

## Typhoid Fever Slide Set Facilitators Guide

The purpose of this guide is to provide facilitators with direction for leading the Typhoid Fever Slide Set. The below guide will give you tips, definitions and points to expand on for every slide of the six modules.

This slide set is designed to be used by universities, hospitals, health organizations, and other entities to educate students or staff on typhoid and its global impact.

### **OVERVIEW:**

This slide set consists of the following modules:

- Module 1: Typhoid Epidemiology
- Module 2: Transmission and Pathogenesis
- Module 3: Diagnostics
- Module 4: Treatment
- Module 5: Prevention
- Module 6: Related Diseases

### **DURATION:**

Each module should take about 30-45 minutes.

### **PREPARATION REQUIRED**

- Read the *Facilitator's Guide* notes and review the PowerPoint slides for this unit. We have provided you with guidance, but you may want to add your own notes to further guide you

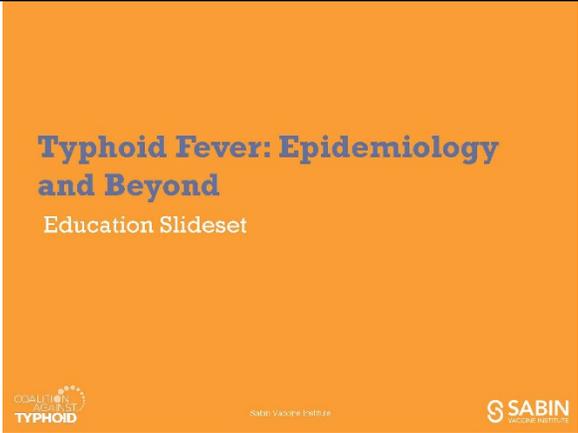
### **MATERIALS/EQUIPMENT**

- Computer
- Projector

### **RESOURCES/HANDOUTS**

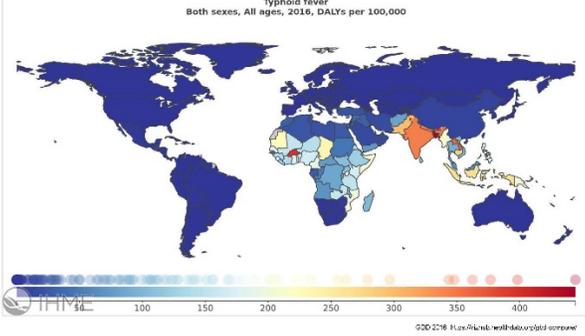
- PowerPoint presentation

**Guide to Module 1:**

MODULE 1: TYPHOID EPIDEMIOLOGY		
Slide Number		Facilitator Tips
1		<p>Hello and welcome. This series of presentations will provide you with comprehensive information on typhoid, including the burden of disease; transmission and pathogenesis; diagnosis; treatment; prevention; and related diseases. There are six modules in total that build on each other for a complete understanding of the disease.</p> <p>This course was designed for public health students and professionals who may need knowledge of how to combat typhoid, or typhoid advocates who need an overview on the disease.</p> <p>At the end of it, I hope you will come away with a basic understanding of enteric fever.</p>
2		<p>This first module will cover the epidemiology of typhoid.</p>

<p>3</p>	<p style="text-align: center;"><b>LEARNING OBJECTIVES</b></p> <p>In this module you will:</p> <ol style="list-style-type: none"> <li>1. Learn the basics of typhoid epidemiology</li> <li>2. Identify populations most at risk for typhoid</li> <li>3. Recognize global disease trends and learn about the existing knowledge gaps</li> </ol>  	<p>In this module, you will:</p> <ul style="list-style-type: none"> <li>• Learn the basics of typhoid epidemiology</li> <li>• Identify populations most at risk for typhoid</li> <li>• Recognize global disease trends and learn about the existing knowledge gaps</li> </ul>
<p>4</p>	<p style="text-align: center;"><b>INTRODUCTION TO ENTERIC FEVER</b></p> <ul style="list-style-type: none"> <li>• Enteric fever collectively refers to typhoid and paratyphoid fevers</li> <li>• Typhoid fever is a systemic infection caused by the bacteria <i>Salmonella enterica</i> serovar Typhi (<i>S. Typhi</i>) <ul style="list-style-type: none"> <li>• Waterborne or foodborne transmission</li> <li>• Fecal-oral route of infection</li> <li>• Bacteria lives only in humans</li> </ul> </li> <li>• Paratyphoid fever is caused by the bacteria <i>Salmonella enterica</i> serovar Paratyphi A/B/C <ul style="list-style-type: none"> <li>• Paratyphoid is less common and typically less severe than typhoid</li> </ul> </li> <li>• Typhoid can be prevented through access to clean water, improved sanitation and hygiene infrastructure, and vaccines</li> </ul>  	<p>Enteric fever collectively refers to typhoid and paratyphoid fevers.</p> <p>Typhoid fever is a systemic infection caused by the bacteria <i>Salmonella enterica</i> serovar Typhi, also commonly known as <i>S. Typhi</i>. A serovar, for those wondering, is a distinct variation in a bacterial species.</p> <p>Typhoid is waterborne or foodborne, transmitted through the fecal-oral route, meaning an infected person will shed <i>S. Typhi</i> bacteria in their fecal matter, which might, for example, end up in a water source and infect the person consuming that water. <i>S. Typhi</i> bacteria only lives in humans. The transmission process is covered more deeply in Module 2.</p> <p>Paratyphoid fever is caused by the bacteria <i>Salmonella enterica</i> serovar Paratyphi. You'll notice that typhoid and paratyphoid are just different serovars of the same bacterial species. Typhoid is typically more common and severe than paratyphoid. Paratyphoid will be covered more in depth in Module 6.</p> <p>Typhoid can be prevented through access to clean water, improved sanitation and hygiene infrastructure, and vaccines.</p>

		<p>Specific preventative measures will be discussed in Module 5. For now, let's move on to the prevalence of typhoid.</p>
<p>5</p>	<p style="text-align: center;"><b>INCIDENCE OF TYPHOID</b></p> <ul style="list-style-type: none"> <li>• Approximately 12 million cases per year <ul style="list-style-type: none"> <li>• Multiple unreported subclinical and mild infections occur for each clinical case</li> </ul> </li> <li>• More than 128,000 deaths per year <ul style="list-style-type: none"> <li>• 1-4% case fatality with treatment</li> <li>• 10-20% case fatality without treatment</li> </ul> </li> <li>• Complications arise in 10-15% of untreated patients <ul style="list-style-type: none"> <li>• Intestinal perforation, hemorrhage of the intestine and septic shock</li> </ul> </li> <li>• These estimates are limited by the lack of reliable surveillance data</li> </ul> <div style="display: flex; justify-content: space-between; align-items: center; margin-top: 20px;">   </div>	<p>There are approximately 12 million typhoid cases per year, with multiple unreported subclinical and mild infections occurring for each clinical case. It is a common cause of morbidity in low- and middle-income countries.</p> <p>More than 128,000 deaths occur from typhoid in a year. Deaths occur in an estimated 1-4% of cases that receive treatment and 10-20% of cases that are not treated.</p> <p><i>[Drug resistance, which threatens these numbers, will be covered in Module 4]</i></p> <p>Complications develop in 10-15% of untreated patients. Complications can include intestinal perforation, hemorrhage of the intestine and septic shock.</p> <p>There is a lack of reliable surveillance data on typhoid, so these estimates are limited. The actual burden of typhoid may be higher than what is currently estimated.</p>
<p>6</p>	<p style="text-align: center;"><b>GEOGRAPHIC DISTRIBUTION OF TYPHOID</b></p> <ul style="list-style-type: none"> <li>• Mainly restricted to low- and middle-income countries <ul style="list-style-type: none"> <li>• Highest incidence is found in Southeast Asia and Indian subcontinent <ul style="list-style-type: none"> <li>• Pakistan + India + Bangladesh = 85% of the world's cases</li> </ul> </li> <li>• Also prevalent in Africa, although substantial knowledge gaps exist <ul style="list-style-type: none"> <li>• Recent findings reveal incidence in some areas may be high as in Asia</li> </ul> </li> <li>• Oceania has high incidence of typhoid except in high-income countries such as Australia and New Zealand</li> </ul> </li> <li>• Most typhoid cases in high-income countries occur among travelers returning from endemic countries</li> </ul> <div style="display: flex; justify-content: space-between; align-items: center; margin-top: 20px;">   </div>	<p>Typhoid is mainly restricted to low- and middle-income countries, with the highest incidence in Southeast Asia and the Indian subcontinent. Pakistan, India and Bangladesh account for approximately 85% of the world's cases.</p> <p>Typhoid is also prevalent in Africa, but much less is known about the burden on this continent due to a lack of data. Recent findings show that the incidence of typhoid in some parts of Africa may be as high as in Asia.</p> <p>Typhoid incidence can also be high in parts of Oceania, such as Papua New Guinea, but low in high-income countries like Australia and New Zealand.</p>

		<p>A minimal number of cases occur yearly in high-income countries in North America and Western Europe with the majority of cases occurring in travelers returning from endemic countries.</p>
<p>7</p>	<p><b>MAP OF GEOGRAPHIC DISTRIBUTION</b></p> <p>Typoid fever Both sexes, All ages, 2016, DALYs per 100,000</p>  <p>COALITION AGAINST TYPHOID</p> <p>SABIN VACCINE INSTITUTE</p>	<p>On this map you can see the distribution of typhoid and the countries most at risk.</p> <p>You can see that high income countries like the United States are at a low risk for typhoid. These countries eliminated typhoid with technological advancements in water and sanitation infrastructure.</p> <p>You can also see the high concentration of typhoid in the Indian sub-continent.</p>
<p>8</p>	<p><b>SUSCEPTIBILITY AND TRENDS</b></p> <ul style="list-style-type: none"> <li>• <b>Age:</b> Children suffer the highest incidence of typhoid <ul style="list-style-type: none"> <li>• 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</li> <li>• 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</li> </ul> </li> <li>• <b>Income:</b> Associated with low socioeconomic status</li> <li>• <b>Location:</b> High incidence documented in overcrowded areas with poor access to improved water and sanitation <ul style="list-style-type: none"> <li>• Examples: Urban slums, refugee camps</li> </ul> </li> </ul> <p><small>Oishi, R., et al. "Age, Socioeconomic Status, and the Burden of Typhoid Fever in the Asian Countries: Disease Burden and Implications for Control." <i>Journal of Global Health</i>. 2016; 7(1):1-10. doi:10.2196/jgh.2016.0001</small></p> <p><small>Oishi, R., et al. "Age, Socioeconomic Status, and the Burden of Typhoid Fever in the Asian Countries: Disease Burden and Implications for Control." <i>Journal of Global Health</i>. 2016; 7(1):1-10. doi:10.2196/jgh.2016.0001</small></p> <p>COALITION AGAINST TYPHOID</p> <p>SABIN VACCINE INSTITUTE</p>	<p>There are certain factors that make people more susceptible to typhoid. One of them is age. Children suffer the highest incidence of typhoid, according to studies. A study conducted in Indonesia, India and Pakistan found an annual incidence of 180-494 blood-culture confirmed cases per 100,000 in children five to 15 years old. In Pakistan, children two to four years old had an incidence of 405/100,000, and children less than two years had an incidence of 443/100,000.</p> <p>Another factor is income. Typhoid is associated with low socio-economic status and is a disease of inequity, disproportionately impacting those that do not have access to clean water or improved sanitation infrastructure.</p> <p>Location or neighborhood can also increase susceptibility to typhoid. A higher incidence of typhoid has been linked to overcrowded areas with poor access to clean water or improved sanitation. Those areas would include urban slums and refugee camps.</p>

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### COSTS OF TYPHOID

Direct	Indirect
<b>Medical Expenses</b> <ul style="list-style-type: none"> <li>Physician fees</li> <li>Diagnostic tests</li> <li>Hospitalization</li> <li>Emergency room</li> <li>Medication</li> </ul>	<b>Lost Income/Productivity</b> <ul style="list-style-type: none"> <li>Patient's lost income</li> <li>Caretaker's lost income</li> <li>Interrupted education</li> <li>Long-term morbidity</li> <li>Time lost from patient's other beneficial activities</li> </ul>
<b>Non-Medical Expenses</b> <ul style="list-style-type: none"> <li>Transportation</li> <li>Food &amp; beverages to aid treatment</li> <li>Lodging and meals for caretaker</li> </ul>	<ul style="list-style-type: none"> <li>Time lost from caretaker's other beneficial activities</li> </ul>



In this chart, you can see both the direct and indirect costs of typhoid on a patient. Beyond paying hospitalization fees, a direct cost of typhoid, patients and their caretakers lose income from time off from their employment. For children, a major cost of typhoid is missed school days. These are indirect costs of the disease.

Additionally, typhoid does not just financially hurt the patient, but also a country's health system by taking up resources that could be used for other health issues.

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### 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



Chakrabarti S, Hossain J, E S, Dasgupta R, B Nair J (2016) Endemic fever of India: current epidemiology and future directions. Tropical Medicine & International Health 21(10): 1705-1712. <https://doi.org/10.1111/tmi.12702>



Now, let's zoom in and take a country-level look at typhoid in India. Typhoid is endemic in India, with incidence rate estimates of 340 per 100,000 in children 2-5, 493 per 100,000 in children 5-15, and 120 per 100,000 in adults older than 15.

In India, you see many of the factors that increase the risk for typhoid that we previously discussed. Seventy-seven million do not have access to safe drinking water and 769 million lack improved sanitation. Additionally, due to urbanization, India has a large slum population estimated at 158.42 million. Finally, 67% of households do not drink treated water, putting them at risk of drinking contaminated water.

In India, like many Asian countries, typhoid cases peak during the rainy season, from July to October. The chance of water contamination is higher during the rainy season due to flooding of sewage drains and damage to water and sewage infrastructure.

<p>11</p>	<p><b>SNAPSHOT: TYPHOID OUTBREAK IN UGANDA</b></p> <ul style="list-style-type: none"> <li>• Outbreak in Kampala from February-June 2015</li> <li>• Main source: contaminated water and juice <ul style="list-style-type: none"> <li>• 26% of patients consumed water and ~50% drank local passion-fruit juice from busy taxi park area</li> <li>• Most patients were men between 20-39 years old</li> <li>• Almost all worked in the market at the taxi park</li> </ul> </li> <li>• 10,230 suspected cases</li> <li>• 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</li> </ul> <p><small>CCO Use Health - Uganda: TYP Data Card: Current Disease Definition (2015). Retrieved from <a href="https://www.cco.org/uganda/typhoid">https://www.cco.org/uganda/typhoid</a>. Accessed 10/10/2015.</small></p> <p><small>Kisumu, S. N., Saito, J., Ndiraga, F., Pierre, C., Opiyo, D. W., Mugo, R., ... &amp; E. P. (2015). A large and persistent outbreak of typhoid fever caused by consuming contaminated water and street-vended beverages, Kampala, Uganda, January–June 2015. <i>PLoS ONE</i>, 10(11), 1–7. <a href="https://doi.org/10.1371/journal.pone.0141400">https://doi.org/10.1371/journal.pone.0141400</a></small></p>  	<p>Let's take a closer look at typhoid in a different part of the world. An outbreak of typhoid spread in Kampala, Uganda, from February to June 2015.</p> <p>The main source of the outbreak was contaminated water and juice. Twenty-six percent of patients consumed water and 50% of patients consumed passion-fruit juice sold near a busy taxi park in the capital city. Most of the patients were men between 20-39 years old that worked near the taxi park.</p> <p>Suspected cases were widespread. More than 10,000 people were suspected of having typhoid. However, few of them had their diagnoses confirmed. Typhoid can be difficult to diagnosis, especially for physicians without the proper diagnostic tools. This will be further discussed in Module 3.</p> <p>In response, the Ministry of Health used communications campaigns to encourage the public to treat their drinking water at home rather than buy water and juice from local vendors.</p>
<p>12</p>	<p><b>KNOWLEDGE GAPS</b></p> <ul style="list-style-type: none"> <li>• There are gaps in our knowledge of the global distribution of typhoid due to: <ul style="list-style-type: none"> <li>• Lack of resources: Facilities in endemic settings often do not have the capability for diagnostic tests</li> <li>• Lack of reliable diagnostics: The diagnostic tests commonly used are not highly accurate</li> <li>• Lack of reporting: Inadequate surveillance systems in place</li> </ul> </li> <li>• More data are needed to help governments prioritize health care resources and enact cost-effective means of reducing the burden of typhoid</li> </ul>  	<p>You may have noticed during the previous slides that there is a lot that we still don't know about typhoid.</p> <p>While we have estimates, the actual global distribution of typhoid is unknown due to the lack of resources. In many facilities where typhoid is endemic, they simply don't have the capacity to run a diagnostic test on suspected typhoid cases. Additionally, there is a lack of reliable diagnostics tests as many commonly used tests are not highly accurate. Finally, there is a lack of reporting as many countries do not have a comprehensive surveillance system to report data.</p> <p>Data on typhoid is important to help governments prioritize health care</p>

		resources cost-effectively to reduce the typhoid burden.
13	<p style="text-align: center;"><b>TYPHOID AND SUSTAINABLE DEVELOPMENT</b></p> <ul style="list-style-type: none"> <li>• Typhoid is linked to socioeconomic inequity and stands as an obstacle to ending poverty</li> <li>• Typhoid control is important to reaching multiple Sustainable Development Goals, including: <ul style="list-style-type: none"> <li>• Goal 3: Ensure healthy lives and promote well-being for all at all-ages</li> <li>• Goal 6: Ensure availability and sustainable management of water and sanitation for all</li> <li>• Goal 10: Reduce inequality within and among countries</li> </ul> </li> <li>• 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</li> </ul>  	<p>When we look at typhoid, we want to remember to place it in a global context. Typhoid is linked to socio-economic inequity and an estimated 1.8 billion people are at risk of contracting the disease. Achievement of Sustainable Development Goal 6, “Ensure availability and sustainable management of water and sanitation for all,” could reduce the amount of people at risk of contracting typhoid.</p> <p>As we saw when we went over the different costs associated with typhoid (Slide 9), not only is typhoid a disease of poverty, but it can also be an obstacle to overcoming it. Fighting typhoid is important to achieving two Sustainable Development Goals: Goal 3, “Ensure healthy lives and promote well-being for all ages,” and Goal 10, “Reduce inequality within and among countries.”</p> <p>What other SDGs can you think of that typhoid relates to?</p> <p><i>[Possible answers: Goal 1: No Poverty, Goal 6: Clean Water and Sanitation.]</i></p> <p>As we go over the other modules, keep this global context for typhoid in mind.</p>
14	<p style="text-align: center;"><b>MODULE 1 KEY MESSAGES</b></p> <ol style="list-style-type: none"> <li>1. Typhoid is a preventable bacterial infection spread through contaminated food and water, impacting millions of people in low- and middle-income countries</li> <li>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</li> <li>3. Lack of resources, including diagnostic tools and surveillance networks, makes it difficult to know the real disease burden</li> <li>4. Typhoid is an obstacle to sustainable development and reducing inequality</li> </ol>  	<p>As we conclude this module, let’s review a couple of key takeaways:</p> <p>Typhoid is a preventable bacterial infection spread through contaminated food and water. It impacts millions of people in low- and middle-income countries.</p> <p>Typhoid is estimated to be most prevalent in school-age children, people of low socio-economic status and those living in high-density areas.</p>

Lack of resources like diagnostic tools and surveillance networks makes it difficult to know the real typhoid disease burden.

And lastly, typhoid is an obstacle to sustainable development and reducing inequality.

Does anyone have any questions before we move on to talk about transmission and pathogenesis?

15

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## MODULE 2: TRANSMISSION AND PATHOGENESIS

Slide Number		Facilitator Tips
16		<p>In this module, we'll be building off the introductory knowledge of typhoid gained in Module 1 to talk about the transmission and pathogenesis of typhoid.</p>
17	<p style="text-align: center;"><b>LEARNING OBJECTIVES</b></p> <p><b>In this module, you will:</b></p> <ol style="list-style-type: none"> <li>1. Learn how typhoid is transmitted</li> <li>2. Identify typhoid's pathogenic route</li> <li>3. Learn about the risk factors that lead to the transmission of typhoid</li> <li>4. Learn about possible complications that can occur from typhoid infection</li> </ol> 	<p>In this module, you will learn:</p> <ul style="list-style-type: none"> <li>• How typhoid is transmitted</li> <li>• Typhoid's pathogenic route</li> <li>• The risk factors that lead to the transmission of typhoid</li> <li>• Possible complications that can occur</li> </ul>
18	<p style="text-align: center;"><b>TRANSMISSION OF TYPHOID</b></p> <ul style="list-style-type: none"> <li>• S. Typhi is a human-restricted pathogen, meaning it can only survive long-term in the human body</li> <li>• S. Typhi can survive outside the human body for days in groundwater, pond water or seawater</li> <li>• S. Typhi is transmitted by ingestion of food or water contaminated with human feces containing typhoid bacteria (oral-fecal route)</li> <li>• Large outbreaks are most often caused by:             <ul style="list-style-type: none"> <li>• Contaminated local water sources</li> <li>• Contaminated food sold by vendors</li> </ul> </li> </ul> 	<p>We learned in the last module that typhoid is transmitted through the fecal-oral route and that typhoid is a human-restricted pathogen. We are going to dive deeper into that.</p> <p>S. Typhi can only survive long-term in the human body. It can only survive for several days in different water sources.</p> <p>As we learned, typhoid is transmitted through the ingestion of food or water contaminated with human feces containing typhoid bacteria.</p> <p>Usually large outbreaks are caused by contaminated local water sources or contaminated food sold by vendors. Let's think back to the snapshot in the last module about the Kampala, Uganda outbreak. What was the source of that outbreak?</p> <p><i>[Possible discussion topic: how food and water vendors might spread typhoid to a large</i></p>

		<p><i>number of people if they have unwashed hands or are using water from a contaminated source.]</i></p>				
<p>19</p>	<p><b>RISK FACTORS FOR TRANSMISSION</b></p> <ul style="list-style-type: none"> <li>• Drinking from a contaminated water supply</li> <li>• Consuming drinks or food from street vendors</li> <li>• Consuming raw fruit and vegetables fertilized with sewage</li> <li>• History of contact with typhoid patients</li> <li>• Washing hands without soap</li> <li>• Preparing food with unwashed hands</li> <li>• Living in inadequate housing without improved sanitation</li> <li>• Consuming shellfish grown in contaminated water</li> <li>• Consuming food washed with unclean water</li> </ul>  	<p>Certain factors can increase the risk of typhoid transmission. These can include:</p> <ul style="list-style-type: none"> <li>• Drinking from a contaminated water supply</li> <li>• Consuming drinks or food from street vendors</li> <li>• Consuming raw fruit and vegetables fertilized with sewage</li> <li>• History of contact with typhoid patients</li> <li>• Washing hands without soap</li> <li>• Preparing food with unwashed hands</li> <li>• Living in inadequate housing without improved sanitation</li> <li>• Consuming shellfish grown in contaminated water</li> <li>• Consuming food washed with unclean water</li> </ul> <p>You can see how all of these increase the chance for typhoid bacteria to be consumed.</p>				
<p>20</p>	<p><b>SOURCES OF INFECTION</b></p> <table border="1" data-bbox="332 1241 805 1381"> <thead> <tr> <th data-bbox="332 1241 561 1297">Primary Sources <i>Direct contact with the bacteria</i></th> <th data-bbox="561 1241 805 1297">Secondary Sources <i>Contact with items contaminated with the bacteria</i></th> </tr> </thead> <tbody> <tr> <td data-bbox="332 1297 561 1381"> <ul style="list-style-type: none"> <li>• Feces</li> <li>• Urine (rare)</li> <li>• Direct contact with infected person (rare)</li> </ul> </td> <td data-bbox="561 1297 805 1381"> <ul style="list-style-type: none"> <li>• Contaminated food</li> <li>• Contaminated water</li> </ul> </td> </tr> </tbody> </table>  	Primary Sources <i>Direct contact with the bacteria</i>	Secondary Sources <i>Contact with items contaminated with the bacteria</i>	<ul style="list-style-type: none"> <li>• Feces</li> <li>• Urine (rare)</li> <li>• Direct contact with infected person (rare)</li> </ul>	<ul style="list-style-type: none"> <li>• Contaminated food</li> <li>• Contaminated water</li> </ul>	<p>Primary sources of infection involve direct contact with the bacteria; for example, coming in contact with feces containing the typhoid bacteria.</p> <p>Secondary sources of infection are more common and involve contact with items contaminated by the bacteria, like food or water.</p>
Primary Sources <i>Direct contact with the bacteria</i>	Secondary Sources <i>Contact with items contaminated with the bacteria</i>					
<ul style="list-style-type: none"> <li>• Feces</li> <li>• Urine (rare)</li> <li>• Direct contact with infected person (rare)</li> </ul>	<ul style="list-style-type: none"> <li>• Contaminated food</li> <li>• Contaminated water</li> </ul>					
<p>21</p>	<p><b>SNAPSHOT: OUTBREAK IN PAKISTAN</b></p> <ul style="list-style-type: none"> <li>• October 2004: More than 300 people contracted typhoid in Nek Muhammed village, resulting in 3 fatalities</li> <li>• Village water source: 1 well <ul style="list-style-type: none"> <li>• 100% of laboratory samples confirmed that <i>S. Typhi</i> was present in the well water</li> <li>• High amounts of contaminants (fecal matter, garbage) found in the well</li> <li>• 72% of household water samples tested positive for <i>S. Typhi</i></li> </ul> </li> <li>• Drinking water was determined to be the source of the typhoid fever outbreak</li> <li>• Food samples did not show association with the outbreak</li> </ul> <small data-bbox="337 1927 764 1948">Ferreccio, A., Kaper, J. B., &amp; Kim, S. J. (2005). The distribution of a common but only one of the four typhoid-associated serotypes in a village. BMC Public Health, 5(1), 470. Retrieved from http://dx.doi.org/10.1186/s12874-005-0004-0</small>  	<p>Thinking again about risk factors and transmission of typhoid, let's look at the 2004 outbreak in Pakistan. In Nek Muhammed village, more than 300 people contracted typhoid and three people died.</p> <p>There was one well that served as the village water source. All the lab samples found that <i>S. Typhi</i> was present in the well water, and high amounts of contaminants like fecal matter were found in the well. Additionally, 72% of the</p>				

		<p>households' water supplies tested positive for <i>S. Typhi</i>. Therefore the drinking water was determined to be the source of the outbreak.</p> <p>In this village, one single well was able to infect more than 300 people.</p>
22	<p style="text-align: center;"><b>INFECTION PROCESS</b></p> <p>Infection process of typhoid begins with ingesting <i>S. Typhi</i> bacteria:</p> <ol style="list-style-type: none"> <li>1 • Bacteria invade the small intestine and penetrate the mucosal epithelium into the underlying lymphoid tissue</li> <li>2 • Macrophages ingest the bacteria but are unable to kill them</li> <li>3 • Macrophages carry bacteria to nearby lymph nodes or to reticuloendothelial cells of liver and spleen</li> <li>4 • Bacteria survive and multiply within the reticuloendothelial system</li> <li>5 • Bacteria enter the bloodstream through the lymph nodes</li> <li>6 • Clinical symptoms begin to develop</li> <li>7 • Bacteria invade liver, spleen, bone marrow and gallbladder</li> <li>8 • Bacteria pass into intestines and can be identified in stool samples</li> </ol>  	<p>The infection process for typhoid begins with ingesting <i>S. Typhi</i> bacteria. Once the bacteria are in the small intestine, they are able to penetrate the mucosal epithelium, or the inner lining of the intestine, and go into the underlying lymph tissue. There, macrophages ingest the typhoid bacteria, but are generally unable to kill them. They are able to survive and multiply within the macrophages, which carry them to other parts of the reticuloendothelial system, like the liver and spleen.</p> <p>Once the bacteria have multiplied, they are able to reach the bloodstream through the lymph fluid that drains into the thoracic duct and then to the general circulatory system. Clinical symptoms begin to develop at this point. From the bloodstream, bacteria invade the liver, spleen, bone marrow and gallbladder. They also pass into the intestines and can be identified in stool samples. This cycle in the body can go on and on unless treatment is initiated.</p> <p><i>[Mesenteric refers to the tissues that attach the intestines to the wall of the abdomen.]</i></p> <p><i>The reticuloendothelial system is a network of cells concentrated in the blood, connective tissue, spleen, liver, bone marrow and lymph nodes which play a role in inflammation and immunity.]</i></p>

<p>23</p>	<p><b>FACTORS THAT IMPACT INFECTION</b></p> <ul style="list-style-type: none"> <li>• <b>Amount of bacteria ingested (inocula):</b> The greater the inocula, the more severe the infection</li> <li>• <b>Method of ingestion:</b> Infections caused by foodborne or waterborne transmissions can present differently <ul style="list-style-type: none"> <li>• Foodborne transmission is associated with large inocula and high attack rates over short periods</li> <li>• Waterborne transmission is associated with small inocula</li> </ul> </li> </ul>  	<p>There are two factors that impact infection. One is the amount of bacteria ingested. The greater the amount of bacteria ingested, the more an infection is likely to be severe.</p> <p>The second is the method of ingestion. The method of ingestion affects the speed and severity of infection. Foodborne typhoid transmission is associated with a large amount of ingested bacteria. Foodborne outbreaks of typhoid are often associated with high attack rates over short periods. Waterborne typhoid transmission is associated with a small inocula.</p>
<p>24</p>	<p><b>INCUBATION PERIOD</b></p> <ul style="list-style-type: none"> <li>• Time between becoming infected and developing symptoms is typically 1-3 weeks <ul style="list-style-type: none"> <li>• Can be shorter or longer depending on the amount of bacteria ingested</li> <li>• Ranges from 3-60 days</li> </ul> </li> <li>• The onset of typhoid is gradual with increasing fever and fatigue and eventual onset of symptoms such as headache, abdominal pain and malaise</li> </ul>  	<p>The time between becoming infected and developing symptoms is typically between one and three weeks. It can be shorter or longer depending on the amount of bacteria ingested, ranging from three days up to 60.</p> <p>Typhoid symptoms appear gradually and usually take the form of fever and fatigue at the beginning, and later headache, abdominal pain and malaise.</p>
<p>25</p>	<p><b>PERIOD OF COMMUNICABILITY</b></p> <ul style="list-style-type: none"> <li>• 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</li> <li>• Treatment can shorten the period of communicability <ul style="list-style-type: none"> <li>• About 10% of untreated typhoid patients will continue to be infectious for 3 months</li> </ul> </li> <li>• After treatment, 1-5% of people who recover from typhoid fever continue to harbor S. Typhi bacteria in their intestinal tracts or gallbladders <ul style="list-style-type: none"> <li>• Carriers have an indefinite period of communicability</li> </ul> </li> </ul>  	<p>A patient can transmit typhoid from the first week of illness until after symptoms have ceased. However, treatment can shorten the period of communicability. About a tenth of untreated patients continue to be infectious for three months, and of course some typhoid patients become carriers.</p> <p>After treatment, 1-5% of those who recover from typhoid continue to carry S. Typhi bacteria in their intestinal tracts or their gallbladders. These people are known as carriers. Carriers can transmit typhoid for an indefinite period of time.</p>

<p>26</p>	<p style="text-align: center;"><b>TYPHOID CARRIERS</b></p> <ul style="list-style-type: none"> <li>• Carriers no longer exhibit symptoms of typhoid, but are capable of infecting others</li> <li>• These carriers can harbor the bacteria for years and shed the bacteria in their feces <ul style="list-style-type: none"> <li>• Gallbladder removal can stop carriers from continuing to shed the bacteria</li> </ul> </li> <li>• 4 weeks of oral antibiotic therapy will successfully treat 90% of carriers</li> </ul>  	<p>Some people may not realize they are carriers, as they will no longer exhibit symptoms of typhoid. They also may have had a mild case of typhoid and felt no need to seek treatment, but continue to shed the bacteria unknowingly. Carriers can continue to harbor and shed bacteria in their feces for years.</p> <p>Modern medicine can treat typhoid carriers through gallbladder removal or antibiotic treatment.</p> <p>Carriers are still capable of infecting others. In the next slide we talk about the most famous typhoid carrier.</p>
<p>27</p>	<p style="text-align: center;"><b>SNAPSHOT: TYPHOID MARY</b></p> <ul style="list-style-type: none"> <li>• Mary Mallon was hired in 1906 to cook for the Warren family</li> <li>• 6 of the 11 Warren house residents contracted typhoid</li> <li>• A sanitary engineer was hired to investigate the source of the bacteria <ul style="list-style-type: none"> <li>• Discovered that 7 families Mallon previously cooked for reported cases of typhoid</li> </ul> </li> <li>• Mallon became known as the "first healthy carrier" of typhoid</li> <li>• Mallon was apprehended and isolated for a combined 26 years</li> <li>• After her death, her gallbladder was found to contain <i>S. Typhi</i></li> </ul>  	<p>Mary Mallon, also known as Typhoid Mary, was a cook for the Warren family in the United States. When several members of the family contracted typhoid, a sanitary engineer discovered that the previous seven families Mallon had cooked for had also reported cases of typhoid.</p> <p>Mallon became the first known "healthy carrier" of typhoid. She was apprehended and isolated for a combined 26 years to keep her from continuing to spread disease. After her death, her gallbladder was found to contain <i>S. Typhi</i>. However, these days medicine is usually able to stop a carrier from infecting others.</p> <p>Mary's story shows how many people silent carriers are able to infect unknowingly.</p>
<p>28</p>	<p style="text-align: center;"><b>TYPHOID COMPLICATIONS</b></p> <ul style="list-style-type: none"> <li>• Complications after typhoid infection are uncommon and mostly occur after the fourth week of illness</li> <li>• Complications include: <ul style="list-style-type: none"> <li>• Gastrointestinal bleeding and perforation</li> <li>• Hemodynamic shock</li> <li>• Hepatitis</li> <li>• Encephalopathy</li> <li>• Psychosis</li> <li>• Pneumonia</li> <li>• Meningitis</li> <li>• Thrombocytopenia</li> <li>• Cholecystitis</li> <li>• Renal impairment</li> <li>• Myocarditis</li> </ul> </li> <li>• <i>Immediate treatment of typhoid reduces the risk of complications</i></li> </ul>  	<p>Complications after typhoid infection are uncommon and mostly occur after the fourth week of illness. On the slide is a list of other typhoid complications. Of these, the most common and significant typhoid complications are intestinal bleeding and perforation. Timely diagnostics and treatment is important to prevent patients from developing complications</p>

<p>29</p>	<p style="text-align: center;"><b>INTESTINAL PERFORATIONS</b></p> <ul style="list-style-type: none"> <li>• The most severe complication of typhoid</li> <li>• A hole develops in the ileum of the small intestine or bowel causing leakage into abdominal cavity <ul style="list-style-type: none"> <li>• Also known as ileal perforation</li> <li>• Life-threatening, can lead to sepsis</li> <li>• Requires immediate medical attention</li> </ul> </li> <li>• Surgery is often needed to mend the tears and/or to resect a portion of the intestines</li> <li>• Thought to develop in 1-3% of typhoid cases</li> </ul> <p style="text-align: center;">   </p>	<p>Intestinal perforation, the most severe typhoid complication, is when a hole develops in the small intestine, causing leakage into the abdominal cavity. Because this hole most often forms in the ileum of the small intestine, it is also known as ileal perforation. This complication is life-threatening and can lead to sepsis, requiring immediate medical attention in the form of surgery to mend the tears or resect the intestines. Normally, intestinal perforation only develops in 1-3% of typhoid cases.</p>
<p>30</p>	<p style="text-align: center;"><b>SNAPSHOT: INTESTINAL PERFORATIONS IN UGANDA</b></p> <ul style="list-style-type: none"> <li>• Dec 2007-June 2009: Hospitals in Kasese District received many patients with a febrile illness</li> <li>• High number of intestinal perforations indicated typhoid</li> </ul> <p style="text-align: center;">  </p> <p style="text-align: center;">   </p>	<p>An outbreak in Uganda from 2007-2009 had an unusually high percentage of intestinal perforations.</p> <p>From December 2007 to June 2009, hospitals in the Kasese District received many patients with a febrile illness. The high number of intestinal perforations strongly indicated that they were suffering from typhoid.</p>
<p>31</p>	<p style="text-align: center;"><b>SNAPSHOT: INTESTINAL PERFORATIONS IN UGANDA</b></p> <ul style="list-style-type: none"> <li>• Surveillance networks documented 577 suspected cases, 289 hospitalizations, 249 intestinal perforations and 47 deaths <ul style="list-style-type: none"> <li>• 43% had intestinal perforation (normal rate 1-3%)</li> </ul> </li> <li>• Large number of perforations attributed to underreporting of milder typhoid symptoms and lack of proper medical attention</li> <li>• Limited local microbiological capacity (equipment, supplies and trained personnel) led to diagnostic difficulties and delays in confirming the disease <ul style="list-style-type: none"> <li>• Only 1 hospital in the area had microbiological culture capacity</li> </ul> </li> </ul> <p style="text-align: center;">   </p>	<p>Surveillance networks in the area then documented 577 suspected typhoid cases, 289 hospitalizations, 249 intestinal perforations and 47 deaths. Of all suspected cases, 43% had intestinal perforation.</p> <p>This unusually high percentage of patients with perforation may indicate that the outbreak was much larger than reported.</p> <p>A lack of laboratory capacity led to diagnostic difficulties and delays in confirming the disease, as only one hospital in the area had the capacity for culture confirmation. Increased diagnostic capacity is needed for speedier, appropriate treatment to reduce complications.</p>

<p>32</p>	<p style="text-align: center;"><b>MODULE 2 KEY MESSAGES</b></p> <ol style="list-style-type: none"> <li>1. Typhoid is a human-restricted pathogen</li> <li>2. Typhoid is transmitted via fecal-oral route and begins with ingestion of the <i>S. Typhi</i> bacteria, which invades the bowel</li> <li>3. The incubation period is affected by the method of ingestion and quantity of bacteria ingested</li> <li>4. Typhoid is transmissible until the bacteria is no longer shed through stool</li> <li>5. Complications can occur from typhoid, with the most severe being intestinal perforation</li> </ol> <div style="display: flex; justify-content: space-between; align-items: center; margin-top: 20px;">   </div>	<p>In this module, we have covered some key takeaways regarding transmission and pathogenesis of typhoid:</p> <p>First, typhoid is a human-restricted pathogen, meaning typhoid cannot survive long-term outside the human body.</p> <p>Typhoid is transmitted via the fecal-oral route and begins with the ingestion of <i>S. Typhi</i> bacteria which invades the bowel.</p> <p>The incubation period is affected by the method and quantity of bacteria ingested.</p> <p>Typhoid is communicable for as long as the bacteria is shed through stool.</p> <p>Lastly, complications can occur in patients with typhoid with the most severe being intestinal perforation.</p> <p>Does anyone have any questions before we move on to the next module on diagnostics?</p>
<p>33</p>	<p style="text-align: center;"><b>REFERENCES</b></p> <ol style="list-style-type: none"> <li>1. Bhan, M. K., Bahl, R., Bhatnagar, S., Oshita, Y., Izumiya, H., &amp; Watanabe, H. (2000). Typhoid and paratyphoid fever. <i>Lancet</i> (London, England), 356(9187), 749-52. <a href="https://doi.org/10.1016/S0140-6736(05)67161-4">https://doi.org/10.1016/S0140-6736(05)67161-4</a></li> <li>2. Levine, M. M. (2013). Typhoid fever vaccines. In <i>Vaccines</i> (Sixth Edition, pp. 812-838). Elsevier Inc. <a href="https://doi.org/10.1016/B978-1-4557-0095-5_0082-3">https://doi.org/10.1016/B978-1-4557-0095-5_0082-3</a></li> <li>3. Manangazira, P., Glavincheva, J., Mukoko-Gonea, G., Bara, W., Chimbaru, A., &amp; Ameda, I. (2011). Guidelines for the Management of Typhoid Fever. Retrieved from <a href="http://apps.who.int/medicinedocs/documents/s29544en/s29544en.pdf">http://apps.who.int/medicinedocs/documents/s29544en/s29544en.pdf</a></li> <li>4. Fareocul, A., Khan, A., &amp; Kazmi, S. U. (2009). Investigation of a community outbreak of typhoid fever associated with drinking water. <i>BMC Public Health</i>, 9(1), 470. <a href="https://doi.org/10.1186/1471-2458-9-470">https://doi.org/10.1186/1471-2458-9-470</a></li> <li>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 <a href="http://www.who.int/csr/dp/040403.pdf">http://www.who.int/csr/dp/040403.pdf</a></li> <li>6. Marinak, F., Theodoras, G., Karamanou, M., &amp; Androustou, C. (2013). Vary Mallon (1865-1938) and the history of typhoid fever. <i>Annals of Gastroenterology</i>, 26(2), 132-134. Retrieved from <a href="http://www.ncbi.nlm.nih.gov/pubmed/24714738">http://www.ncbi.nlm.nih.gov/pubmed/24714738</a></li> <li>7. Paily, C. V., Hien, T. T., Dougan, G., White, N. J., &amp; Farrar, J. J. (2002). Typhoid Fever. <i>New England Journal of Medicine</i>, 347(22), 1770-1782. <a href="https://doi.org/10.1056/NEJMa020201">https://doi.org/10.1056/NEJMa020201</a></li> </ol> <div style="display: flex; justify-content: space-between; align-items: center; margin-top: 20px;">   </div>	

## MODULE 3: DIAGNOSTICS

Slide Number		Facilitator Tips
34		In this module, we'll go over the diagnostic processes used for typhoid fever.
35	<h3 style="color: #4F81BD;">LEARNING OBJECTIVES</h3> <p style="color: #E67E22;">In this module, you will:</p> <ol style="list-style-type: none"> <li>1. Learn about symptoms associated with typhoid</li> <li>2. Learn the definitions of suspected case, confirmed case and chronic carrier of typhoid</li> <li>3. Learn about the different diagnostic processes for typhoid</li> </ol> 	<p>By the end of this module, you will:</p> <ul style="list-style-type: none"> <li>• Recognize symptoms associated with typhoid</li> <li>• Learn the definition of a suspected case, confirmed case and chronic carrier of typhoid</li> <li>• Learn the different diagnostic processes for typhoid</li> </ul>
36	<h3 style="color: #4F81BD;">SYMPTOMS OF TYPHOID</h3> <ul style="list-style-type: none"> <li>• Symptoms often develop after typhoid enters the blood stream and may be used to suggest the diagnosis of typhoid</li> <li>• Symptoms include: <ul style="list-style-type: none"> <li style="width: 50%;">• Fever</li> <li style="width: 50%;">• Lethargy</li> <li style="width: 50%;">• Abdominal pain</li> <li style="width: 50%;">• Diarrhea</li> <li style="width: 50%;">• Headaches</li> <li style="width: 50%;">• Rose spots on the chest, abdomen, or back</li> <li style="width: 50%;">• Poor appetite</li> <li style="width: 50%;">• Generalized aches and pains</li> </ul> </li> <li>• Fever, abdominal pain and headache form the “typhoid triad” of symptoms</li> <li>• Nonspecific symptoms of typhoid make laboratory diagnosis necessary to confirm the case and ensure appropriate antimicrobial treatment</li> </ul> 	<p>The symptoms of a typhoid infection may be used to clinically diagnose typhoid. Symptoms include fever, abdominal pain, headaches, poor appetite, generalized aches and pains, lethargy, diarrhea, and “rose spots” on the chest, abdomen or back. Rose spots are a rare rash pattern distinctive to typhoid.</p> <p>Fever, abdominal pain and headaches form the “typhoid triad” of characteristic symptoms of typhoid.</p> <p>Most of these symptoms are nonspecific and similar to other febrile illnesses. Typhoid is difficult to diagnose based on clinical symptoms alone because of similarity to those caused by other infectious diseases. This makes laboratory diagnosis necessary to confirm a case of typhoid.</p>

37

**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



Doctors diagnosing typhoid will use these case definitions in the field:

A suspected case is a patient with fever that has lasted at least three days in absence of confirmatory laboratory result.

A confirmed case is a patient with fever that has lasted at least three days with a laboratory-confirmed positive culture of *S. Typhi* from a normally sterile site. A laboratory diagnosis can include blood culture or bone marrow culture.

A chronic carrier is a patient that continues to excrete *S. Typhi* in stool or urine for more than one year after an episode of typhoid infection.

38

**LABORATORY DIAGNOSIS**

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

Cultures	Sensitivity	Details
Bone Marrow	>80%	<ul style="list-style-type: none"> <li>• Uncomfortable, invasive and impractical</li> <li>• Sensitivity remains high up to 5 days after starting antibiotic treatment</li> </ul>
Blood	40%-60%	<ul style="list-style-type: none"> <li>• Sensitivity increases with greater volumes of blood</li> <li>• Sensitivity decreases greatly over time (by third week of illness, blood culture sensitivity is at 50%)</li> <li>• 100% specificity</li> </ul>
Stool	<50%	<ul style="list-style-type: none"> <li>• Can be tested months following the illness to test for carriage</li> <li>• Sensitivity increases with duration of illness</li> </ul>
Urine	<50%	
Rose Spot	~63%	• May be positive even after antibiotics
Punch Biopsy		



A laboratory diagnosis can confirm a typhoid case. This can include bone marrow culture, which has the highest sensitivity, blood culture, stool culture, urine culture and a rose spot biopsy.

Although bone marrow culture is the most sensitive, it is uncomfortable and invasive for the patient, and impractical for health professionals in low-resource countries. Rose spots can be biopsied, but they are a rare symptom of typhoid. The stool culture test is useful for detecting typhoid carriers.

The preferred method of typhoid diagnosis is the blood culture test, which we will go into in the next slide. Despite having a lower sensitivity rate, it has high specificity.

39

**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



The blood culture test is the most widely used laboratory method to confirm a typhoid diagnosis. However, it is not perfect. Although the specificity is high, sensitivity is relatively low at about 40-60% due to low quantities of *S. Typhi* in blood, and can vary depending on several factors.

Antibiotic usage before a blood culture draw can reduce the number of bacteria present in the sample, making it more difficult to isolate.

Additionally, the sensitivity of the test goes up with a greater volume of blood to test, as we

		<p>saw on the previous slide. However, different volumes of blood should be collected from children and adults.</p> <p>The blood culture test can also be difficult to perform in low-resource settings, as they may lack the required materials and testing labs can be rare.</p> <p>How do you think these factors can impact how typhoid is diagnosed, or the burden of typhoid estimated?</p> <p><i>[Possible discussion topics: common use of over-the-counter antibiotics in typhoid-endemic countries, antibiotic prescription errors, typhoid burden in young children, typhoid prevalence in low-income areas.]</i></p>
40	<p style="text-align: center;"><b>OTHER DIAGNOSTIC TESTS</b></p> <p><b>Antibody-Based Assays</b></p> <ul style="list-style-type: none"> <li>• Widal, Tubex and Typhidot tests detect antibodies produced by the body in response to typhoid exposure</li> <li>• Levels of antibodies in an area differ due to environmental factors <ul style="list-style-type: none"> <li>• 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</li> </ul> </li> <li>• Widal, Tubex and Typhidot tests have low sensitivity and specificity in endemic areas</li> <li>• New serologic tests are under development, but further research is needed</li> </ul> <p><b>Polymerase Chain Reaction (PCR)</b></p> <ul style="list-style-type: none"> <li>• Based on the DNA replication process</li> <li>• Can be performed using blood or urine samples</li> <li>• Currently for research use only</li> </ul>  	<p>There are other diagnostic tests used for typhoid. They include antibody-based assays like Widal, Tubex and Typhidot. They work by detecting antibodies produced by the body in response to typhoid exposure.</p> <p>However, levels of antibodies in a certain population or area differ due to environmental factors. For example, a healthy population in an area highly endemic for typhoid would have higher levels of antibodies due to prior exposure than healthy populations in a non-endemic area. Diagnostic cutoffs have to vary by region. Additionally, antibodies may not be present early in the disease course, causing false negative results.</p> <p>The Widal, Tubex and Typhidot tests have been found to have low sensitivity and specificity in endemic areas. However, there are new serologic tests under development, but further research is needed.</p> <p>Polymerase chain reaction tests are based on the DNA replication process, and are conducted by testing blood and urine. They demonstrate some promising results, but are currently for research use only.</p>

		To date, there are no reliable replacements for blood culture.
41	<p style="text-align: center;"><b>MODULE 3 KEY MESSAGES</b></p> <ol style="list-style-type: none"> <li>1. Typhoid has symptoms similar to other febrile illnesses, which can lead to misdiagnosis and delay in treatment</li> <li>2. Laboratory diagnosis, normally by blood culture, is necessary to confirm a case of typhoid fever</li> <li>3. New serologic tests are under development, but further research is needed</li> </ol> <div style="display: flex; justify-content: space-between; align-items: center; margin-top: 20px;">   </div>	<p>In this module, we have covered the following key takeaways:</p> <p>First, typhoid has symptoms that are similar to many other febrile illnesses, which can lead to misdiagnosis and delay in treatment.</p> <p>Second, you need a laboratory diagnosis to confirm a case of typhoid fever. The most common form of laboratory diagnosis is the blood culture test.</p> <p>Lastly, new serologic tests are under development, but further research is needed.</p> <p>Are there any questions before we move on to treatment?</p>
42	<p style="text-align: center;"><b>REFERENCES</b></p> <ol style="list-style-type: none"> <li>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 <a href="http://www.who.int/csr/don/20031103.pdf">http://www.who.int/csr/don/20031103.pdf</a></li> <li>2. Levine M. M. (2013). Typhoid fever vaccines. In <i>Vaccines</i> (Sixth Edition, pp. 812-836). Elsevier inc. <a href="https://doi.org/10.1016/B978-1-4557-0060-5.00082-3">https://doi.org/10.1016/B978-1-4557-0060-5.00082-3</a></li> <li>3. Sattar, A., Yusuf, M. A., Islam, M. B., &amp; Jehan, W. A. (2014). Different Diagnostic Procedure of Typhoid Fever: A Review Update. <i>Journal of Current and Advance Medical Research</i>, 1(2), 35-41. Retrieved from <a href="http://www.researchgate.net/publication/26031714177">http://www.researchgate.net/publication/26031714177</a></li> <li>4. Arinetti, S. R., Natch, G., &amp; Das, B. K. (2007). Diagnosis of typhoid fever by polymerase chain reaction. <i>Indian Journal of Pediatrics</i>, 74(10), 909-13. Retrieved from <a href="http://www.ncbi.nlm.nih.gov/pubmed/17078448">http://www.ncbi.nlm.nih.gov/pubmed/17078448</a></li> <li>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. <i>BMC Infectious Diseases</i>, 14, 73. <a href="http://dx.doi.org/10.1186/s12874-014-0334-4">http://dx.doi.org/10.1186/s12874-014-0334-4</a></li> <li>6. Akimete, W. O., Sarusi, A. A., &amp; Adedayo, O. K. (2016). Typhoid perforation: Post-operative intensive Care Unit care and outcome. <i>African Journal of Paediatric Surgery: AJP</i>, 13(4), 175-180. <a href="https://doi.org/10.4103/0189-5725.194564">https://doi.org/10.4103/0189-5725.194564</a></li> <li>7. Mogasale, V., Desai, S. N., Mogasale, V. V., Park, J. K., Ochiai, R. L., &amp; Wierzbna T. F. (2014). Case fatality rate and length of hospital stay among patients with typhoid intestinal perforation in developing countries: a systematic literature review. <i>PLoS One</i>, 9(4), e93784. <a href="https://doi.org/10.1371/journal.pone.0093784">https://doi.org/10.1371/journal.pone.0093784</a></li> <li>8. Neil, K. P., Sodha, S. V., Lukwago, L., O'Ipoo, S., Mikolot, M., Simington, S. D., ... Mertz, E. (2012). A Large Outbreak of Typhoid Fever: Associated With a High Rate of Intestinal Perforation in Kasese District, Uganda, 2008-2009. <i>Clinical Infectious Diseases</i>, 54(8), 1091-1099. <a href="https://doi.org/10.1093/cid/cir025">https://doi.org/10.1093/cid/cir025</a></li> </ol> <div style="display: flex; justify-content: space-between; align-items: center; margin-top: 20px;">   </div>	

## MODULE 4: TREATMENT

Slide Number		Facilitator Tips
43		<p>This module will provide an explanation of the treatments used for typhoid fever.</p>
44	<p style="text-align: center;"><b>LEARNING OBJECTIVES</b></p> <p><b>In this module, you will:</b></p> <ol style="list-style-type: none"> <li>1. Learn how typhoid is treated</li> <li>2. Learn about the impact of antibiotic resistance on typhoid treatment</li> <li>3. Observe trends in antibiotic resistance</li> <li>4. Understand solutions for the threat of antibiotic resistance</li> </ol> <p style="text-align: center;">   </p>	<p>In this module you will learn:</p> <ul style="list-style-type: none"> <li>• How typhoid is treated</li> <li>• The impact of antibiotic resistance on typhoid treatment</li> <li>• Trends in antibiotic resistance</li> <li>• And solutions for the threat of antibiotic resistance</li> </ul>
45	<p><b>TYPICAL COURSE OF TYPHOID TREATMENT</b></p> <ul style="list-style-type: none"> <li>• Optimal management depends on early diagnosis and prompt, appropriate antibiotic treatment             <ul style="list-style-type: none"> <li>• 90% of cases can be managed at home with oral antibiotics, bedrest and close medical follow-up</li> <li>• 10-20% of untreated patients will die</li> </ul> </li> <li>• General management of typhoid can include:             <ul style="list-style-type: none"> <li>• Oral or intravenous hydration</li> <li>• Fever reducing medicine (antipyretics)</li> <li>• Appropriate nutrition</li> <li>• Hand-washing and limited contact with susceptible individuals</li> <li>• Regular follow-up and monitoring for complications or relapse</li> </ul> </li> </ul> <p style="text-align: center;">   </p>	<p>When we look at how typhoid is typically treated, we can see that optimal management depends on early diagnosis and prompt and appropriate antibiotic treatment.</p> <p><i>[Possible discussion topic: In Module 3, we learned that typhoid diagnosis can be difficult. How can this impact treating typhoid?]</i></p> <p>The majority of typhoid cases, about 90%, can be managed with oral antibiotics, bedrest, and medical follow-up. Without treatment, however, 10-20% of typhoid cases are fatal.</p> <p>Some other effective general management techniques for typhoid include hydration, fever-reducing medicine, appropriate nutrition, hand-washing, and regular follow-up and monitoring for complications.</p>

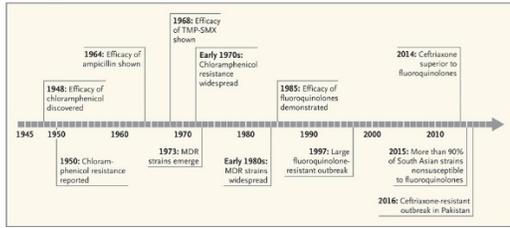
<p>46</p>	<p style="text-align: center;"><b>ANTIBIOTIC TREATMENT</b></p> <ul style="list-style-type: none"> <li>• Antibiotic treatment varies depending on: <ul style="list-style-type: none"> <li>• Severity</li> <li>• Age</li> <li>• Antibiotic resistance</li> <li>• General state of health</li> </ul> </li> <li>• Growing resistance to many first-line antibiotics is leading to increased use of other antibiotics that may be: <ul style="list-style-type: none"> <li>• More expensive</li> <li>• Less effective</li> <li>• Associated with more severe side effects</li> <li>• Associated with higher rate of relapse</li> </ul> </li> </ul> <p style="text-align: center;">   </p>	<p>Antibiotic treatment for typhoid varies depending on severity (including complications), age, antibiotic resistance and the general state of the patient’s health.</p> <p>Because of growing resistance to many first-line antibiotics, medical providers are increasingly using other antibiotics that may have drawbacks, such as being more expensive, less effective, having more severe side effects, and being associated with a higher rate of relapse.</p>
<p>47</p>	<p style="text-align: center;"><b>MANAGING TYPHOID COMPLICATIONS</b></p> <ul style="list-style-type: none"> <li>• Typhoid complications range from mild to severe. Intestinal hemorrhage and perforation are some of the most severe complications</li> <li>• Intestinal hemorrhage <ul style="list-style-type: none"> <li>• Intensive care and monitoring</li> <li>• Blood transfusion</li> </ul> </li> <li>• Intestinal perforations <ul style="list-style-type: none"> <li>• Majority of perforations require surgery</li> <li>• A small portion of the bowel may be cut out if the perforation is very severe</li> <li>• Mortality rates for patients with perforations vary between 10-32%</li> </ul> </li> <li>• Chronic carriers can usually be treated with antibiotics, though gallbladder removal may be required</li> </ul> <p style="text-align: center;">   </p>	<p>Typhoid complications range from mild to severe. As you learned in module 2, intestinal hemorrhage and perforation are some of the most severe complications.</p> <p>Different complications require different kinds of treatments.</p> <p>Intestinal hemorrhage requires intensive care and monitoring. If the hemorrhaging is particularly severe, blood transfusions may be necessary.</p> <p>The majority of intestinal perforations require surgery. This may involve a section of the bowel being cut out if the perforation is very severe. The mortality rate for patients with intestinal perforation can vary between 10-32%.</p> <p>Chronic carriers can usually be treated with antibiotics or gallbladder removal.</p>
<p>48</p>	<p style="text-align: center;"><b>RELAPSE</b></p> <ul style="list-style-type: none"> <li>• 5-20% of patients experience a relapse in typhoid after treatment <ul style="list-style-type: none"> <li>• Higher for patients with antibiotic-resistant typhoid</li> <li>• More likely to occur when a patient has poor access to care and receives inadequate treatment</li> </ul> </li> <li>• Relapse can generally occur 3-4 weeks after a clinical cure</li> <li>• Illness is typically milder and is treated in the same way as initial infections</li> </ul> <p style="text-align: center;">   </p>	<p>Even after treatment, however, 5-20% of patients experience a relapse in typhoid. This percentage is higher for patients with antibiotic-resistant typhoid. Relapse is also more likely when the patient has poor access to care or receives inadequate treatment.</p> <p>Relapse can occur weeks or even months after typhoid has been clinically “cured.” However, the relapse is typically milder and is treated in the same way as the initial infection.</p>

<p>49</p>	<p style="text-align: center;"><b>ANTIBIOTIC RESISTANCE</b></p> <ul style="list-style-type: none"> <li>• Antibiotic resistance happens when bacteria mutates and is able to resist the effect of antibiotics</li> <li>• Can occur naturally, but misuse of antibiotics in humans and animals is accelerating the process <ul style="list-style-type: none"> <li>• &gt;50% of the time antibiotics are not optimally prescribed, not needed, or of the incorrect dosing or duration</li> <li>• Antibiotics are available over-the-counter in many developing countries</li> </ul> </li> <li>• 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 <ul style="list-style-type: none"> <li>• The first known outbreak of extensively drug resistant (XDR) typhoid began in Pakistan in 2016</li> </ul> </li> </ul>  	<p>Antibiotic resistance occurs when bacteria mutates to be able to resist the effect of antibiotics. This occurs naturally, but misuse of antibiotics in humans and animals is accelerating the process.</p> <p>More than half of the time, antibiotics are not optimally prescribed, prescribed in the incorrect dosing or duration, or even unneeded. They are also often available over-the-counter in many developing countries where typhoid is endemic.</p> <p>As a result, multi-drug resistant strains of typhoid are increasing, with many originating in Southern Asia and spreading to Sub-Saharan Africa. They present a threat to the effective treatment of typhoid. In Pakistan, the first known outbreak of extensively drug resistant typhoid began in 2016.</p>
<p>50</p>	<p style="text-align: center;"><b>FIGHTING RESISTANT TYPHOID</b></p> <ul style="list-style-type: none"> <li>• Widespread resistance in 1980s and 1990s to the most common antibiotics (ampicillin, co-trimoxazole, chloramphenicol) <ul style="list-style-type: none"> <li>• Resulted in use of fluoroquinolones and cephalosporins</li> <li>• Resistance to fluoroquinolones is spreading rapidly, and resistance to cephalosporins has been reported</li> </ul> </li> <li>• Combinations of antibiotics are being assessed for affordable options to combat AMR typhoid</li> <li>• Improved laboratory capacity is needed to determine the drug susceptibility of typhoid cases <ul style="list-style-type: none"> <li>• Determining the resistance will help to provide effective treatments and reduce the use of antibiotics that may be ineffective</li> </ul> </li> </ul>  	<p>Drug resistance in typhoid became widespread in the 1980s and 1990s, beginning with the most common antibiotics, ampicillin, co-trimoxazole and chloramphenicol. This results in clinicians having to use fluoroquinolones and cephalosporins.</p> <p>However, now resistance to fluoroquinolones and cephalosporins is increasing. Right now, different combinations of antibiotics are being assessed for affordable options to combat antimicrobial resistant typhoid.</p> <p>Another way to effectively treat antimicrobial resistant typhoid is to use improved laboratory capacity to determine the drug susceptibility of individual typhoid cases before treatment. Proper diagnostic testing can help physicians select antibiotics that will be effective, and reduce use of those that won't be effective.</p>

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### ANTIBIOTIC RESISTANCE TIMELINE

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



COALITION AGAINST TYPHOID | Andrews JK, Carter PH, Charles RC, Ruel ET. Extensively Drug Resistant Typhoid—Are Conjugate Vaccines Answering Last in Tim? *New England Journal of Medicine*. 2016 Oct 18;375(16):1483-5. | SABIN VACCINE INSTITUTE

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

In this figure, MDR denotes multidrug-resistant, and TMP-SMX denotes trimethoprim–sulfamethoxazole. Strains noted to be “nonsusceptible” are intermediately or fully resistant.

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### 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

COALITION AGAINST TYPHOID | Karikó, G, Baneth, G, Giv, L, Jorgensen, D, B, Vokac, A, et al. Typhoid in Kenya associated with a common H58 genotype and resistance to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol. *Antimicrobial Agents and Chemotherapy*. 2015;59(10):3710-15. | SABIN VACCINE INSTITUTE

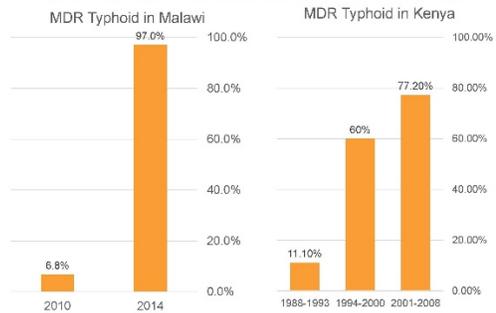
One particular strain of typhoid that has emerged over the past 20 years is becoming particularly resistant and widespread. This strain is called H58, and it has shown resistance to multiple drugs including three frontline antimicrobials: ampicillin, co-trimoxazole, chloramphenicol.

This strain originated in Southern Asia and spread to the Middle East, Pacific Islands and to Sub-Saharan Africa. Kenya announced its first case 10 years ago, and Malawi first saw it five years ago.

H58 genes are becoming a stable part of the typhoid genome, indicating that it is not disappearing soon. Forty-seven percent of typhoid cases sampled from 63 countries between 1992 and 2013 were from the H58 strain. A study in Malawi found that the percentage of typhoid cases that were H58 increased from 6.8% to 97% in only four years, from 2010 to 2014.

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### SNAPSHOT: MDR TYPHOID TRENDS



COALITION AGAINST TYPHOID | Karikó, G, Baneth, G, Giv, L, Jorgensen, D, B, Vokac, A, et al. Typhoid in Kenya associated with a common H58 genotype and resistance to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol. *Antimicrobial Agents and Chemotherapy*. 2015;59(10):3710-15. | SABIN VACCINE INSTITUTE

Let's look closer at MDR typhoid trends in Africa. On these charts, you can see that the rapid increase of MDR typhoid in Malawi has also been somewhat seen in Kenya. These charts show how quickly multi-drug resistance can spread once it is present.

<p>54</p>	<p><b>MDR: A PUBLIC HEALTH EMERGENCY</b></p> <ul style="list-style-type: none"> <li>• Threatens the ability to treat common infectious diseases and can cause prolonged illness, disability and death</li> <li>• Increases the cost of health care by necessitating: <ul style="list-style-type: none"> <li>• Longer hospital stays</li> <li>• More intensive care</li> <li>• Additional tests</li> <li>• More expensive drugs</li> </ul> </li> <li>• Even if new medicines are developed, preventative measures are needed to reduce the spread of infections <ul style="list-style-type: none"> <li>• Vaccination</li> <li>• Hand-washing</li> <li>• Food hygiene</li> </ul> </li> </ul>  	<p>Multi-drug resistance is a public health emergency. It threatens our ability to treat common infectious diseases and can cause patients to have prolonged illness, disability or even death. The cost of health care also increases with drug-resistance due to longer hospital stays, more intensive care, additional testing and more expensive drugs.</p> <p>We talked earlier about new medicines or new combinations of existing medicines. However, what is really necessary to curb typhoid are preventative measures; namely, vaccination, hand-washing and other sanitation measures, and food hygiene. These will all be covered in the next module.</p> <p>Thinking back to Module 1, does anyone remember what the case-fatality rate of typhoid is? For both treated and untreated?</p> <p><i>[Correct answer should be 1-4% for treated versus 10-20% for untreated]</i></p> <p>Imagine if the antibiotics that bring this fatality rate down to 1-4% stopped working. Multi-drug resistance has the potential to turn back the progress made with the help of antibiotics.</p>
<p>55</p>	<p><b>SNAPSHOT: MDR &amp; XDR TUBERCULOSIS</b></p> <ul style="list-style-type: none"> <li>• Global investment in controlling tuberculosis (TB) was insufficiently funded and did not focus enough on prevention or diagnosis</li> <li>• MDR-TB and extensively drug resistant tuberculosis (XDR-TB) emerged in early 1990s</li> <li>• XDR-TB strains are resistant to the strongest drugs <ul style="list-style-type: none"> <li>• Treatment success rate of only 26%</li> </ul> </li> <li>• 2013: 84 countries with XDR-TB</li> <li>• 2016: 117 countries with XDR-TB</li> <li>• Current situation: treatment is 50 to 200 times more expensive and takes 3 times longer to cure than normal TB</li> </ul>  	<p>This is a snapshot of what can happen when multi-drug resistance spins out of control. Global investment in controlling tuberculosis was insufficiently funded and did not focus enough on prevention or diagnosis, allowing MDR-TB and XDR-TB to emerge in the early 90s.</p> <p>XDR-TB is resistant to the strongest antimicrobials, and has a treatment success rate of only 26%. In 2013, 84 countries reporting having XDR-TB. In 2016, that number had risen to 117.</p> <p>The current situation of drug-resistant TB is that treatment is 50-200 times more expensive and takes three times longer to cure than normal TB. The typhoid community can learn from TB to invest in prevention, surveillance and</p>

		<p>diagnostics before multi-drug resistance grows out of control.</p> <p><i>[Discuss the situation of MDR and XDR TB and how that may apply to typhoid, particularly in the light of XDR typhoid in Pakistan]</i></p>
56	<p style="text-align: center;"><b>KEY MESSAGES</b></p> <ol style="list-style-type: none"> <li>1. The majority of typhoid cases can be treated at home with antibiotics, but patients with typhoid complications must seek more extensive care</li> <li>2. When diagnosing typhoid, it is essential to test for drug susceptibility to determine an effective course of antibiotic treatment</li> <li>3. Multi-drug resistant typhoid is a growing global threat and calls for increased investment in prevention and control</li> </ol>  	<p>During this module, you should have learned the following key points:</p> <p>First, the majority of typhoid cases can be treated at home with antibiotics, but patients with complications from typhoid must seek more extensive care.</p> <p>When diagnosing typhoid, testing for drug susceptibility is necessary to determine an effective course of antibiotic treatment.</p> <p>Lastly, multi-drug resistant typhoid is a growing global threat that calls for increased investment in prevention and control.</p> <p>Does anyone have any questions before we move on to the next module, on prevention?</p>
57	<p style="text-align: center;"><b>REFERENCES</b></p> <ol style="list-style-type: none"> <li>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 <a href="http://www.who.int/go/CCD/disease/go_def10.pdf">http://www.who.int/go/CCD/disease/go_def10.pdf</a></li> <li>2. Levine, M. M. (2013). Typhoid fever vaccines. In <i>Vaccines</i> (Sixth Edition), pp. 812–836. Elsevier Inc. <a href="https://doi.org/10.1016/B978-1-4557-0090-5_50009-2">https://doi.org/10.1016/B978-1-4557-0090-5_50009-2</a></li> <li>3. Bhutta, Z. A. (2008). Current concepts in the diagnosis and treatment of typhoid fever. <i>BMJ (Clinical Research Ed.)</i>, 333(7558), 76–82. <a href="https://doi.org/10.1136/bmj.333.7558.76">https://doi.org/10.1136/bmj.333.7558.76</a></li> <li>4. Chhab, N. T., Parry, C. M., Ly, N. T., Ha, H. D., Thong, M. X., Dao, T. S., ... Farnas, J. J. (2000). A randomized controlled comparison of azithromycin and ofloxacin for treatment of multidrug-resistant or nalidixic acid-resistant enteric fever. <i>Antimicrobial Agents and Chemotherapy</i>, 44(7), 1955–9. Retrieved from <a href="http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1195343/">http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1195343/</a></li> <li>5. Bhutta, Z. A., Ahmad, K. A., Khan, L. H., Rahman, S., &amp; Shafiq, Z. A. (2011). Factors associated with typhoid relapse in the era of multiple drug resistant strains. <i>doi.org/10.1186/1745-2974-11-159 <a href="https://doi.org/10.1186/1745-2974-11-159">https://doi.org/10.1186/1745-2974-11-159</a></i></li> <li>6. CDC. (2015). <i>Antimicrobial Resistance (Antibiotic/Antimicrobial Resistance)</i> [CDC]. Retrieved from <a href="https://www.cdc.gov/drugresistance/about.html">https://www.cdc.gov/drugresistance/about.html</a></li> <li>7. Kariuki, S., Kivuthi, G., Kimani, M., Mwangi, D. M., Muturia, J., Masyek, J., ... Dougan, G. (2010). Typhoid in Kenya is associated with a dominant multidrug-resistant <i>Salmonella enterica</i> serovar Typhi haplotype that is also widespread in Southeast Asia. <i>Journal of Clinical Microbiology</i>, 48(6), 2171–6. <a href="https://doi.org/10.1128/JCM.01985-09">https://doi.org/10.1128/JCM.01985-09</a></li> <li>8. Harsh, B. N., &amp; Menon, G. A. (2011). Antimicrobial resistance in typhoidal salmonellae. <i>Indian Journal of Medical Microbiology</i>, 29(2), 223–9. <a href="https://doi.org/10.4103/0974-6875.89004">https://doi.org/10.4103/0974-6875.89004</a></li> <li>9. Feeley, N. A., Gaswell, K., Wong, V., Masfala, C., Selemani, G., Kummwenda, S., ... Heylman, R. S. (2015). Rapid Emergence of Multidrug Resistant, H59-Lineage <i>Salmonella</i> Typhi in Blantyre, Malawi. <i>PLoS Neglected Tropical Diseases</i>, 9(4), e0003746. <a href="https://doi.org/10.1371/journal.pntd.0003746">https://doi.org/10.1371/journal.pntd.0003746</a></li> <li>10. WHO   Antimicrobial resistance (AMR). WHO. Retrieved from <a href="http://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance">http://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance</a></li> <li>11. Abubakar, I., Zignol, M., Falzon, D., Ravignone, M., Doku, L., Hasham, S., ... Zumla, A. (2017). Drug-resistant tuberculosis: time for visionary global leadership. <i>The Lancet Infectious Diseases</i>, 17(6), 529–530. <a href="https://doi.org/10.1016/S1473-3099(17)30300-6">https://doi.org/10.1016/S1473-3099(17)30300-6</a></li> <li>12. <i>Multidrug-Resistant Tuberculosis (MDR-TB) 2016 Update</i> (n.d.). Retrieved from <a href="http://www.who.int/tb/publications/mdr-tb-2016-update.pdf?ua=1">http://www.who.int/tb/publications/mdr-tb-2016-update.pdf?ua=1</a></li> <li>13. Pien, L., &amp; Mordecai, D. (2011). Treatment of drug-resistant tuberculosis: infection and drug resistance. 4, 125–35. <a href="https://doi.org/10.2147/IDR.S16316">https://doi.org/10.2147/IDR.S16316</a></li> </ol>  	<p style="text-align: center;">“References”</p>

## MODULE 5: PREVENTION

Slide Number		Facilitator Tips
58		<p>This module will explore the different ways in which typhoid fever can be prevented.</p>
59	<p style="text-align: center;"><b>LEARNING OBJECTIVES</b></p> <p><b>In this module, you will:</b></p> <ol style="list-style-type: none"> <li>1. Identify typhoid prevention methods</li> <li>2. Learn about water, sanitation and hygiene interventions</li> <li>3. Learn about typhoid vaccines</li> </ol> 	<p>In this module, you will:</p> <ul style="list-style-type: none"> <li>• Identify typhoid prevention methods</li> <li>• Learn about water, sanitation and hygiene interventions</li> <li>• Learn about typhoid vaccines</li> </ul>
60	<p style="text-align: center;"><b>THE PREVENTABLE BURDEN</b></p> <p>Typhoid can be prevented by:</p> <ul style="list-style-type: none"> <li>• Water, sanitation and hygiene (WASH) interventions, including: <ul style="list-style-type: none"> <li>• Providing access to safe drinking water</li> <li>• Ensuring that the community's fecal waste does not contaminate the environment</li> <li>• Encouraging handwashing and safe food production and handling practices</li> </ul> </li> <li>• Vaccination can <ul style="list-style-type: none"> <li>• Protect the most vulnerable, i.e. children</li> <li>• Control outbreaks</li> <li>• Build herd immunity</li> </ul> </li> </ul> 	<p>One of the ways to prevent typhoid is through water, sanitation and hygiene (or WASH) interventions. These can include providing access to safe drinking water, installing latrines or other improved waste disposal methods, educating communities on the importance of hand-washing and encouraging safe food-handling practices. Remember, typhoid is transmitted through contaminated water, which is why it is common in less-industrialized countries that have unsafe drinking-water and inadequate sewage disposal. WASH interventions disrupt the fecal-oral transmission pathway.</p> <p>Typhoid can also be prevented through vaccination. Vaccine interventions can protect the most vulnerable populations, such as children. Vaccines can also be used to control</p>



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### WATER QUALITY INTERVENTIONS

At Point of Use	At Source
Household	Wells, reservoirs
<ul style="list-style-type: none"> <li>Chlorination</li> <li>Household filters</li> <li>Sedimentation</li> <li>Water storage sanitation</li> </ul>	<ul style="list-style-type: none"> <li>Chlorination</li> <li>Filtration</li> <li>Improvements in distribution pipes</li> </ul>



Water quality interventions can either occur at the source of the water or at point of use.

Point-of-use interventions take place at the household level and include chlorination, use of household filters, sedimentation, and water storage sanitation.

Chlorination kills bacteria, filtration physically removes contaminants and sedimentation works similarly. Families keep water in a clean storage container for several days, allowing physical contaminants to settle to the bottom and bacteria to die.

Interventions at the water source, like wells and reservoirs, impact larger amounts of people. They can include chlorination and filtration of the entire body of water or improvements in the distribution pipes.

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### SNAPSHOT: U.S. IN THE 20<sup>TH</sup> 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



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To illustrate the powerful difference a proper water treatment system can make, we're going to look at a snapshot of the United States in the twentieth century. In 1900, the typhoid incidence rate was 100 cases per 100,000 people. Typhoid was especially rampant in crowded cities, where water was drawn untreated from rivers which were also sewage repositories.

Interventions at the source including sand filtration, chlorination and improvement in sanitation and infrastructure swiftly reduced the incidence of typhoid in large cities. Although typhoid carriers were still active, by 1920 incidence had dropped to 33.8 cases per 100,000, and in 2006 it was 0.1 per 100,000. The cases that exist in the United States are usually among international travelers.

This illustrates the dramatic decrease in typhoid cases in the United States in the last century due to an increase in water quality interventions and sanitation infrastructure.





### 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



WASH interventions encounter many challenges. Household interventions such as chlorination, use of household filters, sedimentation and water storage sanitation require individual behavior changes, which can be difficult to sustain. Outside of the home, municipal water systems run intermittently which guarantees contamination. Additionally, water distribution pipes can become compromised. Treating water sources requires continuous monitoring and costs can be great. There are also few incentives to reach the poor and invest in maintenance and repair.

There are also many challenges to achieving basic sanitation infrastructure. Wastewater sanitation is often expensive to implement and requires high levels of commitment. Sometimes, in order to relieve costs, the sanitation infrastructure will be made communal. However, there are difficulties of ownership for communal sanitation infrastructure. Sanitation facilities, like toilets, need to be continually cleaned and maintained, but communal sanitation infrastructure runs into questions of ownership and responsibility. Additionally, communal toilets sometimes have problems of accessibility and safety, especially for women.

Sustained change in behavior and perception can also be difficult. Some may not want to use their stored clean water for handwashing, preferring to use it for drinking or cooking. For others, soap may be too expensive.

Many living in typhoid-endemic areas also have a low belief in the efficacy of handwashing in combating typhoid. Can anyone think of reasons why?

*[Possible discussion topics: people may have contracted typhoid after washing their hands incorrectly, they may have contracted a disease with symptoms similar to typhoid after washing their hands, they may have contracted typhoid through another avenue than handwashing]*

		<p><i>couldn't prevent, they may have not washed their hands but never contracted typhoid.]</i></p> <p>Even when knowledge is high, sustaining behavior change is difficult.</p>						
69	<p style="text-align: center;"><b>VALUE OF TYPHOID VACCINES</b></p> <ul style="list-style-type: none"> <li>• Typhoid vaccines: <ul style="list-style-type: none"> <li>• Offer both individual protection and herd immunity (when used in a large-scale vaccination effort)</li> <li>• Complement WASH prevention strategies that may require more time and money to implement</li> <li>• Protect against antibiotic-resistant strains of typhoid</li> <li>• Reduce health care costs to both families and health systems</li> </ul> </li> </ul> <div style="display: flex; justify-content: space-between; align-items: center; margin-top: 20px;">   </div>	<p>Another way to prevent typhoid is through vaccines. Typhoid vaccines offer both individual protection and herd immunity, when used in a large-scale vaccination effort. They also complement WASH prevention strategies that may require more time and money to implement. Typhoid vaccines also provide protection against antibiotic resistant strains of typhoid. When typhoid is unable to spread from person to person, it is unable to evolve. Finally, lower incidence of typhoid can reduce health care costs to both families and to health systems.</p>						
70	<p style="text-align: center;"><b>TYPHOID VACCINES</b></p> <p>Until recently, there were only 2 types of typhoid vaccines on the market:</p> <table border="1" style="width: 100%; border-collapse: collapse; margin: 10px 0;"> <thead> <tr style="background-color: #f4a460;"> <th style="padding: 5px;">Ty21a</th> <th style="padding: 5px;">Vi capsular polysaccharide</th> </tr> </thead> <tbody> <tr> <td style="padding: 5px;">A live attenuated vaccine given through oral capsules</td> <td style="padding: 5px;">An injectable subunit vaccine</td> </tr> <tr> <td style="padding: 5px;"> <ul style="list-style-type: none"> <li>• Must be at least 6 years old</li> <li>• 3 to 4 doses needed</li> <li>• Booster needed every 5 years</li> <li>• 50-80% effective</li> </ul> </td> <td style="padding: 5px;"> <ul style="list-style-type: none"> <li>• Must be at least 2 years old</li> <li>• 1 dose needed</li> <li>• Booster needed every 2-3 years</li> <li>• 50-80% effective</li> </ul> </td> </tr> </tbody> </table> <div style="display: flex; justify-content: space-between; align-items: center; margin-top: 20px;">   </div>	Ty21a	Vi capsular polysaccharide	A live attenuated vaccine given through oral capsules	An injectable subunit vaccine	<ul style="list-style-type: none"> <li>• Must be at least 6 years old</li> <li>• 3 to 4 doses needed</li> <li>• Booster needed every 5 years</li> <li>• 50-80% effective</li> </ul>	<ul style="list-style-type: none"> <li>• Must be at least 2 years old</li> <li>• 1 dose needed</li> <li>• Booster needed every 2-3 years</li> <li>• 50-80% effective</li> </ul>	<p>Until recently, there were two types of typhoid vaccines on the market; the live attenuated vaccine, also known as Ty21a, and the Vi capsular polysaccharide.</p> <p>Ty21a is a live attenuated vaccine given orally. To receive it, you must be at least six years old. A booster is needed every five years after the initial doses. Ty21a is 50-80% effective.</p> <p>The Vi capsular polysaccharide is an injected vaccine. To receive it, you must be at least two years old. A booster is needed every two years after the initial single dose. This vaccine is 50-80% effective.</p> <p>These vaccines are mainly used by travelers from high-income countries and are largely absent from endemic country vaccination programs.</p> <p>Look over this information. Can you think of some reasons why these vaccines might not be implemented widely?</p> <p><i>[Possible discussion topics: the low effectiveness, the need for a booster, and the age limit.]</i></p>
Ty21a	Vi capsular polysaccharide							
A live attenuated vaccine given through oral capsules	An injectable subunit vaccine							
<ul style="list-style-type: none"> <li>• Must be at least 6 years old</li> <li>• 3 to 4 doses needed</li> <li>• Booster needed every 5 years</li> <li>• 50-80% effective</li> </ul>	<ul style="list-style-type: none"> <li>• Must be at least 2 years old</li> <li>• 1 dose needed</li> <li>• Booster needed every 2-3 years</li> <li>• 50-80% effective</li> </ul>							

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**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 H-P. Polysaccharide vaccine in a typhoid fever endemic area using Vi manufactured in China. *Emerging Infectious Diseases*. 2003;9(10):1193-1197. doi:10.1093/eid/cig119



To illustrate the usefulness of typhoid vaccination, we're taking a look at vaccines in Guangxi, China.

The Vi polysaccharide vaccine was used in a 1995 mass vaccination program. This vaccination program targeted students, food-handlers and people living near outbreaks, with re-vaccination taking place every three years. The coverage rate averaged 60-70% for students and 80-85% for food-handlers and people living near outbreaks. At that time, typhoid incidence was 61 cases out of 100,000 among students and 47 out of 100,000 among the general population.

As you can see on the table, vaccination played a major role in typhoid reduction. While WASH improvements during the same period contributed, the improvements were too gradual to account for the drastic fall in typhoid incidence after 1995. Additionally, rates of paratyphoid, which spreads similarly to typhoid, actually increased during the same period.

Four years after the vaccination program, in a 1999 typhoid outbreak, vaccinated students had an 81% lower risk of contracting the disease.

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**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 Burden in Asia (TBD) Background Paper on Identification of Typhoid Fever and Disease Burden in Asia. 2003. Available at: <http://www.sabin.org/typhoid>



Given the benefits this vaccination program had in Guangxi, why do more countries not take this approach? A 2000/2001 survey of policymakers in Asia gave several reasons for why countries are not utilizing typhoid vaccines.

The uncertainty of the true typhoid burden stems from the difficulty of diagnosis and lack of surveillance covered in Modules 1-3.

Typhoid has been able to be easily treated by relatively cheap antibiotics. However, that is changing due to antimicrobial resistance.

Lack of public attention to typhoid vaccination.

Sometimes local government officials are pressured not to report typhoid cases because

		<p>they are an indicator of inadequate water and sanitation systems.</p> <p>The price for vaccines is relatively high.</p> <p>Although water and sanitation improvements are more difficult and expensive, they are also longer-lasting and help prevent many other diseases, so some policymakers would prefer that to vaccination.</p> <p>There is also a lack of awareness of upcoming new-generation vaccines, which we'll get to in the next slide.</p> <p>Policymakers also named an uncertainty of the logistic feasibility of vaccinating children. This stems from the older age at which current typhoid vaccines are approved for (i.e. not for infants).</p>
<p>73</p>	<p><b>NEW TYPHOID CONJUGATE VACCINES (TCVs)</b></p> <ul style="list-style-type: none"> <li>• Third generation of typhoid vaccines <ul style="list-style-type: none"> <li>• Antigen is coupled to a carrier protein</li> <li>• The World Health Organization has prequalified Typbar-TCV®, allowing WHO, UNICEF and other United Nations procurement agencies to purchase the vaccine</li> </ul> </li> <li>• Benefits of conjugate vaccines: <ul style="list-style-type: none"> <li>• Long duration of protection</li> <li>• Can be administered to children less than 2 years old</li> <li>• Fewer doses required</li> <li>• Can be administered through routine immunization programs</li> </ul> </li> <li>• 2 conjugate vaccines, Typbar-TCV and Peda Typh™, have national licensure in India <ul style="list-style-type: none"> <li>• Roll out of conjugate vaccine in endemic countries is within reach in the coming years</li> </ul> </li> </ul>  	<p>Typhoid conjugate vaccines – or TCVs – are the third generation of typhoid vaccines. The “conjugate” in the name means that the polysaccharide antigen from typhoid is “conjugated” or coupled to a carrier protein. One typhoid conjugate vaccine, Typbar-TCV®, has been prequalified by the World Health Organization (WHO), allowing WHO, UNICEF and other United Nations procurement agencies to purchase the vaccine.</p> <p>These vaccines offer many benefits over current typhoid vaccines. They provide a long duration of protection, can be administered to children less than two years old and fewer doses are required. Because of this, they can be administered through routine childhood immunization programs.</p> <p>Two conjugate vaccines have been licensed in India, and rollout of conjugate vaccines in other endemic countries is within reach in the coming years.</p>

<p>74</p>	<p style="text-align: center;"><b>Typbar-TCV®</b></p> <p style="text-align: center;"><b>Typbar-TCV</b></p> <p>An injectable conjugate vaccine, manufactured by Bharat Biotech</p> <ul style="list-style-type: none"> <li>• Can be administered to children below 2 years of age</li> <li>• Immunity for at least 3 years</li> <li>• 1 dose needed</li> <li>• 87% efficacy*</li> </ul> <ul style="list-style-type: none"> <li>• In December 2017, achieved prequalification by the WHO</li> <li>• Prequalification indicates that a vaccine meets international standards and serves as an endorsement of quality, efficacy and safety</li> <li>• With prequalification, Typbar-TCV can be purchased by WHO, UNICEF and other United Nations procurement agencies to help finance TCVs in low-resource countries</li> </ul> <p><small>*Efficacy based on 2009-2010 outbreak in Malawi. See: Jha, G., Galvani, M. M., Morse, M., et al. (2014). The impact of typhoid fever in Malawi: a case-control study. <i>PLoS ONE</i>, 9(12), e111111. doi:10.1371/journal.pone.0111111</small></p>  	<p>One of the TCVs already licensed in India is the Typbar-TCV, manufactured by Bharat Biotech. This vaccine can be administered to children below two years of age, offers immunity of at least three years, and only requires one dose. A human challenge model found that this vaccine had an efficacy of 87%, which is higher than the previously available typhoid vaccines.</p> <p>In December 2017, Typbar-TCV 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 is able to be purchased by WHO, UNICEF, and other United Nations procurement agencies to help finance TCVs in low-resource countries.</p>
<p>75</p>	<p style="text-align: center;"><b>GLOBAL POLICY FOR TCVS</b></p> <ul style="list-style-type: none"> <li>• TCVs are poised for distribution in endemic countries</li> <li>• The WHO recommends the following use of typhoid conjugate vaccines: <ul style="list-style-type: none"> <li>• TCVs should be used in endemic countries for children greater than 6 months of age</li> <li>• TCVs should be prioritized in countries with the highest burden and/or a growing burden of drug-resistant typhoid</li> <li>• TCVs should be used for outbreak response and in specific groups of people at high risk</li> </ul> </li> <li>• Gavi, the Vaccine Alliance released \$85 million in funding to support the introduction of the TCVs in low-income countries <ul style="list-style-type: none"> <li>• Funds will enable bulk purchases of TCVs</li> <li>• Countries are expected to begin applying for Gavi support in 2018 for vaccine introduction in 2019 and 2020</li> </ul> </li> </ul>  	<p>TCVs are poised for distribution in low-income countries where typhoid is endemic. The WHO recommends the TCV should be used in endemic countries to all children over six months of age. The TCV should be prioritized in countries with the highest typhoid burden or growing burden of drug-resistant typhoid. Finally, TCVs should be used for outbreak response and in specific groups of people at high risk.</p> <p>In December 2017, Gavi, the Vaccine Alliance, released \$85 million in funding to support the introduction of TCVs in low-income countries. Countries are expected to begin applying for Gavi support in 2018 for vaccine introduction in 2019 and 2020.</p>
<p>76</p>	<p style="text-align: center;"><b>SNAPSHOT: VACCINE DEMAND IN MALAWI</b></p> <ul style="list-style-type: none"> <li>• 2009/2010: Outbreak of typhoid detected in southwest Malawi with 784 cases and 44 deaths reported in 17 villages</li> <li>• Investigation of vaccine acceptability during 2010 found: <ul style="list-style-type: none"> <li>• The disease widely feared due to rapid spread</li> <li>• Widespread skepticism of WASH interventions: <ul style="list-style-type: none"> <li>• Disease believed to be spread by "bad air" or wind</li> <li>• All villagers follow same hygiene practices, but only some got sick</li> </ul> </li> <li>• Firm belief in power of vaccines in preventing illness: <ul style="list-style-type: none"> <li>• Belief that benefits far outweigh negative reactions</li> <li>• Social pressure to receive vaccine as later illness will be blamed on refusers</li> <li>• Vaccine effectiveness of 60% did not decrease acceptability, perceived as an improvement over present situation [15]</li> </ul> </li> </ul> </li> </ul> <p><small>Wang, T., Davis, S., et al. (2014). Vaccine acceptability in Malawi: a case-control study. <i>PLoS ONE</i>, 9(12), e111111. doi:10.1371/journal.pone.0111111</small></p>  	<p>To look at the demand for vaccines in typhoid-endemic areas, we're taking a snapshot of a typhoid outbreak in Malawi. In the process we'll also look at the challenges of other types of typhoid prevention interventions.</p> <p>In 2009 and 2010, an outbreak of typhoid spread in Southwest Malawi, with 784 cases and 44 deaths reported in 17 villages.</p> <p>A study taking place in this area during 2010 found that the disease was widely feared due to</p>

		<p>its rapid spread. There was also widespread skepticism of the efficacy of WASH interventions. Villagers believed the disease was spread by “bad air” or wind; they also observed that all villagers followed the same hygienic practices, but only some got sick.</p> <p>However, the study found firm belief in the power of vaccines in preventing illness. Villagers believed that the benefits far outweighed negative reactions. The study found that there would be considerable social pressure to receive the vaccine, as later illness would be blamed on refusers. The study found that even when they were told the vaccine effectiveness was as low as 60%, the acceptability did not decrease, because they perceived it as an improvement over the present situation.</p>
<p>77</p>	<p style="text-align: center;"><b>KEY MESSAGES</b></p> <ol style="list-style-type: none"> <li>1. WASH and vaccination interventions can prevent typhoid. When integrated, they can have maximal impact</li> <li>2. In the long-term, prevention is cheaper and more effective than treatment, and can have ripple effects on antimicrobial resistance and other diseases</li> <li>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</li> <li>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</li> </ol> <div style="display: flex; justify-content: space-between; align-items: center; margin-top: 20px;">   </div>	<p>During this module, you should have gained the following key points:</p> <p>First, WASH and vaccination interventions can prevent typhoid and, when integrated, can have maximal impact.</p> <p>Secondly, prevention is cheaper and more effective in the long-term than treatment, and can have ripple effects on antimicrobial resistance and other diseases.</p> <p>Third, 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.</p> <p>Fourth, 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 two. Vaccination programs are immediate and can offer widespread protection.</p> <p>Are there any questions before we move on to the final module on related diseases?</p>



## MODULE 6: RELATED DISEASES

Slide Number		Facilitator Tips
79		<p>This module will provide an overview of two typhoid-related diseases, paratyphoid and invasive nontyphoidal <i>Salmonella</i> disease.</p>
80	<p style="text-align: center;"><b>LEARNING OBJECTIVES</b></p> <p><b>In this module, you will:</b></p> <ol style="list-style-type: none"> <li>1. Learn about paratyphoid and invasive nontyphoidal <i>Salmonella</i> (iNTS) disease</li> <li>2. Observe global trends for paratyphoid and iNTS disease</li> <li>3. Review at risk groups for paratyphoid and iNTS disease</li> </ol> 	<p>By the end of this module, you will:</p> <ul style="list-style-type: none"> <li>• Learn about paratyphoid and invasive nontyphoidal <i>Salmonella</i> (iNTS) disease</li> <li>• Observe global trends for paratyphoid and iNTS disease</li> <li>• Review at risk groups for paratyphoid and iNTS disease</li> </ul>
81	<p style="text-align: center;"><b>THE OTHER ENTERIC FEVER: PARATYPHOID</b></p> <ul style="list-style-type: none"> <li>• Paratyphoid is caused by <i>Salmonella enterica</i> serotype Paratyphi A, B, or C</li> <li>• S. Typhi and S. Paratyphi are commonly known as enteric fevers</li> <li>• Paratyphoid is clinically similar to typhoid, but is generally milder with a shorter incubation period</li> <li>• Humans are the only reservoir for S. Paratyphi             <ul style="list-style-type: none"> <li>• Bacteria are transmitted by consumption of contaminated water and food (fecal-oral route)</li> </ul> </li> </ul> 	<p>We mentioned in an earlier module that typhoid is also known as an “enteric fever”, a term which refers to both typhoid and paratyphoid.</p> <p>Paratyphoid is caused by <i>Salmonella enterica</i> serotypes Paratyphi A, B, or C. You’ll remember that typhoid is caused by <i>Salmonella enterica</i> serotype Typhi, so you can see that these two diseases are closely related.</p> <p>Paratyphoid is clinically similar to typhoid, producing many of the same types of symptoms, but it’s generally milder and has a shorter incubation period.</p> <p>Like with typhoid, humans are the only reservoir for paratyphoid. The bacteria is transmitted through the fecal-oral route by consuming contaminated water and food.</p>

<p>82</p>	<p><b>PREVALENCE AND DISTRIBUTION OF PARATYPHOID</b></p> <ul style="list-style-type: none"> <li>• S. Paratyphi A is most common with 4.5 million cases per year <ul style="list-style-type: none"> <li>• 8% relapse rate</li> </ul> </li> <li>• Southeast Asia and the Indian subcontinent are experiencing increasing incidences of S. Paratyphi A <ul style="list-style-type: none"> <li>• S. Paratyphi A can account for up to 50% of <i>Salmonella</i> isolates among patients with enteric fever in some countries</li> </ul> </li> <li>• Unlike typhoid and nontyphoidal <i>Salmonella</i>, there is not a high burden of paratyphoid in Sub-Saharan Africa <ul style="list-style-type: none"> <li>• Some cases seen in West Africa</li> </ul> </li> </ul>  	<p>Paratyphoid is not as widespread as typhoid. There are about 4.5 million cases per year, the majority caused by S. Paratyphi A. There is an estimated 8% relapse rate.</p> <p>Incidence of paratyphoid is highest in Southeast Asia and the Indian subcontinent, which is experiencing rising rates of Paratyphoid A. In some places, Paratyphoid A can account for up to half of <i>Salmonella</i> bloodstream isolates among patients with enteric fever—meaning that in some places in Southeast Asia and the Indian subcontinent, paratyphoid is as common as typhoid.</p> <p>Unlike typhoid and nontyphoidal <i>Salmonella</i>, however, there isn't a high burden of paratyphoid in Sub-Saharan Africa. It has been in seen in small numbers in West Africa, but has never been seen in Southern, Central or Eastern Africa.</p>
<p>83</p>	<p><b>PARATYPHOID DIAGNOSIS AND TREATMENT</b></p> <p><b>Clinical Diagnosis:</b></p> <ul style="list-style-type: none"> <li>• S. Paratyphi A symptoms include fever, jaundice, thrombosis, rose spots and systemic infections</li> <li>• S. Paratyphi B has similar non-specific febrile illness symptoms but can also have symptoms similar to non-specific salmonella gastroenteritis</li> </ul> <p><b>Laboratory Diagnosis:</b></p> <ul style="list-style-type: none"> <li>• No reliable serological test</li> <li>• Bone marrow or blood culture is gold standard</li> </ul> <p><b>Treatment:</b></p> <ul style="list-style-type: none"> <li>• Treated with antibiotics depending on the sensitivity patterns of S. Paratyphi isolates in the area</li> </ul> <p><b>Complications:</b></p> <ul style="list-style-type: none"> <li>• Similar to S. Typhi, complications include intestinal perforation, meningitis and multi-organ abscesses</li> </ul>  	<p>Much of the process of diagnosis and treatment for paratyphoid is similar to that for typhoid. Paratyphoid A, which is the most common paratyphoid serotype, has symptoms including fever, jaundice, thrombosis, and systemic infections. Paratyphoid B, which is much rarer, has similar non-specific symptoms, but can also have symptoms more similar to gastroenteritis.</p> <p>There is no reliable serological test for paratyphoid. As in typhoid, bone marrow or blood culture is the best way to determine paratyphoid. A laboratory test is necessary to distinguish between typhoid and paratyphoid.</p> <p>Strategies and challenges of treating paratyphoid are similar to those for typhoid. Paratyphoid is treated with different antibiotics, depending on the sensitivity patterns of paratyphoid isolates in the area.</p> <p>Complications are similar to typhoid, including intestinal perforation, meningitis and multi-organ abscesses.</p>

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**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



Paratyphoid can be prevented with the same WASH interventions discussed in the previous module, as it is spread through the fecal-oral pathway. The challenges for WASH interventions remain the same as we've discussed—namely, slow to implement and expensive.

Currently, there's no licensed paratyphoid vaccine, although four vaccines are in development. There's a growing urgency for paratyphoid vaccines due to a rise in incidence for Paratyphoid A, emerging drug resistance, and evidence that Paratyphoid A has a greater tendency towards resistance than S. Typhi. Drug resistance has the same impact on treatment of the disease as it does on typhoid: treatment becomes more expensive, difficult, and time consuming, so prevention becomes more necessary.

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**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



Tsai YC, Wang B, Wang J, Wang S, Zhang J, Zhou Y, et al. (2010) A Large-Scale Enteric Fever Outbreak in China Caused by Imported Wastewater. PLoS ONE 5(12): e139874. doi:10.1371/journal.pone.0139874



Let's take a look at a paratyphoid outbreak in China. Beginning in 1998, paratyphoid began to be increasingly reported in China. In 2010, an outbreak of 601 cases of paratyphoid was reported in Yuanjiang county.

The cause of the outbreak was identified as raw vegetables sold at a market. The vegetables were grown on land near a hospital. A severe drought forced farmers to use improperly treated wastewater from the hospital rather than spring water to irrigate their vegetables. The isolates from the outbreak cases matched those in the wastewater. This created a cycle of continuous contamination and infection in the community.

In order to stop the outbreak, authorities prohibited the selling of raw vegetables at restaurants and prohibited planting vegetables in contaminated fields. The hospital also enacted more thorough procedures to disinfect their wastewater.

What do you notice about this case that stands out to you?

		<p>[Discussion can touch on the method(s) of transmission in this case, the possible impact of drought and weather conditions on disease spread and wider implications of that, and their opinion of the effectiveness of the interventions used to stop the outbreak.]</p>
86	<p><b>NONTYPHOIDAL <i>SALMONELLA</i> (NTS) &amp; INVASIVE NONTYPHOIDAL <i>SALMONELLA</i> (iNTS) DISEASE</b></p> <ul style="list-style-type: none"> <li>• NTS is a major cause of diarrheal disease globally <ul style="list-style-type: none"> <li>• 93 million infections per year</li> <li>• Estimated 4.8 million disability-adjusted life years lost in 2010</li> </ul> </li> <li>• iNTS disease is a top cause of bloodstream infection <ul style="list-style-type: none"> <li>• iNTS disease is most commonly caused by <i>S. enterica</i> serovars Typhimurium and Enteritidis</li> <li>• 3.4 million infections estimated in 2010</li> <li>• Case fatality rate of 20-25%</li> <li>• True incidence likely unknown</li> <li>• Global ratio of NTS to iNTS disease is 28:1, but 1:1 in Africa</li> </ul> </li> </ul>  	<p>We're now going to discuss nontyphoidal <i>Salmonella</i> (or NTS) and invasive nontyphoidal <i>Salmonella</i> (or iNTS) disease.</p> <p>NTS, caused by <i>Salmonella</i> bacteria that aren't <i>S. Typhi</i> or <i>S. Paratyphi</i>, is a major cause of diarrheal disease globally, causing 93 million infections per year. An estimated 4.8 million Disability Adjusted Life Years (DALYs) are lost per year due to NTS.</p> <p>iNTS disease, which is when NTS invades the bloodstream, is a top cause of bloodstream infection and most commonly caused by <i>Salmonella enterica</i> serovars Typhimurium or Enteritidis. In 2010, there were an estimated 3.4 million iNTS disease infections, with a case-fatality rate of 20-25%. However, estimates of iNTS disease incidence and mortality are not well documented.</p> <p>Knowledge of iNTS disease is low because there is a dearth of population-based surveillance data on bloodstream infections in Africa, where the burden of iNTS disease is heaviest. While the global ratio of NTS to iNTS disease is 28:1, studies have shown that the ratio of NTS to iNTS disease in Africa is 1:1, meaning that the invasive version of nontyphoidal salmonella is just as common as the non-invasive.</p>

<p>87</p>	<p><b>iNTS DISEASE: GEOGRAPHIC DISTRIBUTION AND TRANSMISSION</b></p> <ul style="list-style-type: none"> <li><b>Distribution:</b> Most prevalent in Sub-Saharan Africa <ul style="list-style-type: none"> <li>Almost 2 million cases in 2010 in Sub-Saharan Africa</li> <li>Incidence is highest among children and middle aged adults</li> </ul> </li> <li><b>Transmission:</b> Little is known about environmental reservoirs and main methods of transmission <ul style="list-style-type: none"> <li>Transmission for iNTS disease may differ greatly from observable transmission patterns for NTS in high-income countries</li> <li>It is thought that transmission between humans – inside and outside health care facilities – may be important in Sub-Saharan Africa</li> </ul> </li> </ul>  	<p>iNTS disease is most prevalent in Sub-Saharan Africa. In 2010, there were almost 2 million cases of iNTS disease in Sub-Saharan Africa with incidence highest among children and middle-aged adults.</p> <p>Little is known about the main methods of transmission for iNTS disease or about environmental reservoirs, especially how they may differ from transmission patterns observed for NTS infection in high-income nations. It is thought that transmission between humans—possibly inside health care facilities—may be important in Sub-Saharan Africa.</p>
<p>88</p>	<p><b>iNTS DISEASE RISK FACTORS</b></p> <p><b>Age:</b></p> <ul style="list-style-type: none"> <li>Children aged 12-18 months old</li> <li>Adults aged 25-45 years old</li> </ul> <p><b>Other immune defects:</b></p> <ul style="list-style-type: none"> <li>HIV <ul style="list-style-type: none"> <li>20% of African children with iNTS disease are HIV infected</li> <li>95% of adult iNTS disease cases are infected with HIV</li> </ul> </li> <li>Malaria</li> <li>Malnutrition</li> <li>Sickle cell anemia</li> </ul> <p><b>Environment:</b></p> <ul style="list-style-type: none"> <li>Peaks during rainy season coinciding with increased incidences of malaria and malnutrition</li> </ul>  	<p>Children aged 12-18 months and adults 25-45 years old are at the highest risk for iNTS disease. The disease largely impacts those suffering from immune defects. In children, it is often associated with malnutrition, while in adults, iNTS disease is particularly associated with HIV, although HIV increases risk in both adults and children.</p> <p>20% of African children with iNTS disease are also HIV infected, while 95% of adult iNTS disease cases are infected with HIV. Other conditions like malaria and sickle cell anemia are associated with iNTS disease.</p> <p>It's possible that there are environmental factors as well. iNTS disease peaks during the rainy season, but this also coincides with increased incidence of malaria and malnutrition.</p>
<p>89</p>	<p><b>iNTS DISEASE DIAGNOSIS AND TREATMENT</b></p> <p><b>Diverse clinical presentation:</b></p> <ul style="list-style-type: none"> <li>Fever</li> <li>Hepatosplenomegaly (swelling of the liver and spleen)</li> <li>Respiratory symptoms</li> <li>Diarrhea is often absent</li> </ul> <p><b>Symptoms are nonspecific:</b></p> <ul style="list-style-type: none"> <li>Can be confused with malaria and pneumonia</li> <li>Laboratory tests are needed to confirm diagnosis</li> </ul> <p><b>Treatment:</b></p> <ul style="list-style-type: none"> <li>Antimicrobial treatment</li> <li>Growing antimicrobial resistance has led to the need of more expensive treatments</li> </ul>  	<p>iNTS disease has a diverse clinical presentation. Most often, it presents as fever, hepatosplenomegaly, meaning enlargement of liver and spleen, and respiratory symptoms. Unlike in NTS, diarrhea is often absent.</p> <p>The symptoms of iNTS disease are nonspecific and easily confused for those of malaria and pneumonia, so laboratory tests are needed to confirm diagnosis.</p> <p>Treatment for iNTS disease is done with antimicrobials. However, like in typhoid and paratyphoid, growing antimicrobial resistance is</p>

		<p>a problem in iNTS disease leading to the need for more expensive treatments.</p> <p>Additionally, treatments often have to vary as many patients already have a different disease (HIV, Malaria), so treatment must take into account any co-infections.</p>
90	<p><b>NTS &amp; iNTS DISEASE PREVENTION</b></p> <ul style="list-style-type: none"> <li>• Need for surveillance in order to tailor prevention methods by determining: <ul style="list-style-type: none"> <li>• True burden of disease</li> <li>• Disease trends</li> </ul> </li> <li>• No vaccine currently available, but there are efforts to advance vaccines against the most common serotypes of NTS</li> <li>• Vaccines could target: <ul style="list-style-type: none"> <li>• Immunosuppressed persons (living with HIV)</li> <li>• People at risk of malaria</li> <li>• People living with food insecurity</li> </ul> </li> <li>• Non-vaccine prevention efforts require more understanding of NTS sources and modes of transmission</li> </ul>  	<p>A lack of knowledge about NTS and iNTS disease is a major challenge to implementing both vaccine and non-vaccine prevention methods. NTS and iNTS disease surveillance could tell us the true burden of the disease as well as disease trends.</p> <p>Currently there is no vaccine available, but there are efforts underway to advance vaccines against the most common serotypes of NTS. These vaccines could target immunosuppressed people — those living with HIV, for example — people at risk of malaria, and people living with food insecurity.</p> <p>Non-vaccine prevention efforts would require more understanding of sources and modes of transmission.</p>
91	<p><b>SNAPSHOT: iNTS DISEASE IN MALAWI</b></p> <ul style="list-style-type: none"> <li>• 2001-2004: iNTS disease epidemic peaks in Malawi</li> <li>• Post-2004: Incidences fall</li> <li>• Multiple public health interventions were implemented: <ul style="list-style-type: none"> <li>• 2004: Roll-out of antiretroviral therapy (ART)</li> <li>• 2005: Fertilizer subsidy program for subsistence farmers begins to combat malnutrition</li> <li>• 2007: Introduced malaria control interventions</li> </ul> </li> <li>• A study reviewed trends in monthly numbers of childhood iNTS disease at Queen's Hospital, Blantyre, Malawi from 2002-2010 <ul style="list-style-type: none"> <li>• Data suggested that decline in iNTS disease is due to these interventions</li> <li>• Estimated that around 50% of the iNTS disease decline is explained by a decline in malaria</li> <li>• 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)</li> </ul> </li> </ul>   <p><small>Phelan, M. A., Bhatti, D., Haeghebaert, B., Kibwanda, A., Kageyama, A., Cori, R., Hens, N., et al. (2017). Modeling the contribution of water, HIV, fertilizer and control to the decline in childhood invasive meningitis in Blantyre, Malawi. <i>PLoS Neglected Tropical Diseases</i>, 11(12), e0005679. <a href="https://doi.org/10.1371/journal.pntd.0005679">https://doi.org/10.1371/journal.pntd.0005679</a></small></p>	<p>To look at preventing iNTS disease in the field, let's take a snapshot of Malawi, where an iNTS disease epidemic peaked from 2001 to 2004. Remember, there's a strong epidemiological association between malaria, malnutrition, and HIV and iNTS disease. This snapshot highlights those linkages.</p> <p>Incidence of iNTS disease fell after 2004, when multiple public health interventions were implemented. 2004 saw a roll-out of antiretroviral therapy, used to manage HIV. In 2005, a fertilizer subsidy program for subsistence farmers began in order to combat malnutrition, and malaria control interventions went into gear in 2007.</p> <p>Data from a study at Queen's Hospital in Blantyre from 2002 to 2010 suggested that the decline in iNTS disease was due to these interventions. The study estimated that around 50% of the iNTS disease decline is explained by a decline in malaria, while the other</p>

		<p>estimated 50% is explained by changes in the local epidemiology of HIV—both directly and through its impact on malnutrition.</p>
<p>92</p>	<p style="text-align: center;"><b>KEY MESSAGES</b></p> <ol style="list-style-type: none"> <li>1. Paratyphoid, known along with typhoid as enteric fever, is spreading in Southeast Asia and is concerning due to its growing antimicrobial resistance</li> <li>2. NTS and iNTS disease are 2 of the main causes of diarrheal disease and bloodstream infection in Sub-Saharan Africa</li> <li>3. Paratyphoid, NTS and iNTS disease do not have vaccines currently available to prevent the diseases in vulnerable populations</li> </ol> <div style="display: flex; justify-content: space-between; align-items: center; margin-top: 20px;">   </div>	<p>In this module, you should have learned the following key messages.</p> <p>First, paratyphoid, which is known along with typhoid as enteric fever, is showing higher incidence rates in Southeast Asia. This is concerning due to its growing antimicrobial resistance.</p> <p>Second, NTS and iNTS disease are two of the main causes of diarrheal disease and bloodstream infection in Sub-Saharan Africa.</p> <p>Third, paratyphoid, NTS and iNTS disease do not have vaccines currently available to prevent the diseases in vulnerable populations.</p> <p>This is the final module of this program. Are there any questions?</p>
<p>93</p>	<p style="text-align: center;"><b>REFERENCES</b></p> <ol style="list-style-type: none"> <li>1. Buckle, G. C., Walker, C. L. F., &amp; Black, R. E. (2012). Typhoid fever and paratyphoid fever: Systematic review to estimate global morbidity and mortality for 2010. <i>Journal of Global Health</i>, 2(1), 10401. <a href="https://doi.org/10.7195/jogh.02.010401">https://doi.org/10.7195/jogh.02.010401</a></li> <li>2. Martin, L. B., Simon, R., MacLennan, C. A., Tonant, S. M., Sahastrabudhu, S., &amp; Khan, M. I. (2018). Status of paratyphoid fever vaccine research and development. <i>Vaccine</i>, 36(29), 2000–2002. <a href="https://doi.org/10.1016/j.vaccine.2018.08.100">https://doi.org/10.1016/j.vaccine.2018.08.100</a></li> <li>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, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2015. <i>Lancet</i>, 2016, 388: 1545–602.</li> <li>4. Bhan, M. K., Bahl, R., Bhatnagar, S., Oshihai, Y., Itumiya, H., &amp; Watanabe, H. (2000). Typhoid and paratyphoid fever. <i>Lancet (London, England)</i>, 356(9487), 749–62. <a href="https://doi.org/10.1016/S0140-6736(00)87181-4">https://doi.org/10.1016/S0140-6736(00)87181-4</a></li> <li>5. Crump, J. A., &amp; Mintz, E. D. (2010). Global trends in typhoid and paratyphoid fever. <i>Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America</i>, 50(2), 241–8. <a href="https://doi.org/10.1093/cid/cir041">https://doi.org/10.1093/cid/cir041</a></li> <li>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. <i>PLoS Neglected Tropical Diseases</i>, 9(7), e0003859. <a href="https://doi.org/10.1371/journal.pntd.0003859">https://doi.org/10.1371/journal.pntd.0003859</a></li> <li>7. Ao, T. T., Feeley, N. A., Gordon, M. A., Keddy, K. H., Angulo, F. J., &amp; Crump, J. A. (2015). Global Burden of Invasive Nontyphoidal Salmonella Disease, 2010. <i>Emerging Infectious Diseases</i>, 21(8), 941–949. <a href="https://doi.org/10.3201/eid2108.143999">https://doi.org/10.3201/eid2108.143999</a></li> <li>8. Feeley, N. A., Dougan, S., Kingsley, R. A., Heyderman, R. S., &amp; Gordon, M. A. (2012). Invasive non-typhoidal salmonella disease: an emerging and neglected tropical disease in Africa. <i>Lancet (London, England)</i>, 379(9839), 2498–99. <a href="https://doi.org/10.1016/S0140-6736(11)61752-2">https://doi.org/10.1016/S0140-6736(11)61752-2</a></li> <li>9. Crump, J. A., &amp; Heyderman, R. S. (2015). A Perspective on Invasive Salmonella Disease in Africa. <i>Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America</i>, 61 Suppl 4(Suppl 4), S235–40. <a href="https://doi.org/10.1093/cid/civ029">https://doi.org/10.1093/cid/civ029</a></li> <li>10. Feeley, N. A., Everett, D., Faragher, E. B., Rosa-Felner, A., Kang'ambwa, 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. <i>PLoS Neglected Tropical Diseases</i>, 9(7), e0003579. <a href="https://doi.org/10.1371/journal.pntd.0003579">https://doi.org/10.1371/journal.pntd.0003579</a></li> </ol> <div style="display: flex; justify-content: space-between; align-items: center; margin-top: 20px;">   </div>	<p style="text-align: center;">“References”</p>