K., Agtini, M. D., … Domi Typhoid Study Group, the D. T. S. (2008). A study of typhoid fever in five Asian countries: disease burden and implications for controls. *Bulletin of the World Health Organization*, *86*(4), 260–8. http://doi.org/10.2471/blt.06.039818
10. Poulos, C., Riewpaiboon, A., Stewart, J. F., Clemens, J., Guh, S., Agtini, M., … DOMI Typhoid COI Study Group. (2011). Cost of illness due to typhoid fever in five Asian countries. *Tropical Medicine & International Health*, *16*(3), 314–323. http://doi.org/10.1111/j.1365-3156.2010.02711.x
11. Divyashree, S., Nabarro, L. E. B., Veeraraghavan, B., & Rupali, P. (2016). Enteric fever in India: current scenario and future directions. *Tropical Medicine & International Health*, *21*(10), 1255–1262. http://doi.org/10.1111/tmi.12762
12. CDC Global Health - Stories - Uganda FETP Gets Crash Course in Disease Detection. (2015). Retrieved from https://www.cdc.gov/globalhealth/stories/uganda_disease_detection.htm
13. Kabwama, S. N., Bulage, L., Nsubuga, F., Pande, G., Oguttu, D. W., Mafigiri, R., … Zhu, B.-P. (2017). A large and persistent outbreak of typhoid fever caused by consuming contaminated water and street-vended beverages: Kampala, Uganda, January - June 2015. *BMC Public Health*, *17*(1), 23. https://doi.org/10.1186/s12889-016-4002-0
14. Water and Sanitation - United Nations Sustainable Development. (n.d.). Retrieved June 7, 2017, from http://www.un.org/sustainabledevelopment/water-and-sanitation/
15. Vos, Theo et al. (2017). Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016 *The Lancet* , Volume 390 , Issue 10100, 1211 - 1259

MODULE 2: TRANSMISSION AND PATHOGENESIS



COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

LEARNING OBJECTIVES

In this module, you will:

1. Learn how typhoid is transmitted
2. Identify typhoid's pathogenic route
3. Learn about the risk factors that lead to the transmission of typhoid
4. Learn about possible complications that can occur from typhoid infection

TRANSMISSION OF TYPHOID

- *S.* Typhi is a human-restricted pathogen, meaning it can only survive long-term in the human body
- *S*. Typhi can survive outside the human body for days in groundwater, pond water or seawater
- *S*. Typhi is transmitted by ingestion of food or water contaminated with human feces containing typhoid bacteria (oral-fecal route)
- Large outbreaks are most often caused by:
    - Contaminated local water sources
    - Contaminated food sold by vendors

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

RISK FACTORS FOR TRANSMISSION

- Drinking from a contaminated water supply
- Consuming drinks or food from street vendors
- Consuming raw fruit and vegetables fertilized with sewage
- History of contact with typhoid patients
- Washing hands without soap
- Preparing food with unwashed hands
- Living in inadequate housing without improved sanitation
- Consuming shellfish grown in contaminated water
- Consuming food washed with unclean water

SOURCES OF INFECTION

Primary Sources *Direct contact with the bacteria*	**Secondary Sources** *Contact with items contaminated with the bacteria*
• Feces • Urine (rare) • Direct contact with infected person (rare)	• Contaminated food • Contaminated water

SNAPSHOT: OUTBREAK IN PAKISTAN

- October 2004: More than 300 people contracted typhoid in Nek Muhammed village, resulting in 3 fatalities
- Village water source: 1 well
  - 100% of laboratory samples confirmed that *S.* Typhi was present in the well water
  - High amounts of contaminants (fecal matter, garbage) found in the well
  - 72% of household water samples tested positive for *S.* Typhi
- Drinking water was determined to be the source of the typhoid fever outbreak
- Food samples did not show association with the outbreak

Farooqui, A., Khan, A., & Kazmi, S. U. (2009). Investigation of a community outbreak of typhoid fever associated with drinking water. *BMC Public Health*, *9*(1), 476. https://doi.org/10.1186/1471-2458-9-476

INFECTION PROCESS

Infection process of typhoid begins with ingesting *S.* Typhi bacteria:

1
- Bacteria invade the small intestine and penetrate the mucosal epithelium into the underlying lymphoid tissue

2
- Macrophages ingest the bacteria but are unable to kill them

3
- Macrophages carry bacteria to nearby lymph nodes or to reticuloendothelial cells of liver and spleen

4
- Bacteria survive and multiply within the reticuloendothelial system

5
- Bacteria enter the bloodstream through the lymph nodes

6
- Clinical symptoms begin to develop

7
- Bacteria invade liver, spleen, bone marrow and gallbladder

8
- Bacteria pass into intestines and can be identified in stool samples

FACTORS THAT IMPACT INFECTION

- **Amount of bacteria ingested (inocula):** The greater the inocula, the more severe the infection
- **Method of ingestion:** Infections caused by foodborne or waterborne transmissions can present differently
    - Foodborne transmission is associated with large inocula and high attack rates over short periods
    - Waterborne transmission is associated with small inocula

INCUBATION PERIOD

- Time between becoming infected and developing symptoms is typically 1-3 weeks
  - Can be shorter or longer depending on the amount of bacteria ingested
  - Ranges from 3-60 days
- The onset of typhoid is gradual with increasing fever and fatigue and eventual onset of symptoms such as headache, abdominal pain and malaise

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

PERIOD OF COMMUNICABILITY

- Typhoid can be transmitted from the first week of illness until after symptoms have ceased and the infected person has stopped shedding bacteria in his/her feces
- Treatment can shorten the period of communicability
  - About 10% of untreated typhoid patients will continue to be infectious for 3 months
- After treatment, 1-5% of people who recover from typhoid fever continue to harbor *S.* Typhi bacteria in their intestinal tracts or gallbladders
  - Carriers have an indefinite period of communicability

TYPHOID CARRIERS

- Carriers no longer exhibit symptoms of typhoid, but are capable of infecting others
- These carriers can harbor the bacteria for years and shed the bacteria in their feces
  - Gallbladder removal can stop carriers from continuing to shed the bacteria
  - 4 weeks of oral antibiotic therapy will successfully treat 90% of carriers

SNAPSHOT: TYPHOID MARY

- Mary Mallon was hired in 1906 to cook for the Warren family
- 6 of the 11 Warren house residents contracted typhoid
- A sanitary engineer was hired to investigate the source of the bacteria
  - Discovered that 7 families Mallon previously cooked for reported cases of typhoid
- Mallon became known as the “first healthy carrier” of typhoid
- Mallon was apprehended and isolated for a combined 26 years
- After her death, her gallbladder was found to contain *S.* Typhi

TYPHOID COMPLICATIONS

- Complications after typhoid infection are uncommon and mostly occur after the fourth week of illness
- Complications include:
  - Gastrointestinal bleeding and perforation
  - Hepatitis
  - Psychosis
  - Meningitis
  - Cholecystitis
  - Myocarditis
  - Hemodynamic shock
  - Encephalopathy
  - Pneumonia
  - Thrombocytopenia
  - Renal impairment

- *Immediate treatment of typhoid reduces the risk of complications*

INTESTINAL PERFORATIONS

- The most severe complication of typhoid
- A hole develops in the ileum of the small intestine or bowel causing leakage into abdominal cavity
  - Also known as ileal perforation
  - Life-threatening, can lead to sepsis
  - Requires immediate medical attention
- Surgery is often needed to mend the tears and/or to resect a portion of the intestines
- Thought to develop in 1-3% of typhoid cases

SNAPSHOT: INTESTINAL PERFORATIONS IN UGANDA

- Dec 2007-June 2009: Hospitals in Kasese District received many patients with a febrile illness
- High number of intestinal perforations indicated typhoid

Neil, K. P., Sodha, S. V., Lukwago, L., O-tipo, S., Mikoleit, M., Simington, S. D., … Mintz, E. (2012). A Large Outbreak of Typhoid Fever Associated With a High Rate of Intestinal Perforation in Kasese District, Uganda, 2008-2009. *Clinical Infectious Diseases*, *54*(8), 1091–1099. https://doi.org/10.1093/cid/cis025

SNAPSHOT: INTESTINAL PERFORATIONS IN UGANDA

- Surveillance networks documented 577 suspected cases, 289 hospitalizations, 249 intestinal perforations and 47 deaths
    - 43% had intestinal perforation (normal rate 1-3%)
- Large number of perforations attributed to underreporting of milder typhoid symptoms and lack of proper medical attention
- Limited local microbiological capacity (equipment, supplies and trained personnel) led to diagnostic difficulties and delays in confirming the disease
    - Only 1 hospital in the area had microbiological culture capacity

Neil, K. P., Sodha, S. V., Lukwago, L., O-tipo, S., Mikoleit, M., Simington, S. D., … Mintz, E. (2012). A Large Outbreak of Typhoid Fever Associated With a High Rate of Intestinal Perforation in Kasese District, Uganda, 2008-2009. *Clinical Infectious Diseases*, *54*(8), 1091–1099. https://doi.org/10.1093/cid/cis025

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

MODULE 2 KEY MESSAGES

1. Typhoid is a human-restricted pathogen
2. Typhoid is transmitted via fecal-oral route and begins with ingestion of the *S.* Typhi bacteria, which invades the bowel
3. The incubation period is affected by the method of ingestion and quantity of bacteria ingested
4. Typhoid is transmissible until the bacteria is no longer shed through stool
5. Complications can occur from typhoid, with the most severe being intestinal perforation

REFERENCES

1. Bhan, M. K., Bahl, R., Bhatnagar, S., Oshihoi, Y., Izumiya, H., & Watanabe, H. (2000). Typhoid and paratyphoid fever. *Lancet (London, England)*, *366*(9487), 749–62. https://doi.org/10.1016/S0140-6736(05)67181-4
2. Levine, M. M. (2013). Typhoid fever vaccines. In *Vaccines* (Sixth Edition, pp. 812–836). Elsevier Inc. https://doi.org/10.1016/B978-1-4557-0090-5.00082-3
3. Manangazira, P., Glavintcheva, I., Mutukwa-Gonese, G., Bara, W., Chimbaru, A., & Ameda, I. (2011). *Guidelines for the Management of Typhoid Fever*. Retrieved from http://apps.who.int/medicinedocs/documents/s20994en/s20994en.pdf
4. Farooqui, A., Khan, A., & Kazmi, S. U. (2009). Investigation of a community outbreak of typhoid fever associated with drinking water. *BMC Public Health*, *9*(1), 476. https://doi.org/10.1186/1471-2458-9-476
5. World Health Organization Communicable Disease Surveillance and Response Vaccines and Biologicals. Background document: The diagnosis, treatment and prevention of typhoid fever (2003). Retrieved from http://www.who.int/rpc/TFGuideWHO.pdf
6. Marineli, F., Tsoucalas, G., Karamanou, M., & Androutsos, G. (2013). Mary Mallon (1869-1938) and the history of typhoid fever. *Annals of Gastroenterology*, *26*(2), 132–134. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24714738
7. Parry, C. M., Hien, T. T., Dougan, G., White, N. J., & Farrar, J. J. (2002). Typhoid Fever. *New England Journal of Medicine*, *347*(22), 1770–1782. https://doi.org/10.1056/NEJMra020201

MODULE 3: DIAGNOSTICS

LEARNING OBJECTIVES

In this module, you will:

1. Learn about symptoms associated with typhoid
2. Learn the definitions of suspected case, confirmed case and chronic carrier of typhoid
3. Learn about the different diagnostic processes for typhoid

SYMPTOMS OF TYPHOID

- Symptoms often develop after typhoid enters the blood stream and may be used to suggest the diagnosis of typhoid
- Symptoms include:
  - Fever
  - Abdominal pain
  - Headaches
  - Poor appetite
  - Generalized aches and pains
  - Lethargy
  - Diarrhea
  - Rose spots on the chest, abdomen, or back
- Fever, abdominal pain and headache form the "typhoid triad" of symptoms
- Nonspecific symptoms of typhoid make laboratory diagnosis necessary to confirm the case and ensure appropriate antimicrobial treatment

TYPHOID CASE DEFINITIONS

- **Suspected Case:** A patient with a fever that has lasted at least 3 days in absence of a laboratory-confirmed result
- **Confirmed Case:** A patient with a fever that has lasted at least 3 days with a laboratory-confirmed bacterial culture of *S.* Typhi from a normally sterile site (e.g. blood or bone marrow culture)
- **Chronic Carrier:** A patient that excretes *S.* Typhi in stool or urine for at least 1 year after an episode of typhoid infection

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

LABORATORY DIAGNOSIS

Clinical samples suitable for culture of *S.* Typhi:

Cultures	Sensitivity	Details
Bone Marrow	>80%	• Uncomfortable, invasive and impractical • Sensitivity remains high up to 5 days after starting antibiotic treatment
Blood	40%-60%	• Sensitivity increases with greater volumes of blood • Sensitivity decreases greatly over time (by third week of illness, blood culture sensitivity is at 50%) • 100% specificity
Stool	<50%	• Can be tested months following the illness to test for carriage • Sensitivity increases with duration of illness
Urine	<50%	
Rose Spot Punch Biopsy	~63%	• May be positive even after antibiotics

Christopher M Parry, Lalith Wijedoru, Amit Arjyal & Stephen Baker (2014) The utility of diagnostic tests for enteric fever in endemic locations, Expert Review of Anti-infective Therapy, 9:6, 711-725, DOI: 10.1586/eri.11.47

Sattar, A., Yusuf, M. A., Islam, M. B., & Jahan, W. A. (2014). Different Diagnostic Procedure of Typhoid Fever: A Review Update. *Journal of Current and Advance Medical Research*, *1*(2), 35–41. Retrieved from http://www.banglajol.info/index.php/JCAMR/article/view/20517/14177

BLOOD CULTURE

- Most widely used method to diagnose typhoid
- Blood should be collected before antibiotic usage to properly isolate the bacteria
  - The number of bacteria present in the sample can decrease with antibiotic usage, making it more difficult to isolate
- Different volumes of blood are needed from children and adults for a culture diagnosis
  - 2-4 mL collected from toddlers and preschool children
  - 10-15 mL collected from schoolchildren and adults
- Difficult to undertake in low-resource settings due to lack of required materials and few testing laboratories

OTHER DIAGNOSTIC TESTS

Antibody-Based Assays

- Widal, Tubex and Typhidot tests detect antibodies produced by the body in response to typhoid exposure
- Levels of antibodies in an area differ due to environmental factors
  - Healthy populations in highly endemic areas have higher levels of antibodies than healthy populations in a non-endemic area, so diagnostic cutoffs vary by region
- Widal, Tubex and Typhidot tests have low sensitivity and specificity in endemic areas
- New serologic tests are under development, but further research is needed

Polymerase Chain Reaction (PCR)

- Based on the DNA replication process
- Can be performed using blood or urine samples
- Currently for research use only

MODULE 3 KEY MESSAGES

1. Typhoid has symptoms similar to other febrile illnesses, which can lead to misdiagnosis and delay in treatment
2. Laboratory diagnosis, normally by blood culture, is necessary to confirm a case of typhoid fever
3. New serologic tests are under development, but further research is needed

REFERENCES

1. World Health Organization Communicable Disease Surveillance and Response Vaccines and Biologicals. Background document: The diagnosis, treatment and prevention of typhoid fever (2003). Retrieved from http://www.who.int/rpc/TFGuideWHO.pdf
2. Levine, M. M. (2013). Typhoid fever vaccines. In *Vaccines* (Sixth Edition, pp. 812–836). Elsevier Inc. https://doi.org/10.1016/B978-1-4557-0090-5.00082-3
3. Sattar, A., Yusuf, M. A., Islam, M. B., & Jahan, W. A. (2014). Different Diagnostic Procedure of Typhoid Fever: A Review Update. *Journal of Current and Advance Medical Research*, *1*(2), 35–41. Retrieved from http://www.banglajol.info/index.php/JCAMR/article/view/20517/14177
4. Ambati, S. R., Nath, G., & Das, B. K. (2007). Diagnosis of typhoid fever by polymerase chain reaction. *Indian Journal of Pediatrics*, *74*(10), 909–13. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17978448
5. Parry, C. M., Thompson, C., Vinh, H., Chinh, N. T., Phuong, L. T., Ho, V. A., … Baker, S. (2014). Risk factors for the development of severe typhoid fever in Vietnam. *BMC Infectious Diseases*, *14*, 73. https://doi.org/10.1186/1471-2334-14-73
6. Akinwale, M. O., Sanusi, A. A., & Adebayo, O. K. (2016). Typhoid perforation: Post-operative Intensive Care Unit care and outcome. *African Journal of Paediatric Surgery : AJPS*, *13*(4), 175–180. https://doi.org/10.4103/0189-6725.194664
7. Mogasale, V., Desai, S. N., Mogasale, V. V, Park, J. K., Ochiai, R. L., & Wierzba, T. F. (2014). Case fatality rate and length of hospital stay among patients with typhoid intestinal perforation in developing countries: a systematic literature review. *PloS One*, *9*(4), e93784. https://doi.org/10.1371/journal.pone.0093784
8. Neil, K. P., Sodha, S. V., Lukwago, L., O-tipo, S., Mikoleit, M., Simington, S. D., … Mintz, E. (2012). A Large Outbreak of Typhoid Fever Associated With a High Rate of Intestinal Perforation in Kasese District, Uganda, 2008-2009. *Clinical Infectious Diseases*, *54*(8), 1091–1099. https://doi.org/10.1093/cid/cis025

MODULE 4: TREATMENT

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

LEARNING OBJECTIVES

In this module, you will:

1. Learn how typhoid is treated
2. Learn about the impact of antibiotic resistance on typhoid treatment
3. Observe trends in antibiotic resistance
4. Understand solutions for the threat of antibiotic resistance

TYPICAL COURSE OF TYPHOID TREATMENT

- Optimal management depends on early diagnosis and prompt, appropriate antibiotic treatment
  - 90% of cases can be managed at home with oral antibiotics, bedrest and close medical follow-up
  - 10-20% of untreated patients will die
- General management of typhoid can include:
  - Oral or intravenous hydration
  - Fever reducing medicine (antipyretics)
  - Appropriate nutrition
  - Hand-washing and limited contact with susceptible individuals
  - Regular follow-up and monitoring for complications or relapse

ANTIBIOTIC TREATMENT

- Antibiotic treatment varies depending on:
  - Severity
  - Age
  - Antibiotic resistance
  - General state of health
- Growing resistance to many first-line antibiotics is leading to increased use of other antibiotics that may be:
  - More expensive
  - Less effective
  - Associated with more severe side effects
  - Associated with higher rate of relapse

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

MANAGING TYPHOID COMPLICATIONS

- Typhoid complications range from mild to severe. Intestinal hemorrhage and perforation are some of the most severe complications
- Intestinal hemorrhage
  - Intensive care and monitoring
  - Blood transfusion
- Intestinal perforations
  - Majority of perforations require surgery
  - A small portion of the bowel may be cut out if the perforation is very severe
  - Mortality rates for patients with perforations vary between 10-32%
- Chronic carriers can usually be treated with antibiotics, though gallbladder removal may be required

RELAPSE

- 5-20% of patients experience a relapse in typhoid after treatment
  - Higher for patients with antibiotic-resistant typhoid
  - More likely to occur when a patient has poor access to care and receives inadequate treatment
- Relapse can generally occur 3-4 weeks after a clinical cure
- Illness is typically milder and is treated in the same way as initial infections

ANTIBIOTIC RESISTANCE

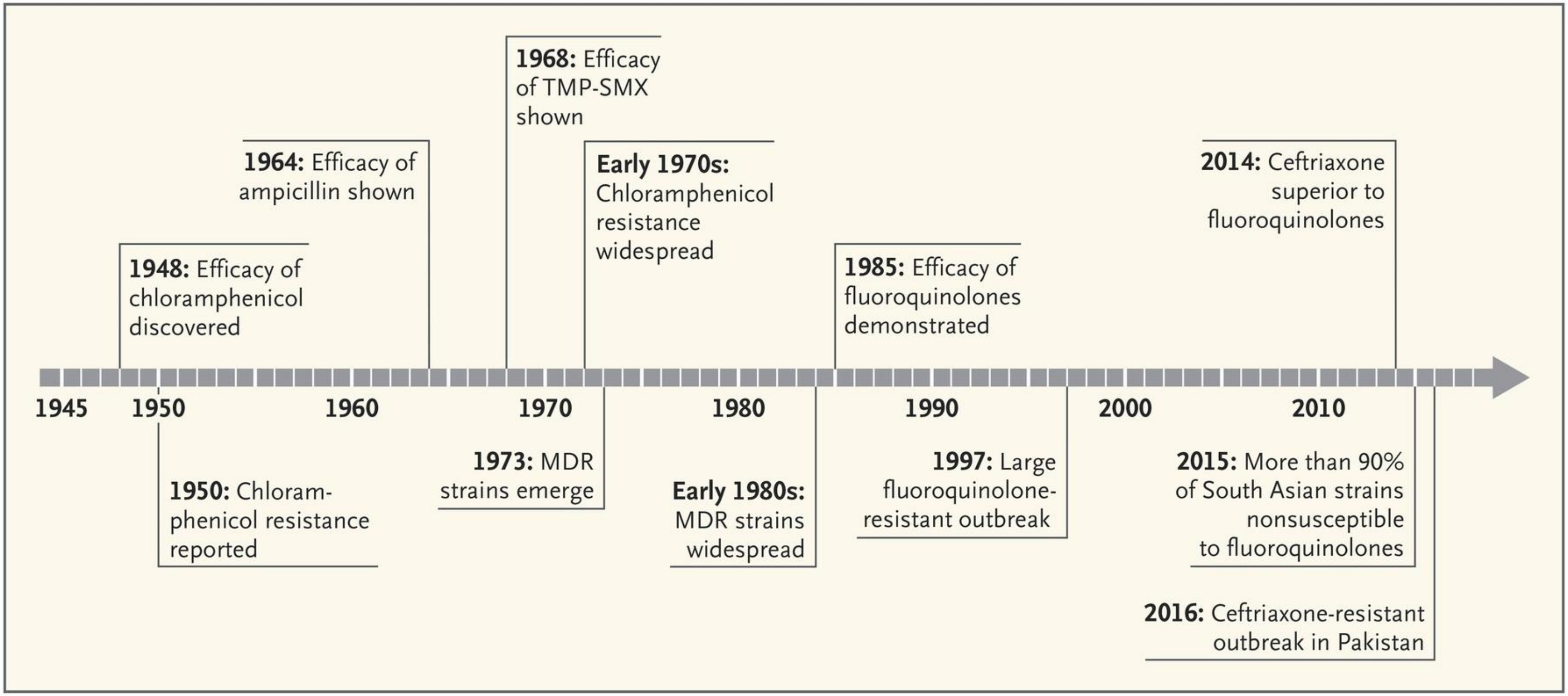
- Antibiotic resistance happens when bacteria mutates and is able to resist the effect of antibiotics
- Can occur naturally, but misuse of antibiotics in humans and animals is accelerating the process
  - >50% of the time antibiotics are not optimally prescribed, not needed, or of the incorrect dosing or duration
  - Antibiotics are available over-the-counter in many developing countries
- Multi-drug resistant strains of typhoid originating in Southern Asia and spreading to Sub-Saharan Africa are a threat to the effective treatment of typhoid
  - The first known outbreak of extensively drug resistant (XDR) typhoid began in Pakistan in 2016

FIGHTING RESISTANT TYPHOID

- Widespread resistance in 1980s and 1990s to the most common antibiotics (ampicillin, co-trimoxazole, chloramphenicol)
  - Resulted in use of fluoroquinolones and cephalosporins
  - Resistance to fluoroquinolones is spreading rapidly, and resistance to cephalosporins has been reported
- Combinations of antibiotics are being assessed for affordable options to combat AMR typhoid
- Improved laboratory capacity is needed to determine the drug susceptibility of typhoid cases
  - Determining the resistance will help to provide effective treatments and reduce the use of antibiotics that may be ineffective

ANTIBIOTIC RESISTANCE TIMELINE

- This figure illustrates the history of antibiotic efficacy studies and the emergence of antimicrobial resistance in *Salmonella* Typhi.



Andrews JR, Qamar FN, Charles RC, Ryan ET. Extensively Drug-Resistant Typhoid—Are Conjugate Vaccines Arriving Just in Time?. New England Journal of Medicine. 2018 Oct 18;379(16):1493-5.

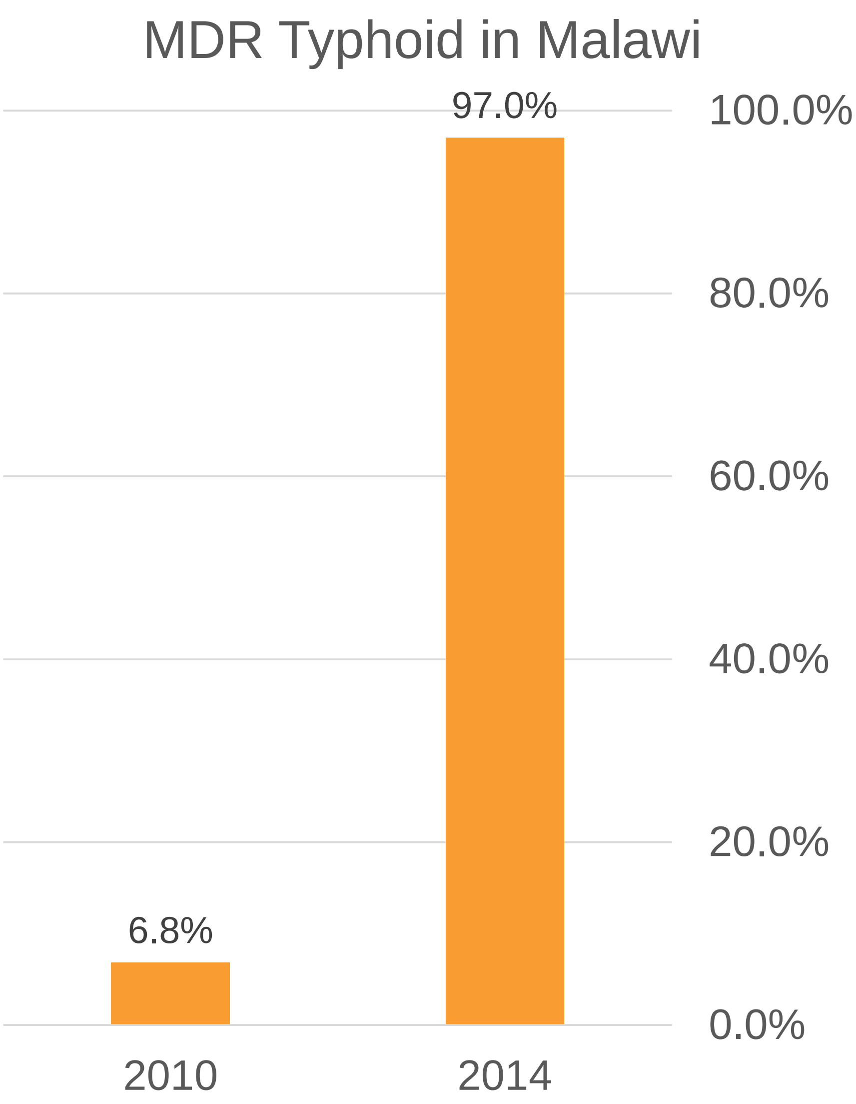
H58 TYPHOID STRAIN

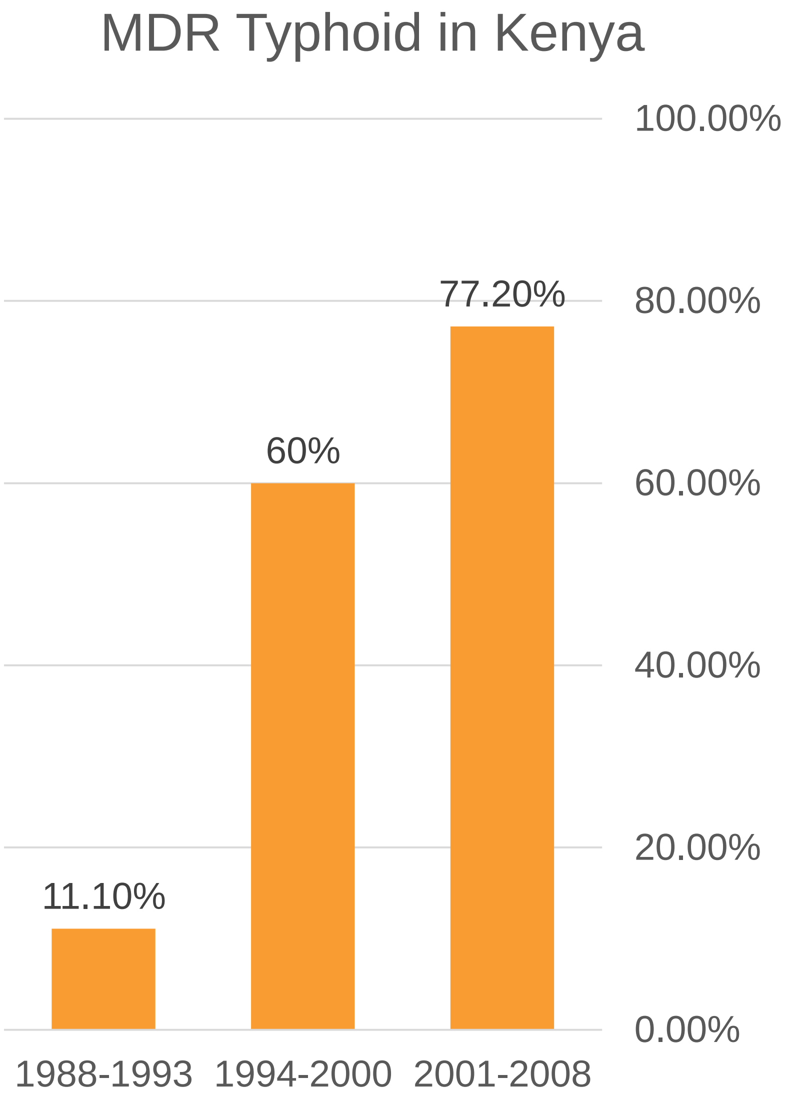
- A multi-drug resistant (MDR) strain that has emerged over the past 20 years
  - MDR strains are resistant to ampicillin, co-trimoxazole and chloramphenicol
- Originated in Southern Asia, spread to Middle East and Pacific Islands, and recently introduced to Sub-Saharan Africa
  - Kenya: First cases of H58 typhoid 10 years ago
  - Malawi: First cases of H58 typhoid 5 years ago
- H58 genes are becoming a stable part of the genome
  - 47% of typhoid cases sampled from 63 countries between 1992 and 2013 were from the H58 strain
  - Study by the Wellcome Trust found H58 typhoid cases in Malawi increased from 6.8% to 97% from 2010 to 2014

Kariuki, S., Revathi, G., Kiiru, J., Mengo, D. M., Mwituria, J., Muyodi, J., … Dougan, G. (2010). Typhoid in Kenya is associated with a dominant multidrug-resistant Salmonella enterica serovar Typhi haplotype that is also widespread in Southeast Asia. *Journal of Clinical Microbiology*, *48*(6), 2171–6

Feasey, N. A., Gaskell, K., Wong, V., Msefula, C., Selemani, G., Kumwenda, S., … Heyderman, R. S. (2015). Rapid Emergence of Multidrug Resistant, H58-Lineage Salmonella Typhi in Blantyre, Malawi. *PLOS Neglected Tropical Diseases*, *9*(4), e0003748.

SNAPSHOT: MDR TYPHOID TRENDS





Feasey, N. A., Gaskell, K., Wong, V., Msefula, C., Selemani, G., Kumwenda, S., … Heyderman, R. S. (2015). Rapid Emergence of Multidrug Resistant, H58-Lineage Salmonella Typhi in Blantyre, Malawi. *PLOS Neglected Tropical Diseases*, *9*(4), e0003748.

Kariuki, S., Revathi, G., Kiiru, J., Mengo, D. M., Mwituria, J., Muyodi, J., … Dougan, G. (2010). Typhoid in Kenya is associated with a dominant multidrug-resistant Salmonella enterica serovar Typhi haplotype that is also widespread in Southeast Asia. *Journal of Clinical Microbiology*, *48*(6), 2171–6.

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

MDR: A PUBLIC HEALTH EMERGENCY

- Threatens the ability to treat common infectious diseases and can cause prolonged illness, disability and death
- Increases the cost of health care by necessitating:
  - Longer hospital stays
  - More intensive care
  - Additional tests
  - More expensive drugs
- Even if new medicines are developed, preventative measures are needed to reduce the spread of infections
  - Vaccination
  - Hand-washing
  - Food hygiene

SNAPSHOT: MDR & XDR TUBERCULOSIS

- Global investment in controlling tuberculosis (TB) was insufficiently funded and did not focus enough on prevention or diagnosis
- MDR-TB and extensively drug resistant tuberculosis (XDR-TB) emerged in early 1990s
- XDR-TB strains are resistant to the strongest drugs
    - Treatment success rate of only 26%
- 2013: 84 countries with XDR-TB
- 2016: 117 countries with XDR-TB
- Current situation: treatment is 50 to 200 times more expensive and takes 3 times longer to cure than normal TB

Abubakar, I., Zignol, M., Falzon, D., Raviglione, M., Ditiu, L., Masham, S., … Zumla, A. (2013). Drug-resistant tuberculosis: time for visionary political leadership. *The Lancet Infectious Diseases*, *13*(6), 529–539. https://doi.org/10.1016/S1473-3099(13)70030-6

Multidrug-Resistant Tuberculosis (MDR-TB) 2016 Update. (n.d.). Retrieved from http://www.who.int/tb/challenges/mdr/mdr_tb_factsheet.pdf?ua=1

Pinto, L., & Menzies, D. (2011). Treatment of drug-resistant tuberculosis. Infection and Drug Resistance, 4, 129–35. https://doi.org/10.2147/IDR.S10332

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

KEY MESSAGES

1. The majority of typhoid cases can be treated at home with antibiotics, but patients with typhoid complications must seek more extensive care
2. When diagnosing typhoid, it is essential to test for drug susceptibility to determine an effective course of antibiotic treatment
3. Multi-drug resistant typhoid is a growing global threat and calls for increased investment in prevention and control

REFERENCES

1. World Health Organization Communicable Disease Surveillance and Response Vaccines and Biologicals. Background document: The diagnosis, treatment and prevention of typhoid fever (2003). Retrieved from http://www.who.int/rpc/TFGuideWHO.pdf
2. Levine, M. M. (2013). Typhoid fever vaccines. In *Vaccines* (Sixth Edition, pp. 812–836). Elsevier Inc. https://doi.org/10.1016/B978-1-4557-0090-5.00082-3
3. Bhutta, Z. A. (2006). Current concepts in the diagnosis and treatment of typhoid fever. *BMJ (Clinical Research Ed.)*, *333*(7558), 78–82. https://doi.org/10.1136/bmj.333.7558.78
4. Chinh, N. T., Parry, C. M., Ly, N. T., Ha, H. D., Thong, M. X., Diep, T. S., … Farrar, J. J. (2000). A randomized controlled comparison of azithromycin and ofloxacin for treatment of multidrug-resistant or nalidixic acid-resistant enteric fever. *Antimicrobial Agents and Chemotherapy*, *44*(7), 1855–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10858343
5. Bhutta, Z. A., Ahmad, K. A., Khan, L. H., Roshan, B., & Bhutta, Z. A. (2011). Factors associated with typhoid relapse in the era of multiple drug resistant strains. *Doi.org*, *5*(10), 727–731. https://doi.org/10.3855/jidc.1192
6. CDC. (2015). About Antimicrobial Resistance | Antibiotic/Antimicrobial Resistance | CDC. Retrieved from https://www.cdc.gov/drugresistance/about.html
7. Kariuki, S., Revathi, G., Kiiru, J., Mengo, D. M., Mwituria, J., Muyodi, J., … Dougan, G. (2010). Typhoid in Kenya is associated with a dominant multidrug-resistant Salmonella enterica serovar Typhi haplotype that is also widespread in Southeast Asia. *Journal of Clinical Microbiology*, *48*(6), 2171–6. https://doi.org/10.1128/JCM.01983-09
8. Harish, B. N., & Menezes, G. A. (2011). Antimicrobial resistance in typhoidal salmonellae. *Indian Journal of Medical Microbiology*, *29*(3), 223–9. https://doi.org/10.4103/0255-0857.83904
9. Feasey, N. A., Gaskell, K., Wong, V., Msefula, C., Selemani, G., Kumwenda, S., … Heyderman, R. S. (2015). Rapid Emergence of Multidrug Resistant, H58-Lineage Salmonella Typhi in Blantyre, Malawi. *PLOS Neglected Tropical Diseases*, *9*(4), e0003748. https://doi.org/10.1371/journal.pntd.0003748
10. WHO | Antimicrobial resistance. (2016). *WHO*. Retrieved from http://www.who.int/mediacentre/factsheets/fs194/en/
11. Abubakar, I., Zignol, M., Falzon, D., Raviglione, M., Ditiu, L., Masham, S., … Zumla, A. (2013). Drug-resistant tuberculosis: time for visionary political leadership. *The Lancet Infectious Diseases*, *13*(6), 529–539. https://doi.org/10.1016/S1473-3099(13)70030-6
12. *Multidrug-Resistant Tuberculosis (MDR-TB) 2016 Update*. (n.d.). Retrieved from http://www.who.int/tb/challenges/mdr/mdr_tb_factsheet.pdf?ua=1
13. Pinto, L., & Menzies, D. (2011). Treatment of drug-resistant tuberculosis. Infection and Drug Resistance, 4, 129–35. https://doi.org/10.2147/IDR.S10332

MODULE 5: PREVENTION

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

LEARNING OBJECTIVES

In this module, you will:

1. Identify typhoid prevention methods
2. Learn about water, sanitation and hygiene interventions
3. Learn about typhoid vaccines

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

THE PREVENTABLE BURDEN

Typhoid can be prevented by:

- Water, sanitation and hygiene (WASH) interventions, including:
  - Providing access to safe drinking water
  - Ensuring that the community's fecal waste does not contaminate the environment
  - Encouraging handwashing and safe food production and handling practices
- Vaccination can
  - Protect the most vulnerable, i.e. children
  - Control outbreaks
  - Build herd immunity

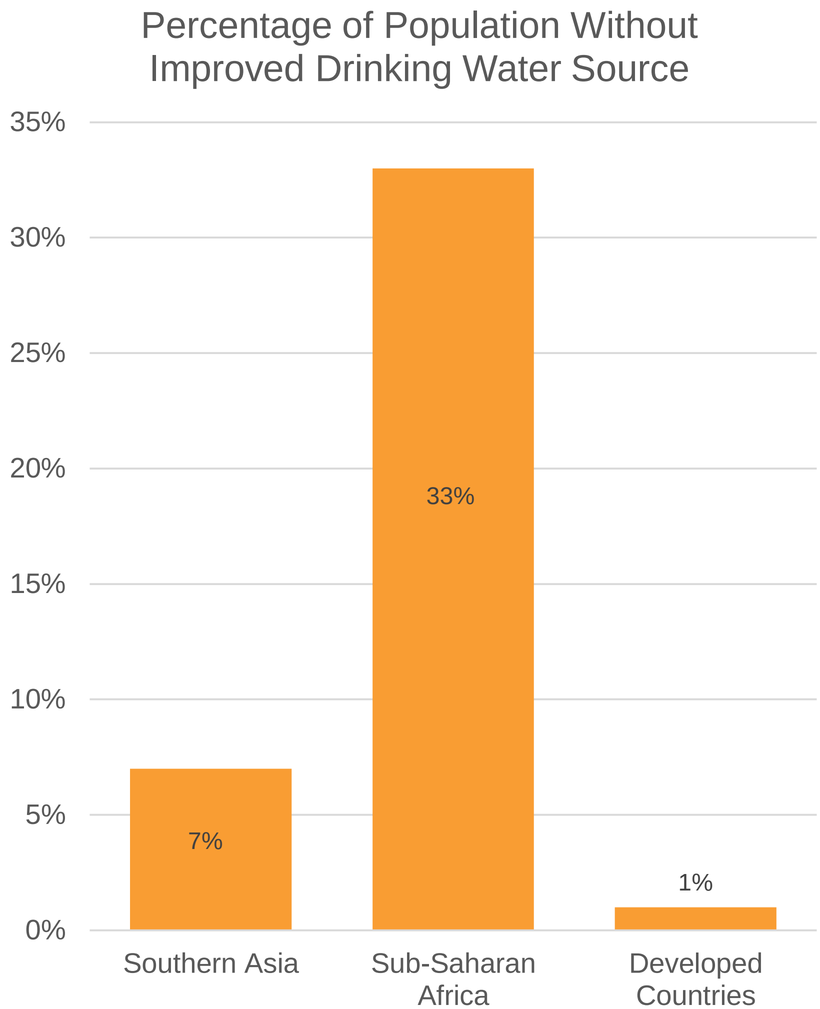
IMPORTANCE OF TYPHOID PREVENTION

- Cost-effective: Prevention is much cheaper than cure
- Reduction of suffering: Allows communities to avoid the negative consequences of missed school or work
- Integration is key: combining vaccines with improvements in safe water, sanitation and hygiene can maximize impact
- Fighting antimicrobial resistance: Preventing typhoid means fewer chances for antimicrobial resistance to develop
- Widely demanded: Vaccines are widely acceptable and demanded in endemic areas
- Ripple effects: WASH interventions can also prevent other waterborne diseases
- Long-term benefit: WASH infrastructure and vaccine programs can greatly reduce disease burden over time

ACCESS TO CLEAN WATER

The Facts:

- 1.8 billion people drink from fecal-contaminated sources
- Typhoid fever is easily transmitted by drinking water contaminated with human feces
- Largest outbreaks of typhoid are often waterborne



UNICEF. (2015) “Progress on Sanitation and Drinking Water”. Retrieved from http://files.unicef.org/publications/files/Progress_on_Sanitation_and_Drinking_Water_2015_Update_.pdf

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

WATER QUALITY INTERVENTIONS

At Point of Use	At Source
Household	Wells, reservoirs
• Chlorination • Household filters • Sedimentation • Water storage sanitation	• Chlorination • Filtration • Improvements in distribution pipes

SNAPSHOT: U.S. IN THE 20TH CENTURY

- 1900: Typhoid incidence of 100 cases /100,000 people
- Rampant in crowded cities like Baltimore and Chicago
  - Water drawn untreated from rivers, which were also sewage repositories
- Interventions included water disinfection and treatment
  - Sand filtration and chlorination
  - Improvement of public sanitation and hygiene infrastructure
  - Despite presence of typhoid carriers, cases in large cities dropped swiftly
- 1920: Typhoid incidence decreased to 33.8 cases/100,000
- 2006: Typhoid incidence of 0.1 cases/100,000
  - Most cases occurring among international travelers

COALITION AGAINST TYPHOID

CDC. (1999). A Century of U.S. Water Chlorination and Treatment: One of the Ten Greatest Public Health Achievements of the 20th Century. *Morb Mortal Wkly Rep, 48(29)*, 621-9.

SABIN VACCINE INSTITUTE

IMPROVED SANITATION INFRASTRUCTURE

Facts:

- 2.4 billion people are without improved sanitation facilities
- Majority of fecal waste worldwide is discharged unsafely into the environment
- 80% of illnesses in low-income countries are linked to poor water and sanitation conditions

Interventions:

- Keeping fecal stream from being released into the environment untreated through wastewater collection and treatment
- Maintaining continuous water supply
- Building sanitation infrastructure like toilets, latrines and septic tanks
- Promoting habitual use of sanitation infrastructure

UNICEF. (2015) "Progress on Sanitation and Drinking Water". Retrieved from http://files.unicef.org/publications/files/Progress_on_Sanitation_and_Drinking_Water_2015_Update_.pdf

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

IMPROVED HEALTHY HYGIENE PRACTICES

Facts:

- 4 out of 10 schools worldwide lack basic water, sanitation and hygiene facilities
- Half of all healthcare facilities lack piped water, 33% lack improved sanitation and 39% lack handwashing soap
- In least developed countries, only 27% had basic handwashing facilities with soap and water, 26% had handwashing facilities lacking soap or water, and 47% had no facility

Interventions:

- Promoting handwashing with soap at critical times (i.e. when preparing food, eating, after defecating)

UNICEF. (2015) "Progress on Sanitation and Drinking Water". Retrieved from http://files.unicef.org/publications/files/Progress_on_Sanitation_and_Drinking_Water_2015_Update_.pdf

SNAPSHOT: HANDWASHING IN VIETNAM

- Typhoid incidence in Vietnam in children under 15 as high as 413 cases/100,000 people
- Handwashing is not common practice
  - Only 3% of mothers washed hands with soap before preparing food; 11% after handling a child's feces
  - Low knowledge of importance of washing with soap
- Vietnam Handwashing Initiative began in 2006
  - Reached 14.2 million women and children through mass media and 2.2 million through interpersonal communication
- Despite greater reported knowledge, behavior change was low due to:
  - Promotion without product: Availability of soap and water at right place and time serves as a physical reminder
  - Changes in messaging: Once audiences have higher knowledge, the messaging must switch to emphasizing behavior change

Lin FY, Ho VA, Bay PV, et al. The epidemiology of typhoid fever in the Dong Thap Province, Mekong Delta region of Vietnam. Am J Trop Med Hyg 2000;62:642-646

Nguyen, Nga Kim; Devine, Jacqueline. 2012. Global Scaling Up Handwashing Project : Results, Impacts, and Learning from Vietnam. Water and sanitation program learning note;. World Bank, Washington, DC. © World Bank. https://openknowledge.worldbank.org/handle/10986/17095 License: CC BY 3.0 IGO."

CHALLENGES OF WATER, SANITATION AND HYGIENE INTERVENTIONS

- Household interventions are characterized by low uptake and systematically exclude the poorest, who are most at risk
- Municipal water systems run intermittently, which guarantees contamination
- Few incentives to reach the poor and invest in maintenance and repair
- Difficulties of ownership for communal (shared) sanitation infrastructure
  - Less safe and accessible than in-home sanitation
- Shared sanitation infrastructure has to be continually cleaned and maintained
- Behavior and perception change is difficult
  - Many do not want to use stored water for handwashing
  - Soap is relatively expensive and used primarily for laundry
- Lack of belief in efficacy of handwashing in combating typhoid

VALUE OF TYPHOID VACCINES

- Typhoid vaccines:
    - Offer both individual protection and herd immunity (when used in a large-scale vaccination effort)
    - Complement WASH prevention strategies that may require more time and money to implement
    - Protect against antibiotic-resistant strains of typhoid
    - Reduce health care costs to both families and health systems

TYPHOID VACCINES

Until recently, there were only 2 types of typhoid vaccines on the market:

Ty21a	Vi capsular polysaccharide
A live attenuated vaccine given through oral capsules	An injectable subunit vaccine
• Must be at least 6 years old • 3 to 4 doses needed • Booster needed every 5 years • 50-80% effective	• Must be at least 2 years old • 1 dose needed • Booster needed every 2-3 years • 50-80% effective

SNAPSHOT: VACCINES IN GUANGXI, CHINA

- Vi polysaccharide vaccine used in a 1995 mass vaccination program
  - Targeted students, food-handlers and people living near outbreaks
  - Revaccination took place every 3 years
  - Coverage rates averaged 60-70% for students and 80-85% for food-handlers and outbreak area residents

Typhoid Incidence Before and After Vaccination		
	1991-1994	1999-2002
Students	61/100,000	0.4-6.1/100,000
General Population	47/100,000	0.7-3.5/100,000

- Vaccination played major role in typhoid reduction, as water and sanitation improvements were very gradual during this period
  - Paratyphoid rates actually increased
- During 1999 outbreak, vaccinated students had an 81% lower risk

Yang HH. Experience of school-based vaccination in a typhoid fever endemic area using Vi manufactured in China. Presentation made at meeting on Typhoid Fever, a Neglected Disease: Towards a Vaccine Introduction Policy, Annecy, France, April 2-4, 2007. PATH Vaccine Resource Library: Typhoid. (2017). Retrieved from https://www.path.org/vaccineresources/typhoid.php

WHY DON'T COUNTRIES UTILIZE TYPHOID VACCINES?

A 2000/2001 survey of policymakers in Asia gave several reasons:

- Uncertainty of the true typhoid disease burden
- Sense of complacency created by the successful use of relatively inexpensive antibiotics
- Lack of public attention
- Political pressure for local government officials not to report typhoid cases
- Relatively high prices of vaccines on the world market
- A preference for water and sanitation improvements over vaccination
- A lack of awareness about the new-generation vaccines
- Uncertainty of the feasibility of mass vaccination of children

Typhoid Immunization Working Group. (2007). *Background Paper on Vaccination against Typhoid Fever using New- Generation Vaccines - presented at the SAGE November 2007 meeting*. Retrieved from http://docplayer.net/21182741-Background-paper-on-vaccination-against-typhoid-fever-using-new-generation-vaccines-presented-at-the-sage-november-2007-meeting.html

NEW TYPHOID CONJUGATE VACCINES (TCVs)

- Third generation of typhoid vaccines
  - Antigen is coupled to a carrier protein
  - The World Health Organization has prequalified Typbar-TCV®, allowing WHO, UNICEF and other United Nations procurement agencies to purchase the vaccine
- Benefits of conjugate vaccines:
  - Long duration of protection
  - Can be administered to children less than 2 years old
  - Fewer doses required
  - Can be administered through routine immunization programs
- 2 conjugate vaccines, Typbar-TCV and Peda Typh™, have national licensure in India
  - Roll out of conjugate vaccine in endemic countries is within reach in the coming years

Typbar-TCV ®

Typbar-TCV
An injectable conjugate vaccine, manufactured by Bharat Biotech
• Can be administered to children below 2 years of age • Immunity for at least 3 years • 1 dose needed • 87% efficacy*

- In December 2017, achieved prequalification by the WHO
  - Prequalification indicates that a vaccine meets international standards and serves as an endorsement of quality, efficacy and safety
  - With prequalification, Typbar-TCV can be purchased by WHO, UNICEF and other United Nations procurement agencies to help finance TCVs in low-resource countries

* Efficacy based on Oxford human challenge model: Jin, C., Gibani, M. M., Moore, M., Juel, H. B., Jones, E., Meiring, J., … Pollard, A. J. (2017). Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial. Lancet (London, England), 390(10111), 2472–2480. https://doi.org/10.1016/S0140-6736(17)32149-9

GLOBAL POLICY FOR TCVS

- TCVs are poised for distribution in endemic countries
- The WHO recommends the following use of typhoid conjugate vaccines:
  - TCVs should be used in endemic countries for children greater than 6 months of age
  - TCVs should be prioritized in countries with the highest burden and/or a growing burden of drug-resistant typhoid
  - TCVs should be used for outbreak response and in specific groups of people at high risk
- Gavi, the Vaccine Alliance released $85 million in funding to support the introduction of the TCVs in low-income countries
  - Funds will enable bulk purchases of TCVs
  - Countries are expected to begin applying for Gavi support in 2018 for vaccine introduction in 2019 and 2020

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

SNAPSHOT: VACCINE DEMAND IN MALAWI

- 2009/2010:Outbreak of typhoid detected in southwest Malawi with 784 cases and 44 deaths reported in 17 villages
- Investigation of vaccine acceptability during 2010 found:
  - The disease widely feared due to rapid spread
  - Widespread skepticism of WASH interventions:
    - Disease believed to be spread by “bad air” or wind
    - All villagers follow same hygiene practices, but only some got sick
  - Firm belief in power of vaccines in preventing illness:
    - Belief that benefits far outweigh negative reactions
    - Social pressure to receive vaccine as later illness will be blamed on refusers
    - Vaccine effectiveness of 60% did not decrease acceptability, perceived as an improvement over present situation [15]

Warne, T., Blum, L. S., Hyde, T., Sejvar, J., Chilima, B., Mintz, E. D., … Chingoli, F. (2014). Formative Investigation of Acceptability of Typhoid Vaccine During a Typhoid Fever Outbreak in Neno District, Malawi. *The American Journal of Tropical Medicine and Hygiene*, *91*(4), 729–737. https://doi.org/10.4269/ajtmh.14-0067

KEY MESSAGES

1. WASH and vaccination interventions can prevent typhoid. When integrated, they can have maximal impact
2. In the long-term, prevention is cheaper and more effective than treatment, and can have ripple effects on antimicrobial resistance and other diseases
3. Shorter-term WASH interventions can help mitigate the spread of typhoid but are not 100% adopted or sustained. Longer-term WASH interventions are costly, but ultimately prevent typhoid, cholera, and many other infectious diseases
4. New typhoid conjugate vaccines overcome many shortfalls of currently available vaccines by offering longer-lasting protection, requiring fewer doses and being suitable for children under 2

REFERENCES

1. World Health Organization Communicable Disease Surveillance and Response Vaccines and Biologicals. Background document: The diagnosis, treatment and prevention of typhoid fever (2003). Retrieved from http://www.who.int/rpc/TFGuideWHO.pdf
2. Typhoid Immunization Working Group. (2007). *Background Paper on Vaccination against Typhoid Fever using New- Generation Vaccines - presented at the SAGE November 2007 meeting*. Retrieved from http://docplayer.net/21182741-Background-paper-on-vaccination-against-typhoid-fever-using-new-generation-vaccines-presented-at-the-sage-november-2007-meeting.html
3. UNICEF. (2015) "Progress on Sanitation and Drinking Water". Retrieved from http://files.unicef.org/publications/files/Progress_on_Sanitation_and_Drinking_Water_2015_Update_.pdf
4. Vollaard, A. M., Ali, S., van Asten, H. A. G. H., Widjaja, S., Visser, L. G., Surjadi, C., & van Dissel, J. T. (2004). Risk Factors for Typhoid and Paratyphoid Fever in Jakarta, Indonesia. *JAMA*, *291*(21), 2607. https://doi.org/10.1001/jama.291.21.2607
5. Parkinson, J. (2009). A Review of the Evidence Base for WASH interventions in Emergency Responses / Relief Operations A Review of the Evidence Base for WASH interventions in Emergency Responses Executive summary. Retrieved from https://www.humanitarianresponse.info/fr/system/files/documents/files/Review-on-the-Evidence-Base-for-WASH-interventions-in-Emergency-Responses-200109.pdf
6. CDC. (1999). A Century of U.S. Water Chlorination and Treatment: One of the Ten Greatest Public Health Achievements of the 20th Century. *Morb Mortal Wkly Rep, 48(29)*, 621-9.
7. Greenwell, J., McCool, J., Kool, J., & Salusalu, M. (2013). Typhoid fever: hurdles to adequate hand washing for disease prevention among the population of a peri-urban informal settlement in Fiji. *Western Pacific Surveillance and Response Journal : WPSAR*, *4*(1), 41–5. https://doi.org/10.5365/WPSAR.2012.3.4.006
8. Lin FY, Ho VA, Bay PV, et al. The epidemiology of typhoid fever in the Dong Thap Province, Mekong Delta region of Vietnam. Am J Trop Med Hyg 2000;62:642-646
9. Nguyen, Nga Kim; Devine, Jacqueline. 2012. Global Scaling Up Handwashing Project : Results, Impacts, and Learning from Vietnam. Water and sanitation program learning note;. World Bank, Washington, DC. © World Bank. https://openknowledge.worldbank.org/handle/10986/17095 License: CC BY 3.0 IGO."
10. Kalra, A., & Mazumdar, P. (2010). Typhoid vaccines - Newer developments. *Journal of Pediatric Sciences*, *2*(5). https://doi.org/10.17334/JPS.59188
11. Yang HH. Experience of school-based vaccination in a typhoid fever endemic area using Vi manufactured in China. Presentation made at meeting on Typhoid Fever, a Neglected Disease: Towards a Vaccine Introduction Policy, Annecy, France, April 2-4, 2007. PATH Vaccine Resource Library: Typhoid. (2017). Retrieved from https://www.path.org/vaccineresources/typhoid.php
12. Take on Typhoid (2017). Typhoid Vaccines. Retrieved from http://www.coalitionagainsttyphoid.org/prevent-treat/typhoid-vaccines/
13. Gavi. (2017). Millions of children set to be protected against typhoid fever. Retrieved from http://www.gavi.org/library/news/press-releases/2017/millions-of-children-set-to-be-protected-against-typhoid-fever/
14. Jin, C., Gibani, M. M., Moore, M., Juel, H. B., Jones, E., Meiring, J., … Pollard, A. J. (2017). Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial. *Lancet (London, England)*, *390*(10111), 2472–2480. https://doi.org/10.1016/S0140-6736(17)32149-9
15. Warne, T., Blum, L. S., Hyde, T., Sejvar, J., Chilima, B., Mintz, E. D., … Chingoli, F. (2014). Formative Investigation of Acceptability of Typhoid Vaccine During a Typhoid Fever Outbreak in Neno District, Malawi. *The American Journal of Tropical Medicine and Hygiene*, *91*(4), 729–737. https://doi.org/10.4269/ajtmh.14-0067

MODULE 6: RELATED DISEASES

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

LEARNING OBJECTIVES

In this module, you will:

1. Learn about paratyphoid and invasive nontyphoidal *Salmonella* (iNTS) disease
2. Observe global trends for paratyphoid and iNTS disease
3. Review at risk groups for paratyphoid and iNTS disease

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

THE OTHER ENTERIC FEVER: PARATYPHOID

- Paratyphoid is caused by *Salmonella enterica* serotype Paratyphi A, B, or C
- *S.* Typhi and *S.* Paratyphi are commonly known as enteric fevers
- Paratyphoid is clinically similar to typhoid, but is generally milder with a shorter incubation period
- Humans are the only reservoir for *S.* Paratyphi
  - Bacteria are transmitted by consumption of contaminated water and food (fecal-oral route)

PREVALENCE AND DISTRIBUTION OF PARATYPHOID

- *S.* Paratyphi A is most common with 4.5 million cases per year
  - 8% relapse rate
- Southeast Asia and the Indian subcontinent are experiencing increasing incidences of *S*. Paratyphi A
  - *S.* Paratyphi A can account for up to 50% of *Salmonella* isolates among patients with enteric fever in some countries
- Unlike typhoid and nontyphoidal *Salmonella*, there is not a high burden of paratyphoid in Sub-Saharan Africa
  - Some cases seen in West Africa

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

PARATYPHOID DIAGNOSIS AND TREATMENT

Clinical Diagnosis:

- *S.* Paratyphi A symptoms include fever, jaundice, thrombosis, rose spots and systemic infections
- *S.* Paratyphi B has similar non-specific febrile illness symptoms but can also have symptoms similar to non-specific salmonella gastroenteritis

Laboratory Diagnosis:

- No reliable serological test
- Bone marrow or blood culture is gold standard

Treatment:

- Treated with antibiotics depending on the sensitivity patterns of *S.* Paratyphi isolates in the area

Complications:

- Similar to *S*. Typhi, complications include intestinal perforation, meningitis and multi-organ abscesses

PARATYPHOID PREVENTION

- Paratyphoid can be prevented with WASH interventions
  - Challenges: slow, expensive
- Currently no licensed paratyphoid vaccine
  - 4 vaccines are in development (Phases I and II)
- Urgency for vaccine due to:
  - Growing incidence *S.* Paratyphi A
  - Growing threat of antimicrobial resistance
  - Evidence that *S*. Paratyphi A has a greater tendency toward resistance than *S*. Typhi

SNAPSHOT: PARATYPHOID OUTBREAK IN CHINA

- 1998: Paratyphoid fever increasingly reported in China
- 2010: Outbreak of 601 cases in Yuanjiang county
- Identified Source: Raw vegetables from Ximen Farm Market
  - Vegetables sold at the market are from land near County People's Hospital
  - Farmers normally used spring water to irrigate the vegetables, but changed to wastewater with severe drought in 2009/2010
  - Wastewater was from County People's Hospital, where enteric fever cases are treated
  - Improperly disinfected hospital wastewater matched most of the isolates from the outbreak cases
- Interventions to successfully stop outbreak:
  - Prohibited selling of raw vegetables at restaurants
  - Prohibited planting vegetables in contaminated fields
  - Hospital enacted more thorough procedures to disinfect wastewater

Yan, M., Yang, B., Wang, Z., Wang, S., Zhang, X., Zhou, Y., … Kan, B. (2015). A Large-Scale Community-Based Outbreak of Paratyphoid Fever Caused by Hospital-Derived Transmission in Southern China. *PLOS Neglected Tropical Diseases*, *9*(7), e0003859. https://doi.org/10.1371/journal.pntd.0003859

NONTYPHOIDAL *SALMONELLA* (NTS) & INVASIVE NONTYPHOIDAL *SALMONELLA* (iNTS) DISEASE

- NTS is a major cause of diarrheal disease globally
  - 93 million infections per year
  - Estimated 4.8 million disability-adjusted life years lost in 2010
- iNTS disease is a top cause of bloodstream infection
  - iNTS disease is most commonly caused by *S. enterica* serovars Typhimurium and Enteritidis
  - 3.4 million infections estimated in 2010
  - Case fatality rate of 20-25%
  - True incidence likely unknown
  - Global ratio of NTS to iNTS disease is 28:1, but 1:1 in Africa

iNTS DISEASE: GEOGRAPHIC DISTRIBUTION AND TRANSMISSION

- **Distribution:** Most prevalent in Sub-Saharan Africa
  - Almost 2 million cases in 2010 in Sub-Saharan Africa
  - Incidence is highest among children and middle aged adults
- **Transmission:** Little is known about environmental reservoirs and main methods of transmission
  - Transmission for iNTS disease may differ greatly from observable transmission patterns for NTS in high-income countries
  - It is thought that transmission between humans – inside and outside health care facilities – may be important in Sub-Saharan Africa

iNTS DISEASE RISK FACTORS

Age:

- Children aged 12-18 months old
- Adults aged 25-45 years old

Other immune defects:

- HIV
  - 20% of African children with iNTS disease are HIV infected
  - 95% of adult iNTS disease cases are infected with HIV
- Malaria
- Malnutrition
- Sickle cell anemia

Environment:

- Peaks during rainy season coinciding with increased incidences of malaria and malnutrition

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

iNTS DISEASE DIAGNOSIS AND TREATMENT

Diverse clinical presentation:

- Fever
- Hepatosplenomegaly (swelling of the liver and spleen)
- Respiratory symptoms
- Diarrhea is often absent

Symptoms are nonspecific:

- Can be confused with malaria and pneumonia
- Laboratory tests are needed to confirm diagnosis

Treatment:

- Antimicrobial treatment
- Growing antimicrobial resistance has led to the need of more expensive treatments

NTS & iNTS DISEASE PREVENTION

- Need for surveillance in order to tailor prevention methods by determining:
  - True burden of disease
  - Disease trends
- No vaccine currently available, but there are efforts to advance vaccines against the most common serotypes of NTS
- Vaccines could target:
  - Immunosuppressed persons (living with HIV)
  - People at risk of malaria
  - People living with food insecurity
- Non-vaccine prevention efforts require more understanding of NTS sources and modes of transmission

SNAPSHOT: iNTS DISEASE IN MALAWI

- 2001-2004: iNTS disease epidemic peaks in Malawi
- Post-2004: Incidences fall
- Multiple public health interventions were implemented:
  - 2004: Roll-out of antiretroviral therapy (ART)
  - 2005: Fertilizer subsidy program for subsistence farmers begins to combat malnutrition
  - 2007: Introduced malaria control interventions
- A study reviewed trends in monthly numbers of childhood iNTS disease at Queen's Hospital, Blantyre, Malawi from 2002-2010
  - Data suggested that decline in iNTS disease is due to these interventions
  - Estimated that around 50% of the iNTS disease decline is explained by a decline in malaria
  - Estimate that around 50% of the iNTS disease decline is explained by changes in the local epidemiology of HIV (directly and through its impact on malnutrition)

COALITION AGAINST TYPHOID

Feasey, N. A., Everett, D., Faragher, E. B., Roca-Feltrer, A., Kang?ombe, A., Denis, B., … Heyderman, R. S. (2015). Modelling the Contributions of Malaria, HIV, Malnutrition and Rainfall to the Decline in Paediatric Invasive Non-typhoidal Salmonella Disease in Malawi. *PLOS Neglected Tropical Diseases*, *9*(7), e0003979. https://doi.org/10.1371/journal.pntd.0003979

SABIN VACCINE INSTITUTE

KEY MESSAGES

1. Paratyphoid, known along with typhoid as enteric fever, is spreading in Southeast Asia and is concerning due to its growing antimicrobial resistance
2. NTS and iNTS disease are 2 of the main causes of diarrheal disease and bloodstream infection in Sub-Saharan Africa
3. Paratyphoid, NTS and iNTS disease do not have vaccines currently available to prevent the diseases in vulnerable populations

REFERENCES

1. Buckle, G. C., Walker, C. L. F., & Black, R. E. (2012). Typhoid fever and paratyphoid fever: Systematic review to estimate global morbidity and mortality for 2010. *Journal of Global Health*, *2*(1), 10401. https://doi.org/10.7189/jogh.02.010401
2. Martin, L. B., Simon, R., MacLennan, C. A., Tennant, S. M., Sahastrabuddhe, S., & Khan, M. I. (2016). Status of paratyphoid fever vaccine research and development. *Vaccine*, *34*(26), 2900–2902. https://doi.org/10.1016/j.vaccine.2016.03.106
3. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388: 1545-602.
4. Bhan, M. K., Bahl, R., Bhatnagar, S., Oshihoi, Y., Izumiya, H., & Watanabe, H. (2000). Typhoid and paratyphoid fever. *Lancet (London, England)*, *366*(9487), 749–62. https://doi.org/10.1016/S0140-6736(05)67181-4
5. Crump, J. A., & Mintz, E. D. (2010). Global trends in typhoid and paratyphoid Fever. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *50*(2), 241–6. https://doi.org/10.1086/649541
6. Yan, M., Yang, B., Wang, Z., Wang, S., Zhang, X., Zhou, Y., … Kan, B. (2015). A Large-Scale Community-Based Outbreak of Paratyphoid Fever Caused by Hospital-Derived Transmission in Southern China. *PLOS Neglected Tropical Diseases*, *9*(7), e0003859. https://doi.org/10.1371/journal.pntd.0003859
7. Ao, T. T., Feasey, N. A., Gordon, M. A., Keddy, K. H., Angulo, F. J., & Crump, J. A. (2015). Global Burden of Invasive Nontyphoidal *Salmonella* Disease, 20101. *Emerging Infectious Diseases*, *21*(6), 941–949. https://doi.org/10.3201/eid2106.140999
8. Feasey, N. A., Dougan, G., Kingsley, R. A., Heyderman, R. S., & Gordon, M. A. (2012). Invasive non-typhoidal salmonella disease: an emerging and neglected tropical disease in Africa. *Lancet (London, England)*, *379*(9835), 2489–99. https://doi.org/10.1016/S0140-6736(11)61752-2
9. Crump, J. A., & Heyderman, R. S. (2015). A Perspective on Invasive Salmonella Disease in Africa. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *61 Suppl 4*(Suppl 4), S235-40. https://doi.org/10.1093/cid/civ709
10. Feasey, N. A., Everett, D., Faragher, E. B., Roca-Feltrer, A., Kang?ombe, A., Denis, B., … Heyderman, R. S. (2015). Modelling the Contributions of Malaria, HIV, Malnutrition and Rainfall to the Decline in Paediatric Invasive Non-typhoidal Salmonella Disease in Malawi. *PLOS Neglected Tropical Diseases*, *9*(7), e0003979. https://doi.org/10.1371/journal.pntd.0003979

Thank you.

For more information, visit coalitionagainsttyphoid.org.

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE