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

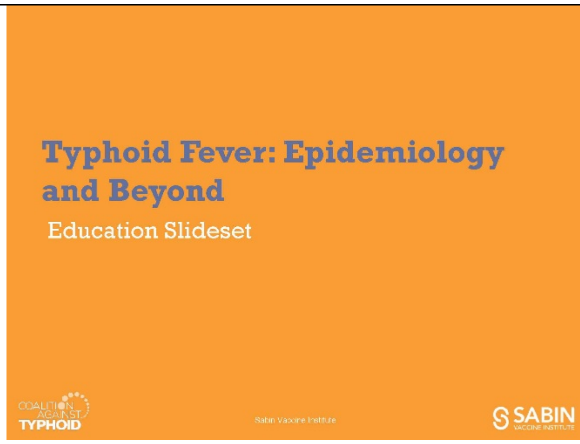
MATERIALS/EQUIPMENT

- Computer
- Projector

RESOURCES/HANDOUTS

- PowerPoint presentation

<u>Guide to Module 1:</u>

<table>
<tr><th colspan="3">MODULE 1: TYPHOID EPIDEMIOLOGY</th></tr>
<tr><td>Slide Number</td><td></td><td>Facilitator Tips</td></tr>
<tr><td>1</td><td>
</td><td> 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. 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. At the end of it, I hope you will come away with a basic understanding of enteric fever. </td></tr>
<tr><td>2</td><td>
</td><td>This first module will cover the epidemiology of typhoid.</td></tr>
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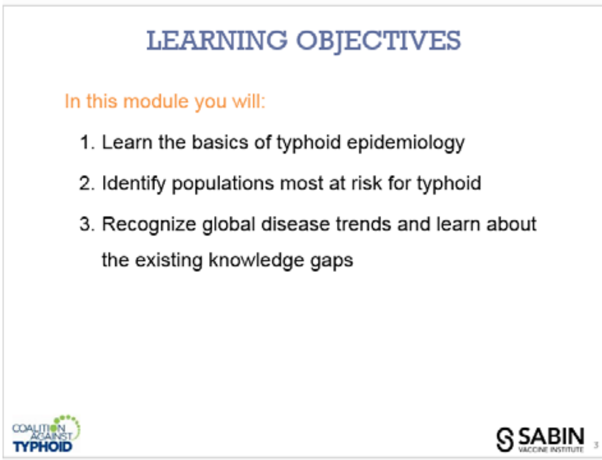
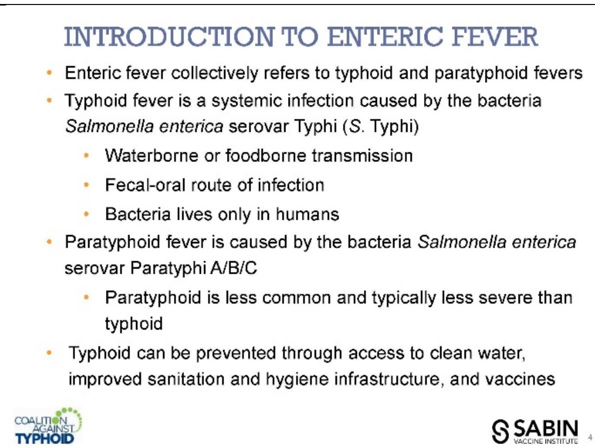
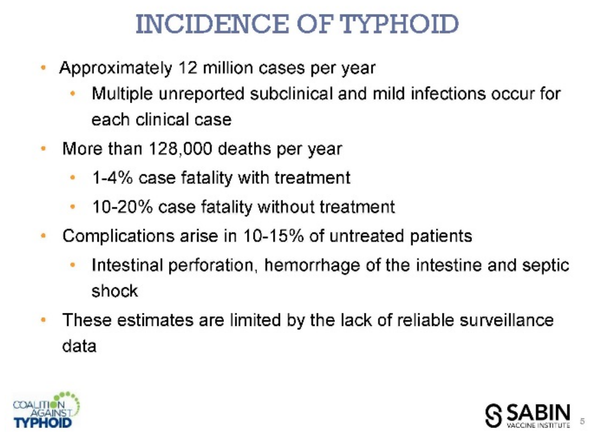
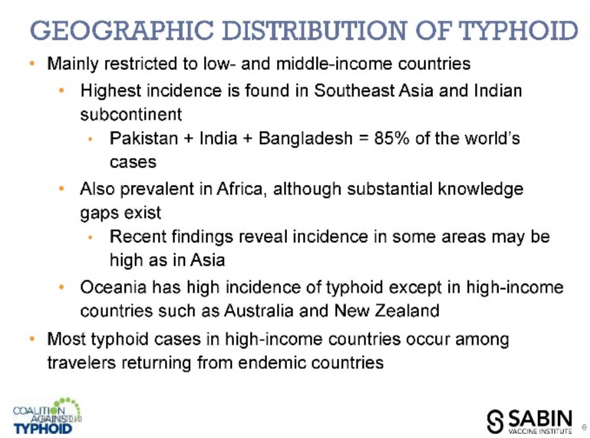
3		In this module, you will: • Learn the basics of typhoid epidemiology • Identify populations most at risk for typhoid • Recognize global disease trends and learn about the existing knowledge gaps
4		Enteric fever collectively refers to typhoid and paratyphoid fevers. Typhoid fever is a systemic infection caused by the bacteria *Salmonella enterica* serovar Typhi, also commonly known as *S.* Typhi. A serovar, for those wondering, is a distinct variation in a bacterial species. Typhoid is waterborne or foodborne, transmitted through the fecal-oral route, meaning an infected person will shed *S.* Typhi bacteria in their fecal matter, which might, for example, end up in a water source and infect the person consuming that water. *S.* Typhi bacteria only lives in humans. The transmission process is covered more deeply in Module 2. Paratyphoid fever is caused by the bacteria *Salmonella enterica* 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. Typhoid can be prevented through access to clean water, improved sanitation and hygiene infrastructure, and vaccines.

		Specific preventative measures will be discussed in Module 5. For now, let's move on to the prevalence of typhoid.
5		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. 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. *[Drug resistance, which threatens these numbers, will be covered in Module 4]* Complications develop in 10-15% of untreated patients. Complications can include intestinal perforation, hemorrhage of the intestine and septic shock. 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.
6		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. 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. 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.

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<tr>
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<td>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.</td>
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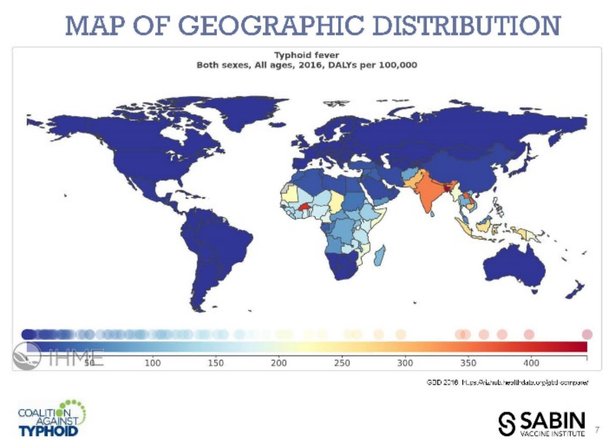
<td>
</td>
<td>On this map you can see the distribution of typhoid and the countries most at risk.

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.

You can also see the high concentration of typhoid in the Indian sub-continent.</td>
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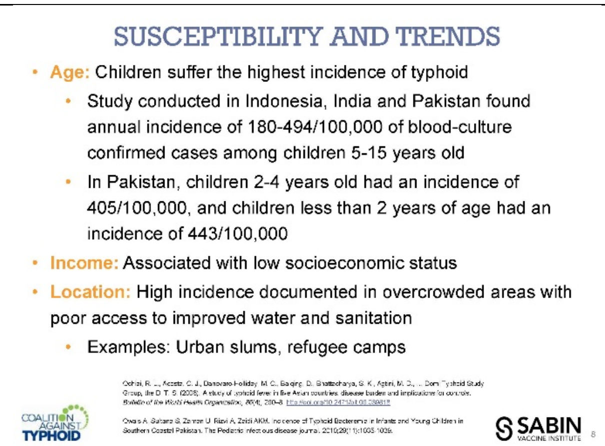
<td>
</td>
<td>There are certain factors that make people more susceptible to typhoid. One of them is age. Children suffer the highest incidence of typhoid, according to studies. A study conducted in Indonesia, India and Pakistan found an annual incidence of 180-494 blood-culture confirmed cases per 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.

Another factor is income. Typhoid is associated with low socio-economic status and is a disease of inequity, disproportionally impacting those that do not have access to clean water or improved sanitation infrastructure.

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.</td>
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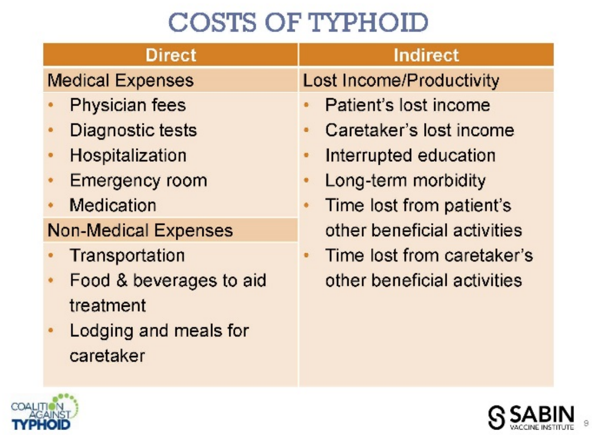

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<td>
In this chart, you can see both the direct and indirect costs of typhoid on a patient. Beyond paying hospitalization fees, a direct cost of typhoid, patients and their caretakers lose income from time off from their employment. For children, a 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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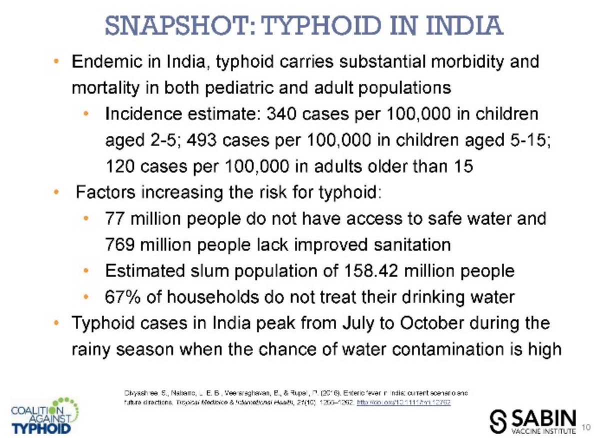

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<td>
Now, let's zoom in and take a country-level look at typhoid in India. Typhoid is endemic in India, with incidence rate estimates of 340 per 100,000 in children 2-5, 493 per 100,000 in children 5-15, and 120 per 100,000 in adults older than 15.

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.
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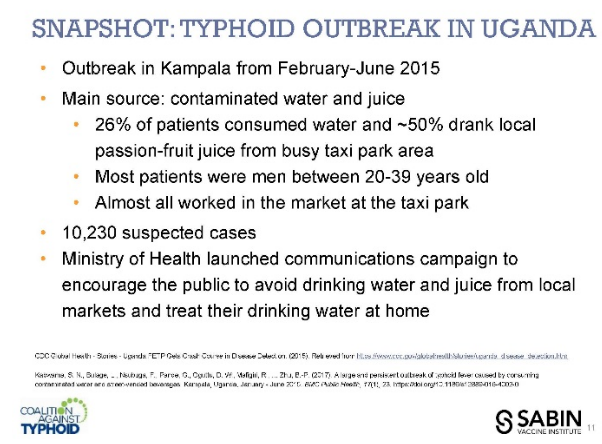
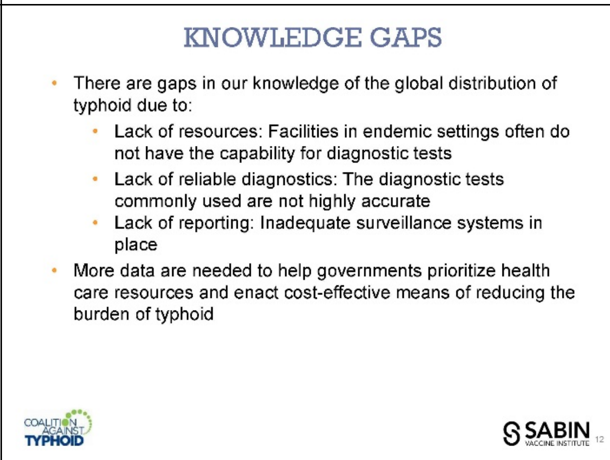
11		Let’s take a closer look at typhoid in a different part of the world. An outbreak of typhoid spread in Kampala, Uganda, from February to June 2015. The main source of the outbreak was contaminated water and juice. Twenty-six percent of patients consumed water and 50% of patients consumed passion-fruit 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. 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. 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.
12		You may have noticed during the previous slides that there is a lot that we still don’t know about typhoid. 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. Data on typhoid is important to help governments prioritize health care

		resources cost-effectively to reduce the typhoid burden.

13	**TYPHOID AND SUSTAINABLE DEVELOPMENT**
	• Typhoid is linked to socioeconomic inequity and stands as an obstacle to ending poverty
	• Typhoid control is important to reaching multiple Sustainable Development Goals, including:
	  • Goal 3: Ensure healthy lives and promote well-being for all at all-ages
	  • Goal 6: Ensure availability and sustainable management of water and sanitation for all
	  • Goal 10: Reduce inequality within and among countries
	• An estimated 1.8 billion people use a source of drinking water that is contaminated with fecal matter, putting them at risk of contracting typhoid fever
	COALITION AGAINST TYPHOID SABIN VACCINE INSTITUTE 13
		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.
		
		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.”
		
		What other SDGs can you think of that typhoid relates to?
		
		[*Possible answers: Goal 1: No Poverty, Goal 6: Clean Water and Sanitation.*]
		
		As we go over the other modules, keep this global context for typhoid in mind.

14	**MODULE 1 KEY MESSAGES** 1. Typhoid is a preventable bacterial infection spread through contaminated food and water, impacting millions of people in low- and middle-income countries 2. Typhoid is estimated to be most prevalent in school-age children, people of low socioeconomic status and those living in high-density areas, such as urban slums 3. Lack of resources, including diagnostic tools and surveillance networks, makes it difficult to know the real disease burden 4. Typhoid is an obstacle to sustainable development and reducing inequality COALITION AGAINST TYPHOID SABIN VACCINE INSTITUTE 14	As we conclude this module, let’s review a couple of key takeaways: Typhoid is a preventable bacterial infection spread through contaminated food and water. It impacts millions of people in low- and middle-income countries. Typhoid is estimated to be most prevalent in school-age children, people of low socio-economic status and those living in high-density areas.

<table>
<tr><td></td><td></td><td>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?</td></tr>
<tr><td>15</td><td>
REFERENCES
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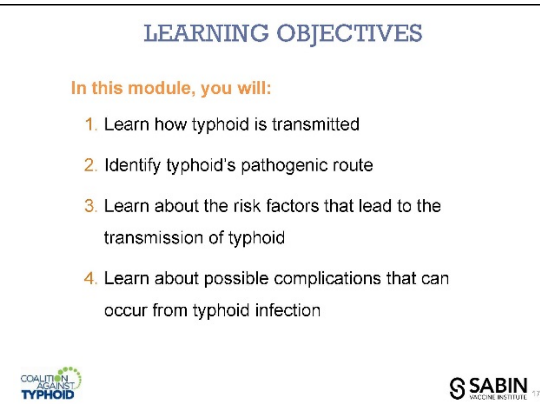
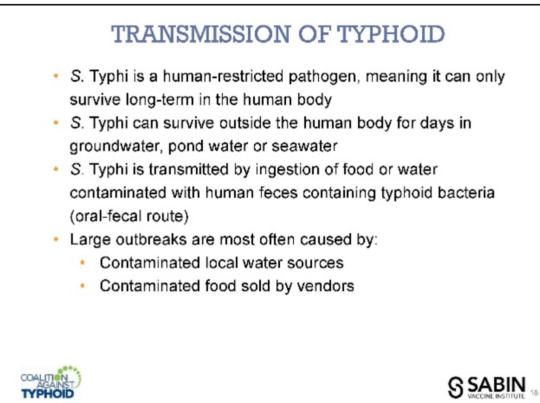
<table>
<tr><th colspan="3">MODULE 2: TRANSMISSION AND PATHOGENESIS</th></tr>
<tr><th>Slide Number</th><th></th><th>Facilitator Tips</th></tr>
<tr><td>16</td><td>
</td><td>In this module, we’ll be building off the introductory knowledge of typhoid gained in Module 1 to talk about the transmission and pathogenesis of typhoid.</td></tr>
<tr><td>17</td><td>
</td><td>In this module, you will learn:
How typhoid is transmitted
Typhoid’s pathogenic route
The risk factors that lead to the transmission of typhoid
Possible complications that can occur</td></tr>
<tr><td>18</td><td>
</td><td>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.

S. Typhi can only survive long-term in the human body. It can only survive for several days in different water sources.

As we learned, typhoid is transmitted through the ingestion of food or water contaminated with human feces containing typhoid bacteria.

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?

[Possible discussion topic: how food and water vendors might spread typhoid to a large</td></tr>
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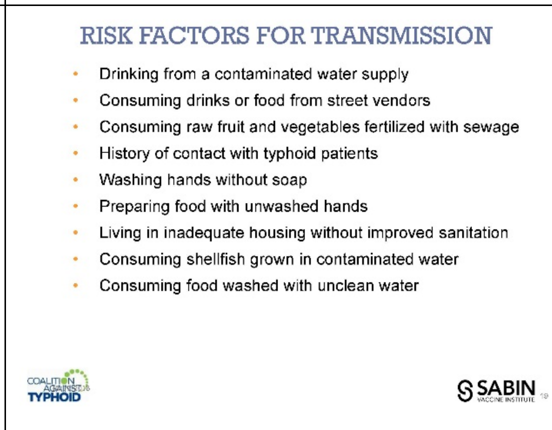
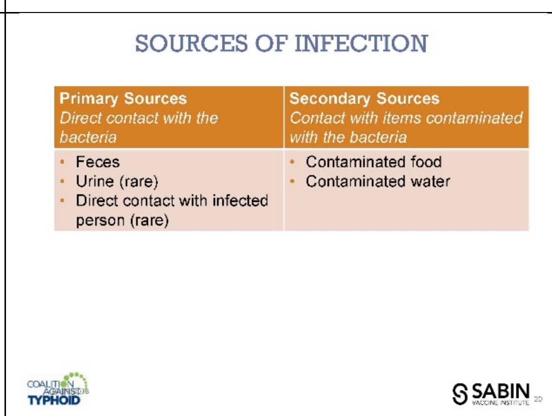
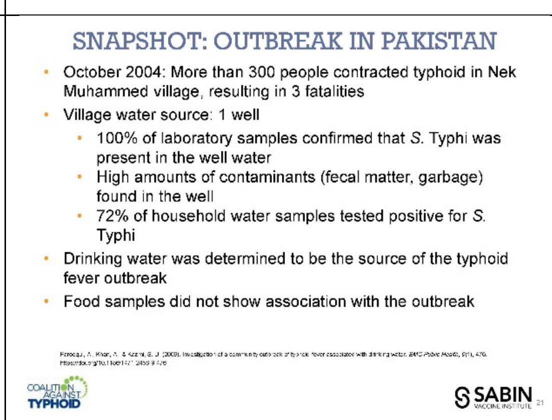
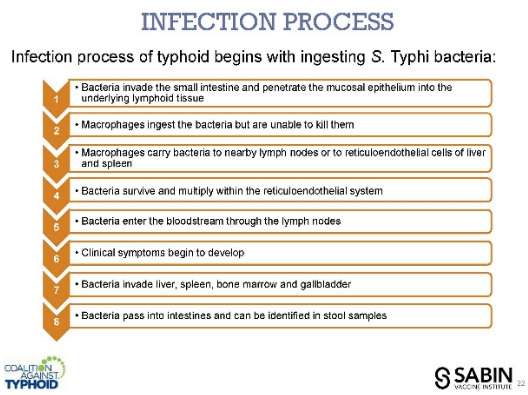
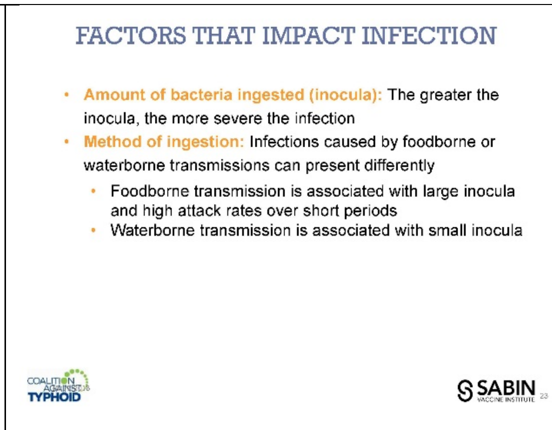
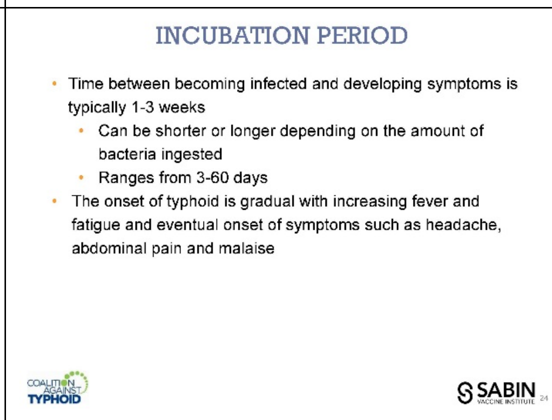
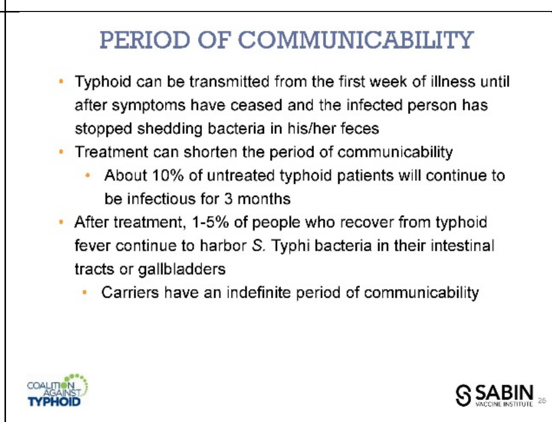
		number of people if they have unwashed hands or are using water from a contaminated source.]
19		Certain factors can increase the risk of typhoid transmission. These can include: • Drinking from a contaminated water supply • Consuming drinks or food from street vendors • Consuming raw fruit and vegetables fertilized with sewage • History of contact with typhoid patients • Washing hands without soap • Preparing food with unwashed hands • Living in inadequate housing without improved sanitation • Consuming shellfish grown in contaminated water • Consuming food washed with unclean water You can see how all of these increase the chance for typhoid bacteria to be consumed.
20		Primary sources of infection involve direct contact with the bacteria; for example, coming in contact with feces containing the typhoid bacteria. Secondary sources of infection are more common and involve contact with items contaminated by the bacteria, like food or water.
21		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. There was one well that served as the village water source. All the lab samples found that *S.* Typhi was present in the well water, and high amounts of contaminants like fecal matter were found in the well. Additionally, 72% of the

		households’ water supplies tested positive for *S.* Typhi. Therefore the drinking water was determined to be the source of the outbreak. In this village, one single well was able to infect more than 300 people.
22		The infection process for typhoid begins with ingesting *S.* Typhi 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. 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. [*Mesenteric refers to the tissues that attach the intestines to the wall of the abdomen.* *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.*]

23		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. 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.
24		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. Typhoid symptoms appear gradually and usually take the form of fever and fatigue at the beginning, and later headache, abdominal pain and malaise.
25		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. 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.

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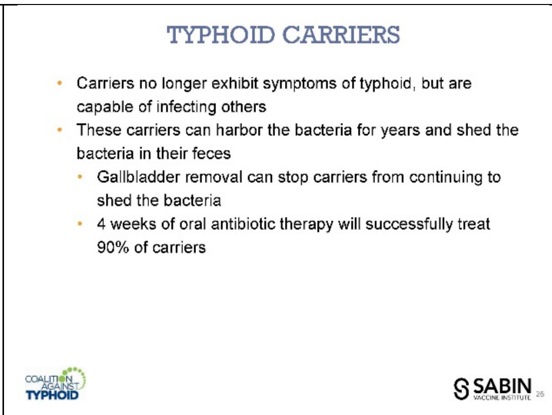
<td>
</td>
<td>Some people may not realize they are carriers, as they will no longer exhibit symptoms of typhoid. They also may have had a mild case of typhoid and felt no need to seek treatment, but continue to shed the bacteria unknowingly. Carriers can continue to harbor and shed bacteria in their feces for years.

Modern medicine can treat typhoid carriers through gallbladder removal or antibiotic treatment.

Carriers are still capable of infecting others. In the next slide we talk about the most famous typhoid carrier.</td>
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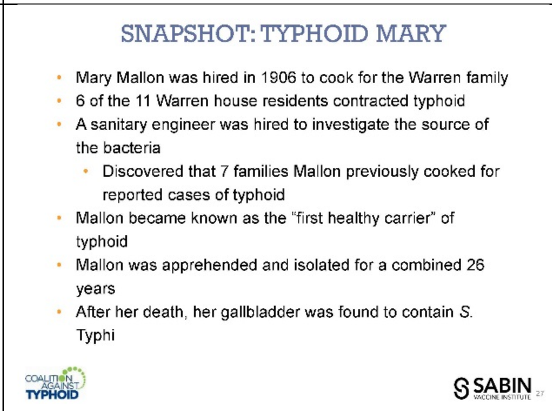
<td>
</td>
<td>Mary Mallon, also known as Typhoid Mary, was a cook for the Warren family in the United States. When several members of the family contracted typhoid, a sanitary engineer discovered that the previous seven families Mallon had cooked for had also reported cases of typhoid.

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 S. Typhi. However, these days medicine is usually able to stop a carrier from infecting others.

Mary's story shows how many people silent carriers are able to infect unknowingly.</td>
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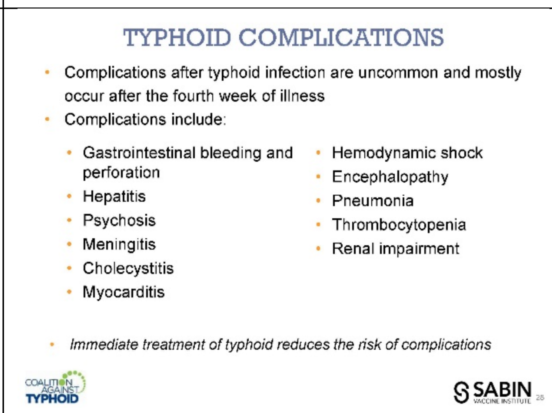
<td>28</td>
<td>
</td>
<td>Complications after typhoid infection are uncommon and mostly occur after the fourth week of illness. On the slide is a list of other typhoid complications. Of these, the most common and significant typhoid complications are intestinal bleeding and perforation. Timely diagnostics and treatment is important to prevent patients from developing complications</td>
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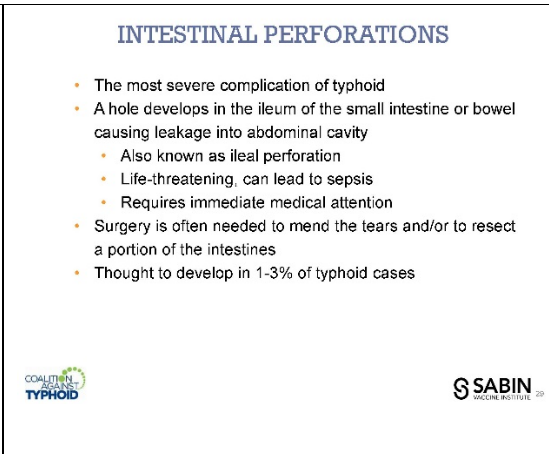
<tr>
<td>29</td>
<td>
</td>
<td>Intestinal perforation, the most severe typhoid complication, is when a hole develops in the small intestine, causing leakage into the abdominal cavity. Because this hole most often forms in the ileum of the small intestine, it is also known as ileal perforation. This 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.</td>
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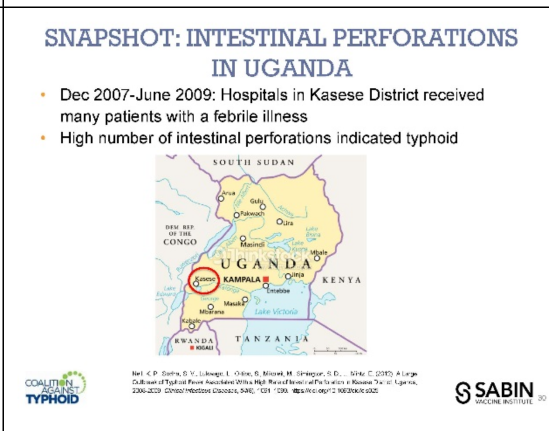
<td>30</td>
<td>
</td>
<td>An outbreak in Uganda from 2007-2009 had an unusually high percentage of intestinal perforations.

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.</td>
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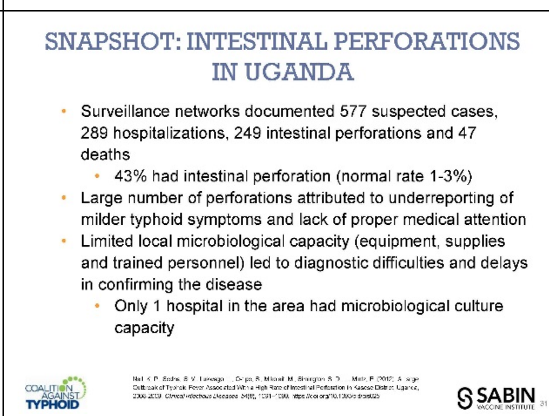
<td>31</td>
<td>
</td>
<td>Surveillance networks in the area then documented 577 suspected typhoid cases, 289 hospitalizations, 249 intestinal perforations and 47 deaths. Of all suspected cases, 43% had intestinal perforation.

This unusually high percentage of patients with perforation may indicate that the outbreak was much larger than reported.

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.</td>
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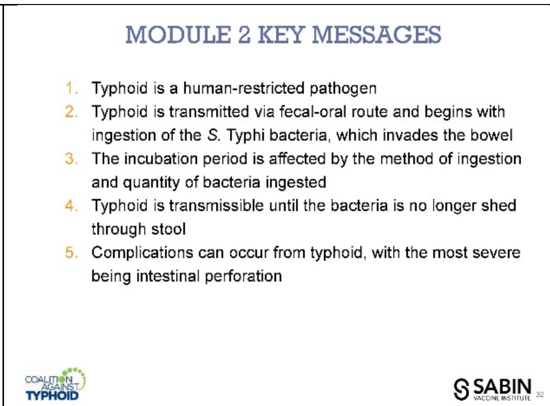
<tr><td>32</td><td>
</td><td>In this module, we have covered some key takeaways regarding transmission and pathogenesis of typhoid:

First, typhoid is a human-restricted pathogen, meaning typhoid cannot survive long-term outside the human body.

Typhoid is transmitted via the fecal-oral route and begins with the ingestion of S. Typhi bacteria which invades the bowel.

The incubation period is affected by the method and quantity of bacteria ingested.

Typhoid is communicable for as long as the bacteria is shed through stool.

Lastly, complications can occur in patients with typhoid with the most severe being intestinal perforation.

Does anyone have any questions before we move on to the next module on diagnostics?</td></tr>
<tr><td>33</td><td>
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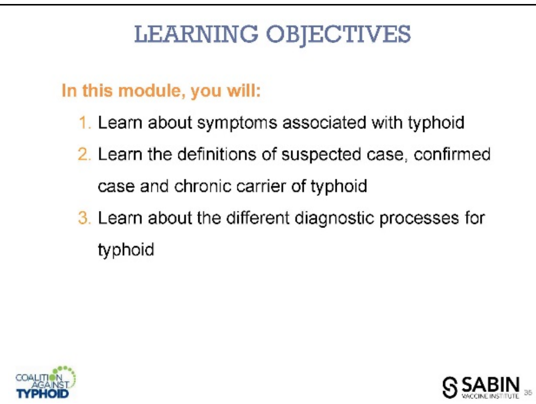
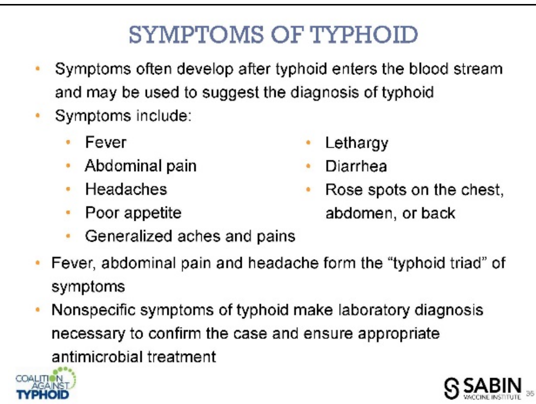
</table>

<table>
<tr><th colspan="3">MODULE 3: DIAGNOSTICS</th></tr>
<tr><td>Slide Number</td><td></td><td>Facilitator Tips</td></tr>
<tr><td>34</td><td>
</td><td>In this module, we'll go over the diagnostic processes used for typhoid fever.</td></tr>
<tr><td>35</td><td>
</td><td>By the end of this module, you will:
Recognize symptoms associated with typhoid
Learn the definition of a suspected case, confirmed case and chronic carrier of typhoid
Learn the different diagnostic processes for typhoid</td></tr>
<tr><td>36</td><td>
</td><td>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.

Fever, abdominal pain and headaches form the "typhoid triad" of characteristic symptoms of typhoid.

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.</td></tr>
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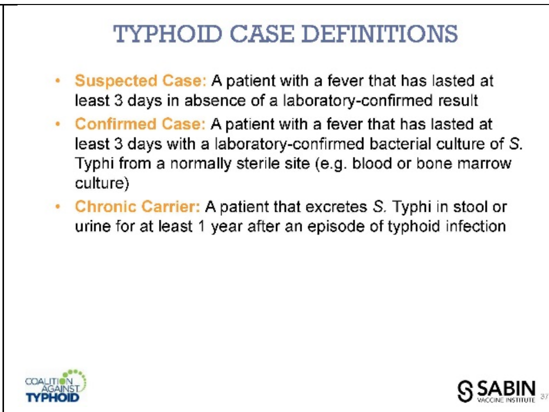
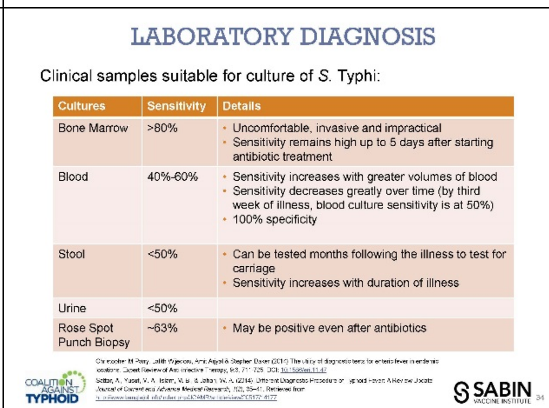
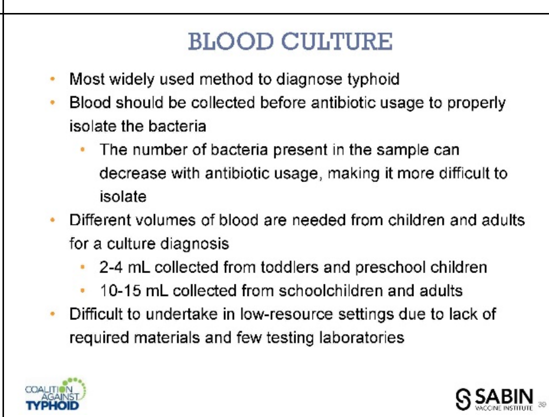
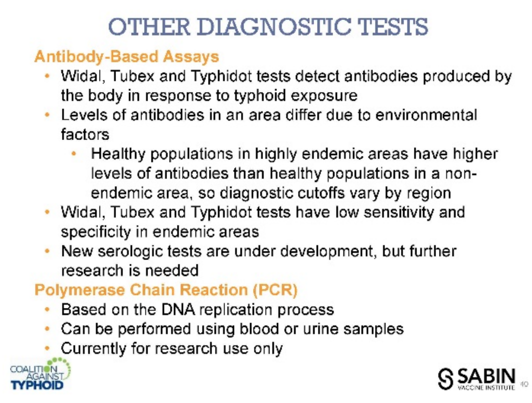
<tr><td>37</td><td>
</td><td> Doctors diagnosing typhoid will use these case definitions in the field:
A suspected case is a patient with fever that has lasted at least three days in absence of confirmatory laboratory result.
A confirmed case is a patient with fever that has lasted at least three days 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. </td></tr>
<tr><td>38</td><td>
</td><td> 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. </td></tr>
<tr><td>39</td><td>
</td><td> 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 </td></tr>
</table>

		saw on the previous slide. However, different volumes of blood should be collected from children and adults. 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. How do you think these factors can impact how typhoid is diagnosed, or the burden of typhoid estimated? [*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.*]
40		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. 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. 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. 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.

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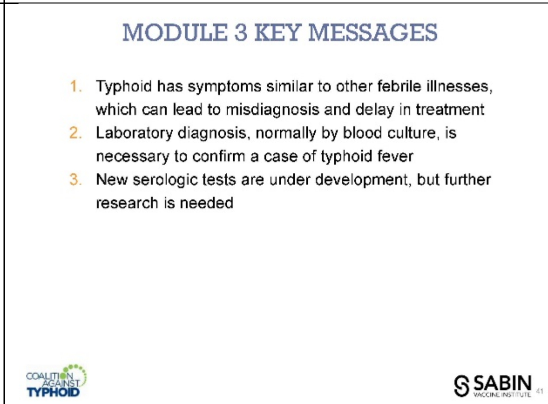
<tr><td></td><td></td><td>To date, there are no reliable replacements for blood culture.</td></tr>
<tr><td>41</td><td>
</td><td>In this module, we have covered the following key takeaways:

First, typhoid has symptoms that are similar to many other febrile illnesses, which can lead to misdiagnosis and delay in treatment.

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.

Lastly, new serologic tests are under development, but further research is needed.

Are there any questions before we move on to treatment?</td></tr>
<tr><td>42</td><td>
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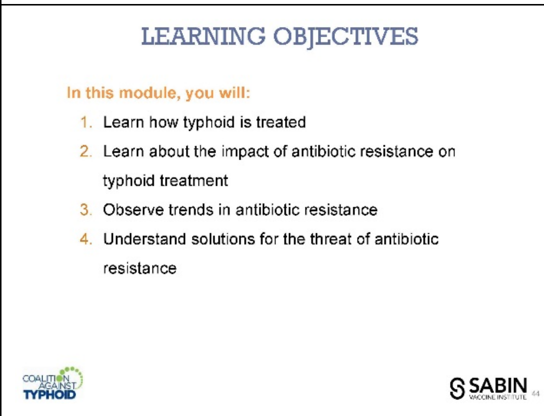
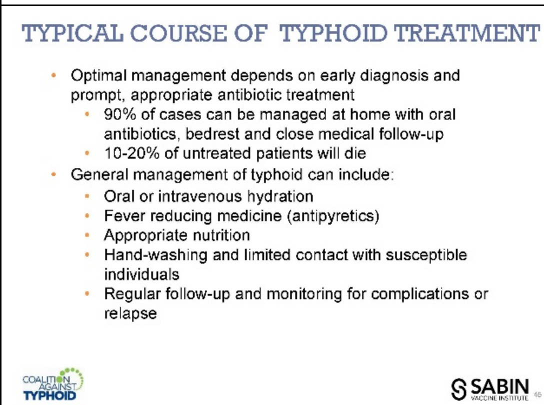
<table>
<tr><th colspan="3">MODULE 4: TREATMENT</th></tr>
<tr><td>Slide Number</td><td></td><td>Facilitator Tips</td></tr>
<tr><td>43</td><td>
</td><td>This module will provide an explanation of the treatments used for typhoid fever.</td></tr>
<tr><td>44</td><td>
</td><td>In this module you will learn:
• How typhoid is treated
• The impact of antibiotic resistance on typhoid treatment
• Trends in antibiotic resistance
• And solutions for the threat of antibiotic resistance</td></tr>
<tr><td>45</td><td>
</td><td>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.

[Possible discussion topic: In Module 3, we learned that typhoid diagnosis can be difficult. How can this impact treating typhoid?]

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.

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.</td></tr>
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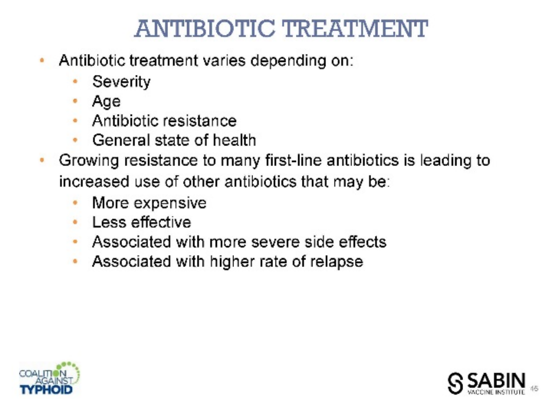
<td>46</td>
<td>
</td>
<td>Antibiotic treatment for typhoid varies depending on severity (including complications), age, antibiotic resistance and the general state of the patient’s health.

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.</td>
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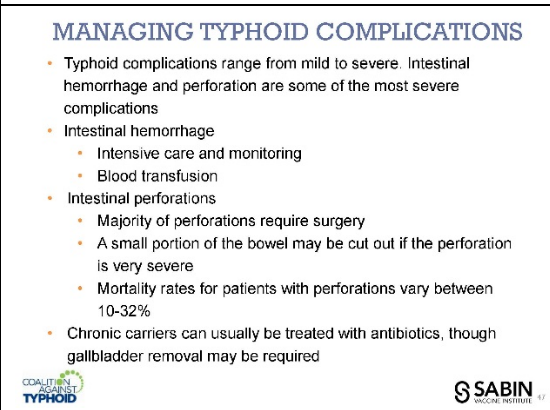
<td>47</td>
<td>
</td>
<td>Typhoid complications range from mild to severe. As you learned in module 2, intestinal hemorrhage and perforation are some of the most severe complications.

Different complications require different kinds of treatments.

Intestinal hemorrhage requires intensive care and monitoring. If the hemorrhaging is particularly severe, blood transfusions may be necessary.

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%.

Chronic carriers can usually be treated with antibiotics or gallbladder removal.</td>
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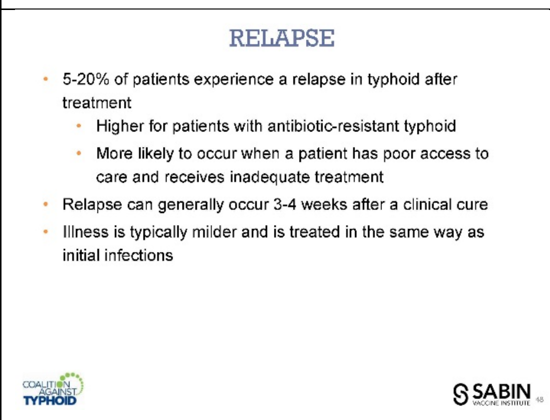
<td>48</td>
<td>
</td>
<td>Even after treatment, however, 5-20% of patients experience a relapse in typhoid. This percentage is higher for patients with antibiotic-resistant typhoid. Relapse is also more likely when the patient has poor access to care or receives inadequate treatment.

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.</td>
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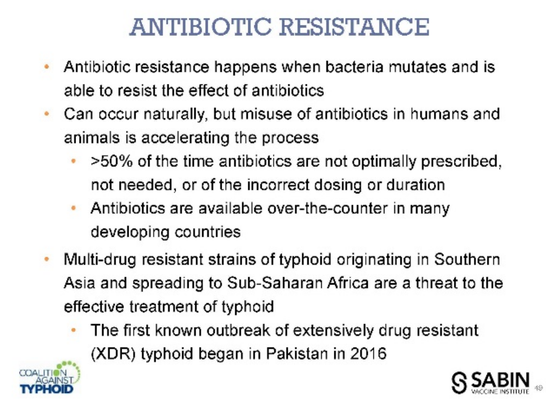
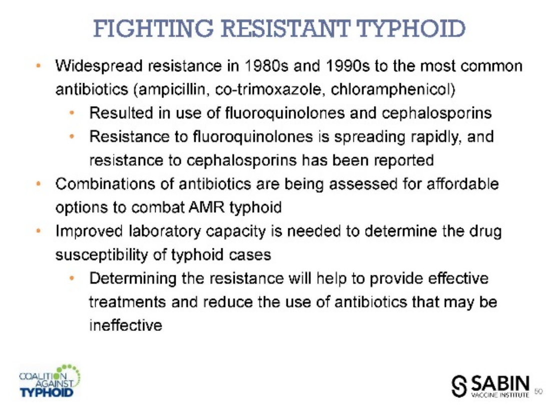
49		Antibiotic resistance occurs when bacteria mutates to be able to resist the effect of antibiotics. This occurs naturally, but misuse of antibiotics in humans and animals is accelerating the process. More than half of the time, antibiotics are not optimally prescribed, prescribed in the incorrect dosing or duration, or even unneeded. They are also often available over-the-counter in many developing countries where typhoid is endemic. 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.
50		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. 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. 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.

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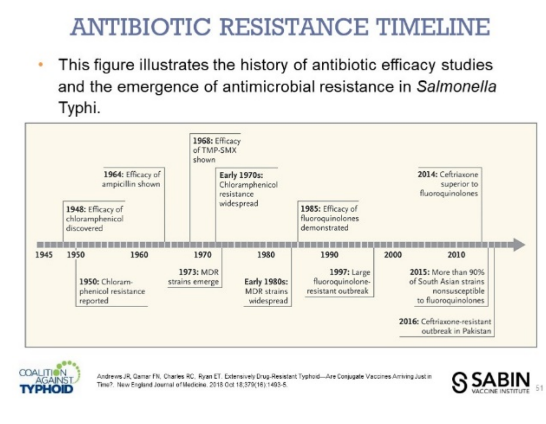
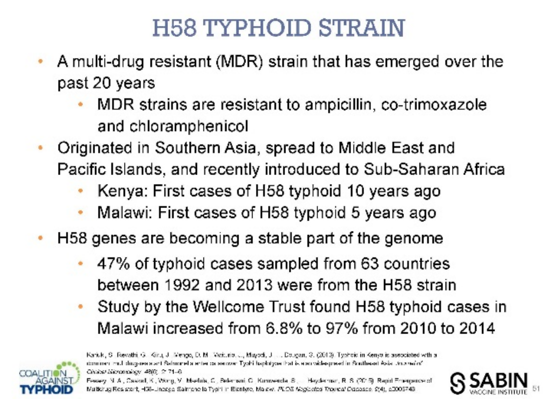
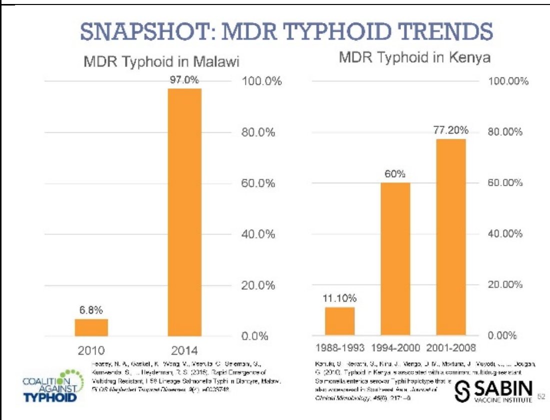
<tr><td>51</td><td>
</td><td>This figure illustrates the history of antibiotic efficacy studies and the emergence of antimicrobial resistance in Salmonella Typhi.

In this figure, MDR denotes multidrug-resistant, and TMP-SMX denotes trimethoprim–sulfamethoxazole. Strains noted to be “nonsusceptible” are intermediately or fully resistant.</td></tr>
<tr><td>52</td><td>
</td><td>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.</td></tr>
<tr><td>53</td><td>
</td><td>Let’s look closer a 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.</td></tr>
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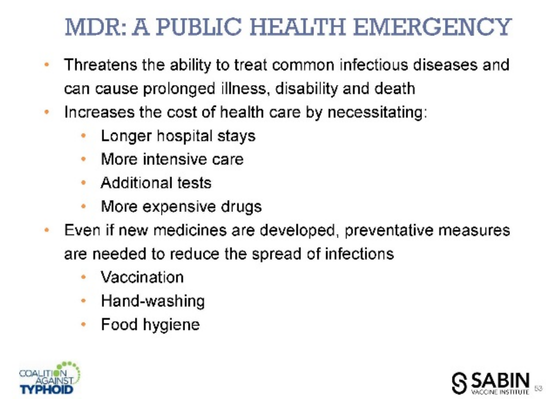
<td>54</td>
<td>
</td>
<td>Multi-drug resistance is a public health emergency. It threatens our ability to treat common infectious diseases and can cause patients to have prolonged illness, disability or even death. The cost of health care also increases with drug-resistance due to longer hospital stays, more intensive care, additional testing and more expensive drugs.

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.

Thinking back to Module 1, does anyone remember what the case-fatality rate of typhoid is? For both treated and untreated?

[Correct answer should be 1-4% for treated versus 10-20% for untreated]

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.</td>
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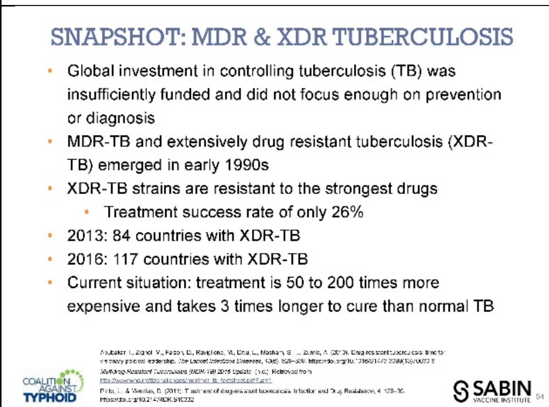
<td>
</td>
<td>This is a snapshot of what can happen when multi-drug resistance spins out of control. Global investment in controlling tuberculosis was insufficiently funded and did not focus enough on prevention or diagnosis, allowing MDR-TB and XDR-TB to emerge in the early 90s.

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.

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</td>
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<td>diagnostics before multi-drug resistance grows out of control.

[Discuss the situation of MDR and XDR TB and how that may apply to typhoid, particularly in the light of XDR typhoid in Pakistan]</td>
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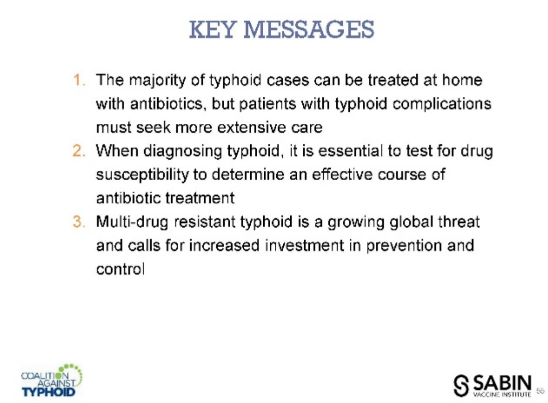
<td>56</td>
<td>
</td>
<td>During this module, you should have learned the following key points:

First, the majority of typhoid cases can be treated at home with antibiotics, but patients with complications from typhoid must seek more extensive care.

When diagnosing typhoid, testing for drug susceptibility is necessary to determine an effective course of antibiotic treatment.

Lastly, multi-drug resistant typhoid is a growing global threat that calls for increased investment in prevention and control.

Does anyone have any questions before we move on to the next module, on prevention?</td>
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<td>57</td>
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<td>“References”</td>
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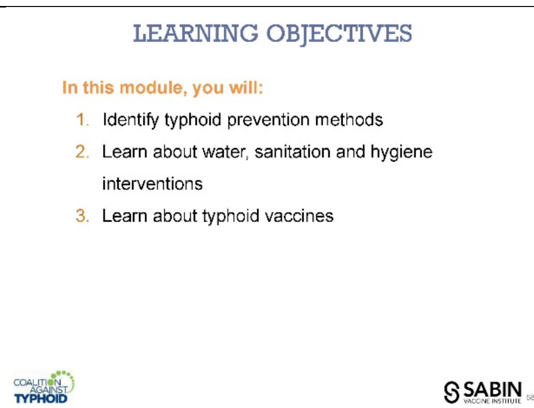
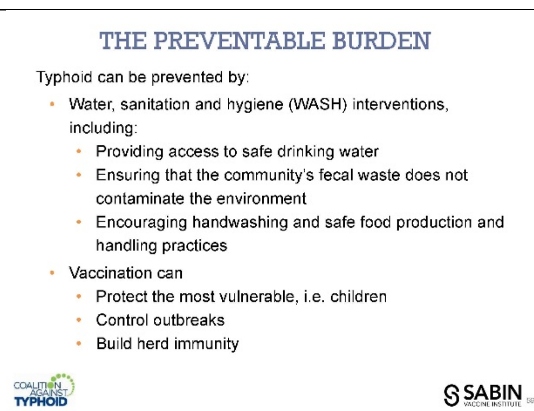
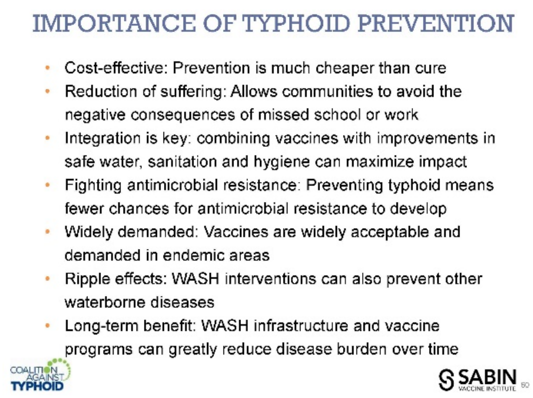
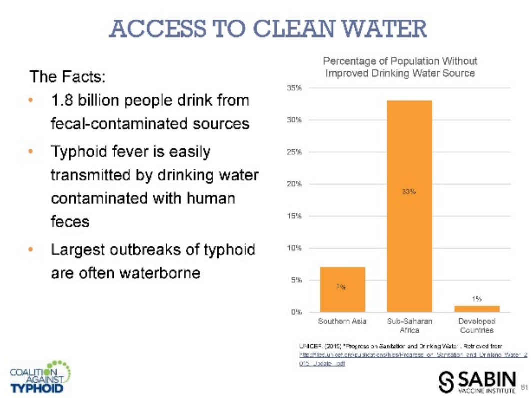
</table>

MODULE 5: PREVENTION		
Slide Number		**Facilitator Tips**
58		This module will explore the different ways in which typhoid fever can be prevented.
59		In this module, you will: • Identify typhoid prevention methods • Learn about water, sanitation and hygiene interventions • Learn about typhoid vaccines
60		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. 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

		an outbreak, or to build herd immunity so that outbreaks are fewer and less dangerous. Keep in mind that all of these preventative measures vary in cost and ease of implementation.
61		As illustrated in the Snapshot XDR TB example in the previous module, prevention is key in the fight against diseases. Prevention is cost-effective, as it is cheaper than providing the cure. It reduces suffering, pain, and fear of disease, and allows communities to avoid missing school or work. Integrating vaccines with WASH maximizes impact and helps fight antimicrobial resistance. Vaccines are widely acceptable and even demanded in endemic areas. WASH interventions can also prevent other waterborne diseases, producing “ripple effects”. The benefits also extend over the long term as well, as WASH and vaccine programs limit disease burden over time.
62		An estimated 1.8 million people drink from fecal-contaminated sources putting them at risk of contracting typhoid. As you can see on the graph, most people without access to an improved drinking water source are in South Asia and Sub-Saharan Africa, where typhoid is endemic. Typhoid fever is easily transmitted by drinking water contaminated with human feces and often the largest outbreaks of typhoid are waterborne. Increasing access to clean water is paramount to preventing typhoid.

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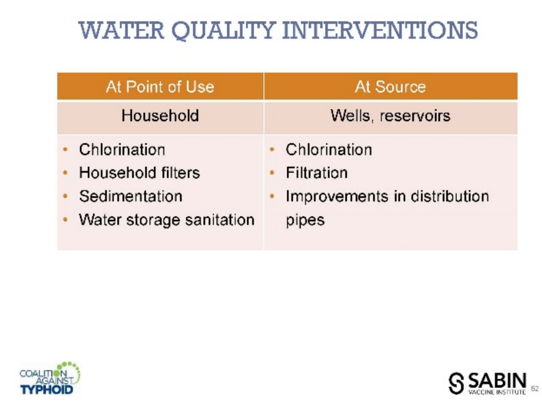
<td>63</td>
<td>
</td>
<td>Water quality interventions can either occur at the source of the water or at point of use.

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.</td>
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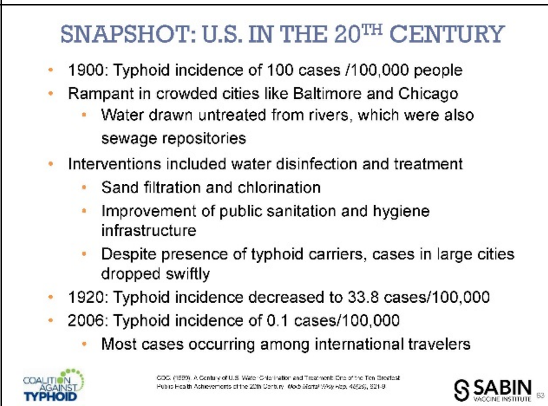
<td>
</td>
<td>To illustrate the powerful difference a proper water treatment system can make, we’re going to look at a snapshot of the United States in the twentieth century. In 1900, the typhoid incidence rate was 100 cases per 100,000 people. Typhoid was especially rampant in crowded cities, where 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.</td>
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<td>
In addition to drinking water improvements, improvements to sanitation infrastructure can make a difference in preventing typhoid.
Worldwide, 2.4 billion people are without improved sanitation facilities that hygienically separates human excreta from human contact. This leads to 85% of wastewater being discharged into the environment. It is no surprise then that 80% of illnesses in low-income countries are linked to poor water and sanitation conditions.
Proper sewage treatment and collection is needed to prevent water contamination. There is also a need to maintain a continuous water supply.
Basic sanitation infrastructure interventions like the building of toilets, latrines and wastewater treatment infrastructure – and health promotion encouraging the habitual use of this infrastructure -- can also help prevent typhoid.
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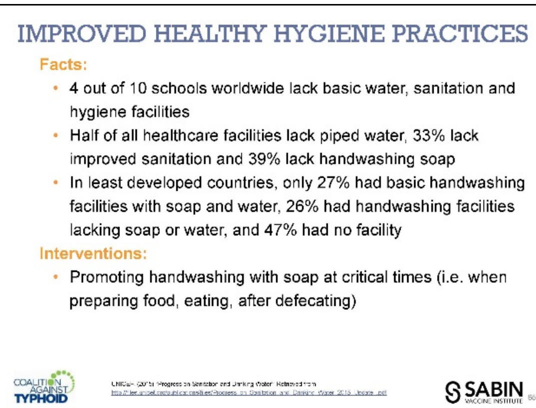

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Another intervention that can help prevent typhoid is to encourage improved hygiene practices. In many typhoid-endemic countries, improved hygiene is not very prevalent. For example, four out of 10 schools lack basic water, sanitation and hygiene facilities. Half of all health care facilities lack piped water, 33% lack improved sanitation and 39% lack handwashing soap. In Least Developed Countries, only 27% had basic handwashing facilities with soap and water, 26% had handwashing facilities lacking soap or water and 47% had no facility.
A hygienic intervention that can prevent typhoid is handwashing with soap at critical times, like before preparing food, before eating and after defecating.
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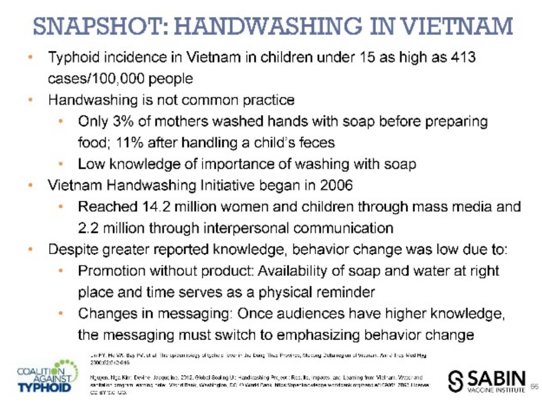

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Let’s take a look at a handwashing intervention in practice in Vietnam.
In some parts of Vietnam, the incidence of typhoid in kids 15 or younger can be as high as 413 cases per 100,000 people.
Handwashing is not a common practice in Vietnam. For example, only 3% of mothers washed their hands with soap before preparing food, and only 11% after handling a child’s feces. There is low knowledge of the importance of using soap to wash in particular.
The Vietnam Handwashing Initiative began in 2006. It reached 14.2 million women and children with messaging on the importance of handwashing through mass media, and 2.2 million through interpersonal communication.
However, despite greater reported knowledge, observed behavior change was low. One of the difficulties was that many wanted to use limited stores of clean water for drinking rather than handwashing, as we discussed on the previous slide.
Other difficulties encountered included promotion without a product. Availability of soap and water at the right time and place serves as a physical reminder and could have made the initiative more successful. Another was not static messaging. Once audiences have higher knowledge, the messaging needs to switch to emphasizing the desired behavior change.
Generally, encouraging individual behavior changes can be difficult.
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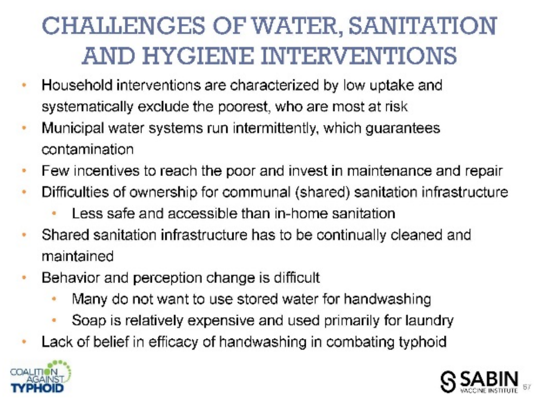
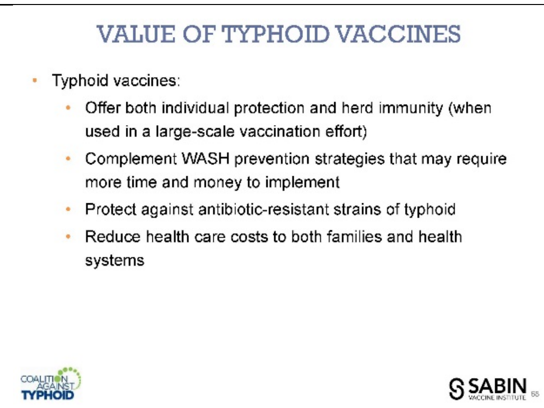
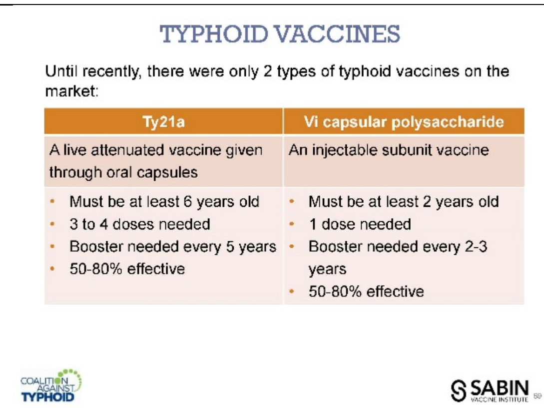
68		WASH interventions encounter many challenges. Household interventions such as chlorination, use of household filters, sedimentation and water storage sanitation require individual behavior changes, which can be difficult to sustain. Outside of the home, municipal water systems run intermittently 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 that handwashing*

		couldn't prevent, they may have not washed their hands but never contracted typhoid.] Even when knowledge is high, sustaining behavior change is difficult.
69		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.
70		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. 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. 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. These vaccines are mainly used by travelers from high-income countries and are largely absent from endemic country vaccination programs. Look over this information. Can you think of some reasons why these vaccines might not be implemented widely? [*Possible discussion topics: the low effectiveness, the need for a booster, and the age limit.*]

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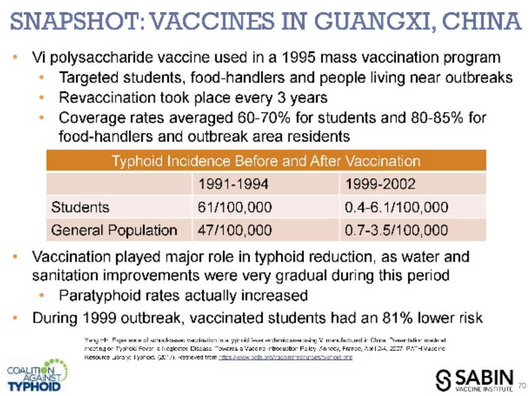

To illustrate the usefulness of typhoid vaccination, we're taking a look at vaccines in Guangxi, China.

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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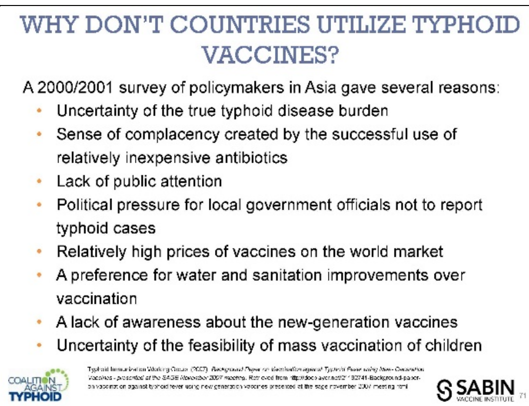


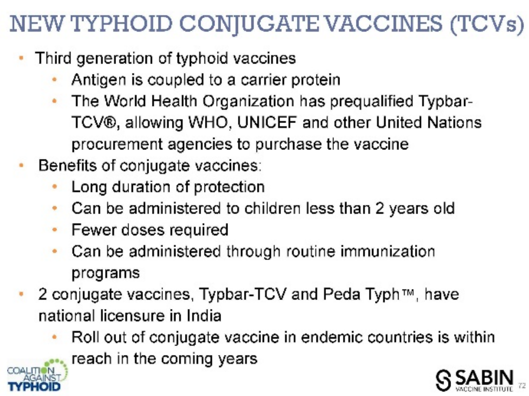
Given the benefits this vaccination program had in Guangxi, why do more countries not take this approach? A 2000/2001 survey of policymakers in Asia gave several reasons for why countries are not utilizing typhoid vaccines.

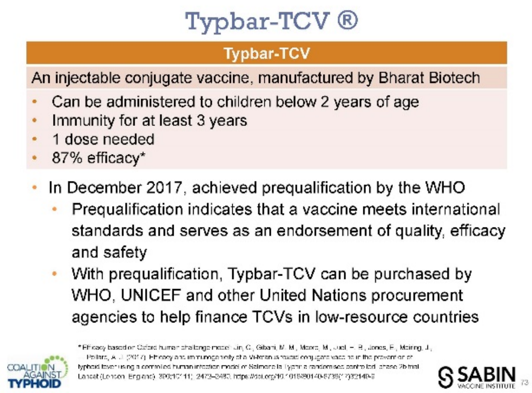
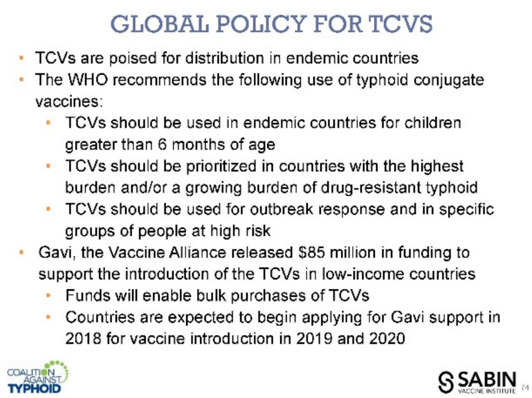
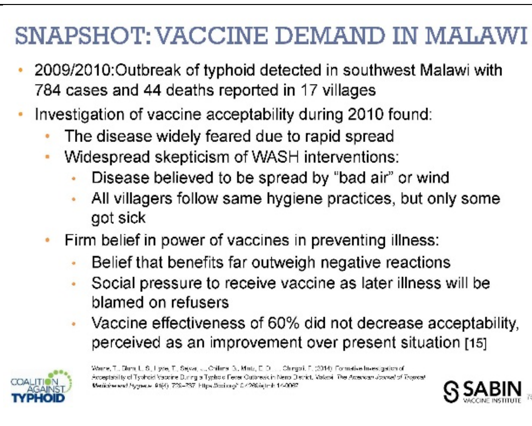
The uncertainty of the true typhoid burden stems from the difficulty of diagnosis and lack of surveillance covered in Modules 1-3.

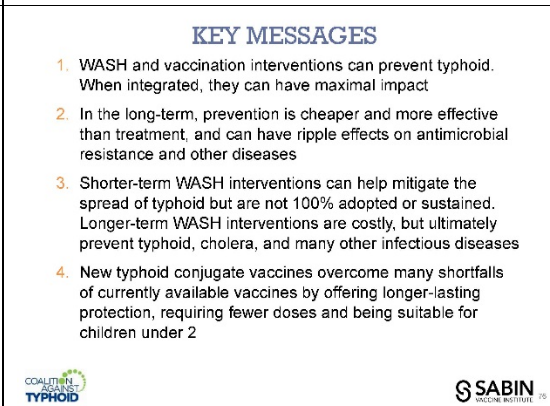
Typhoid has been able to be easily treated by relatively cheap antibiotics. However, that is changing due to antimicrobial resistance.

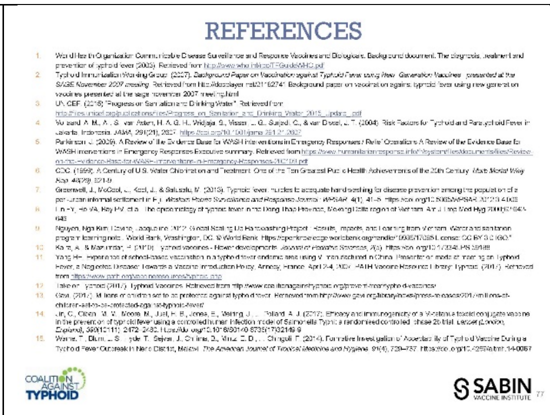
Lack of public attention to typhoid vaccination.

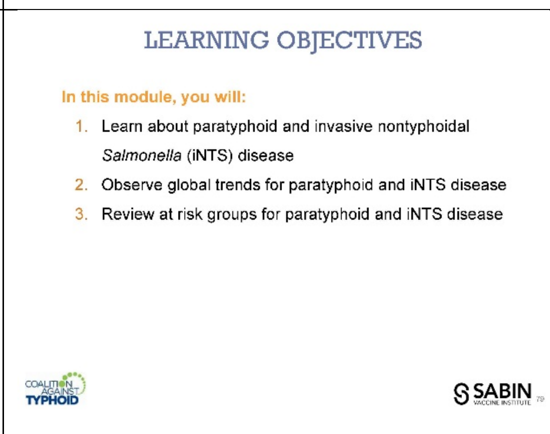
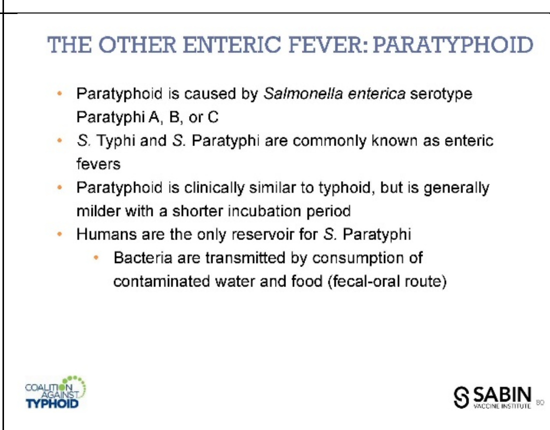
Sometimes local government officials are pressured not to report typhoid cases because

		they are an indicator of inadequate water and sanitation systems. The price for vaccines is relatively high. 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. There is also a lack of awareness of upcoming new-generation vaccines, which we'll get to in the next slide. 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).
73		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. 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. Two conjugate vaccines have been licensed in India, and rollout of conjugate vaccines in other endemic countries is within reach in the coming years.

74		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. 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.
75		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. 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.
76		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. In 2009 and 2010, an outbreak of typhoid spread in Southwest Malawi, with 784 cases and 44 deaths reported in 17 villages. A study taking place in this area during 2010 found that the disease was widely feared due to

		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. 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.
77		During this module, you should have gained the following key points: First, WASH and vaccination interventions can prevent typhoid and, when integrated, can have maximal impact. Secondly, prevention is cheaper and more effective in the long-term than treatment, and can have ripple effects on antimicrobial resistance and other diseases. 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. 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. Are there any questions before we move on to the final module on related diseases?

78		"References"

<table>
<tr><th colspan="3">MODULE 6: RELATED DISEASES</th></tr>
<tr><th>Slide Number</th><th></th><th>Facilitator Tips</th></tr>
<tr><td>79</td><td>
</td><td>This module will provide an overview of two typhoid-related diseases, paratyphoid and invasive nontyphoidal Salmonella disease.</td></tr>
<tr><td>80</td><td>
</td><td>By the end of this module, you will:
Learn about paratyphoid and invasive nontyphoidal Salmonella (iNTS) disease
Observe global trends for paratyphoid and iNTS disease
Review at risk groups for paratyphoid and iNTS disease</td></tr>
<tr><td>81</td><td>
</td><td>We mentioned in an earlier module that typhoid is also known as an “enteric fever”, a term which refers to both typhoid and paratyphoid.

Paratyphoid is caused by Salmonella enterica serotypes Paratyphi A, B, or C. You’ll remember that typhoid is caused by Salmonella enterica serotype Typhi, so you can see that these two diseases are closely related.

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.

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.</td></tr>
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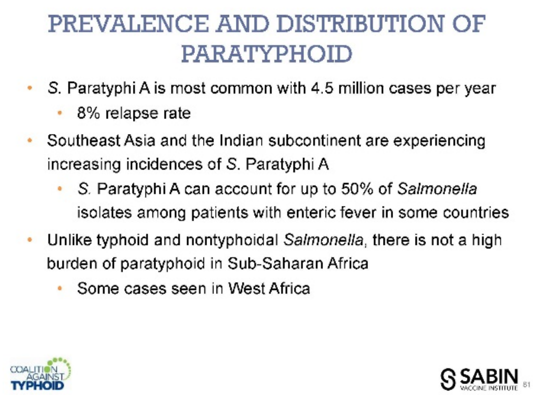

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Paratyphoid is not as widespread as typhoid. There are about 4.5 million cases per year, the majority caused by S. Paratyphi A. There is an estimated 8% relapse rate.
Incidence of paratyphoid is highest in Southeast Asia and the Indian subcontinent, which is experiencing rising rates of Paratyphoid A. In some places, Paratyphoid A can account for up to half of Salmonella 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.
Unlike typhoid and nontyphoidal Salmonella, 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.
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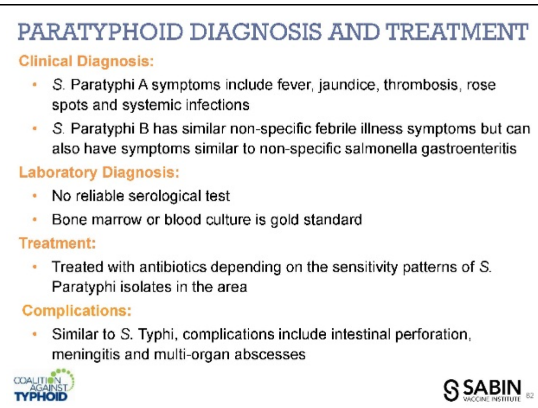

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<td>
Much of the process of diagnosis and treatment for paratyphoid is similar to that for typhoid. Paratyphoid A, which is the most common paratyphoid serotype, has symptoms including fever, jaundice, thrombosis, and systemic infections. Paratyphoid B, which is much rarer, has similar non-specific symptoms, but can also have symptoms more similar to gastroenteritis.
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.
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.
Complications are similar to typhoid, including intestinal perforation, meningitis and multi-organ abscesses.
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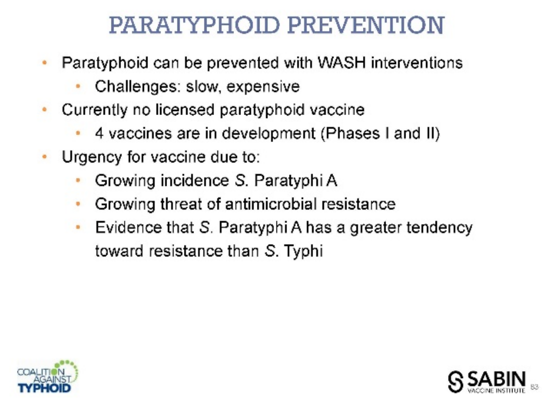
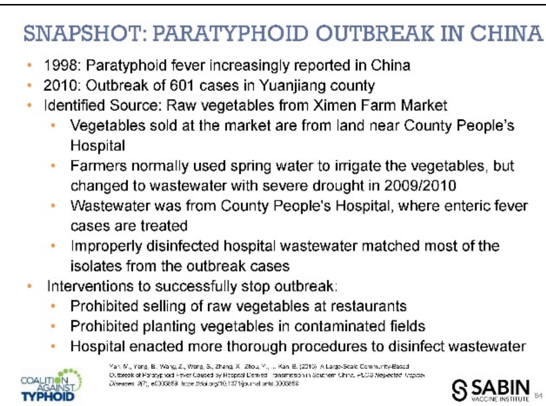
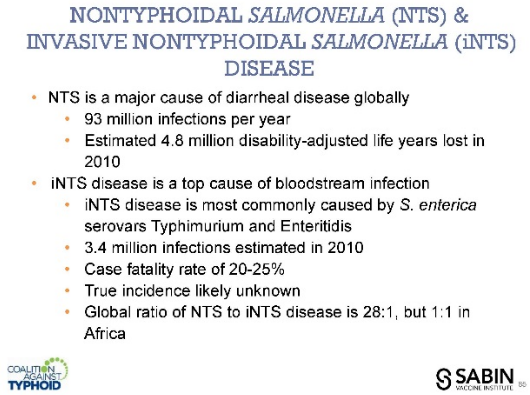
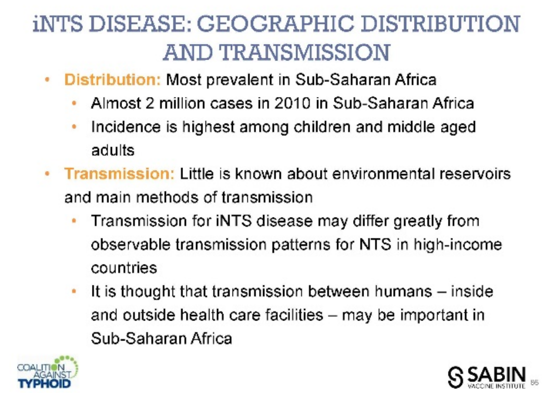
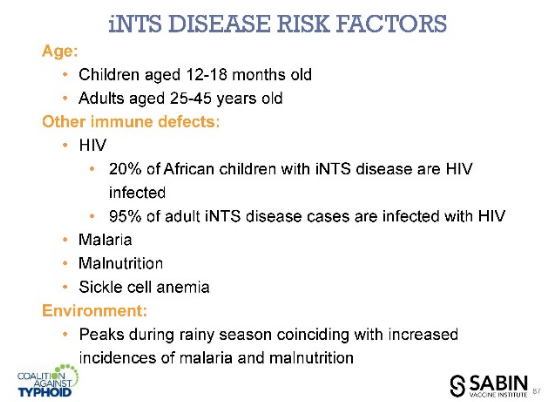
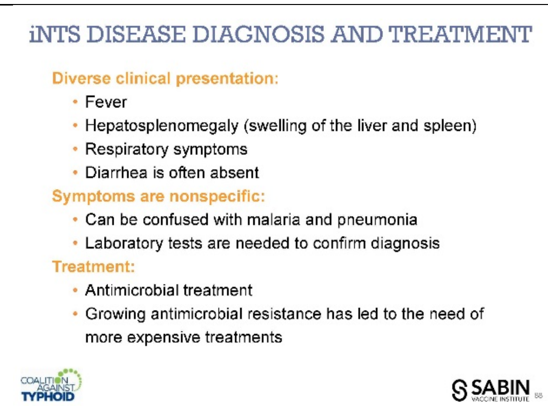
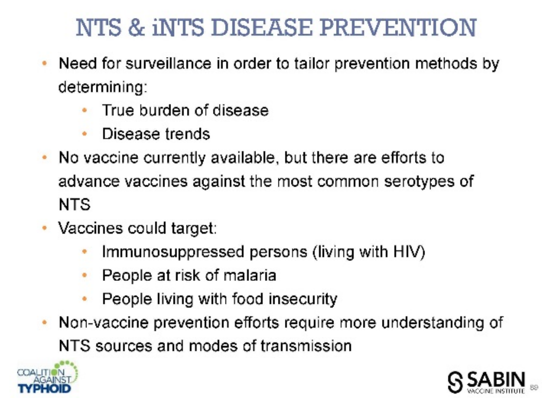
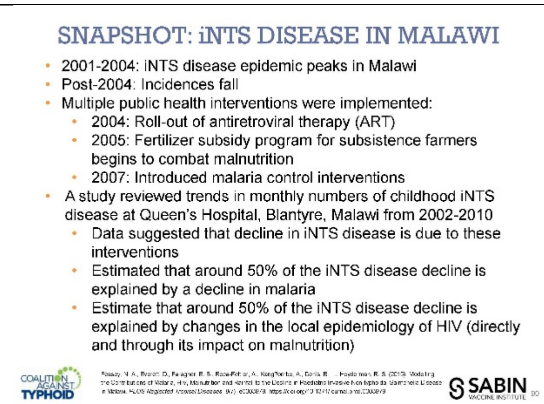
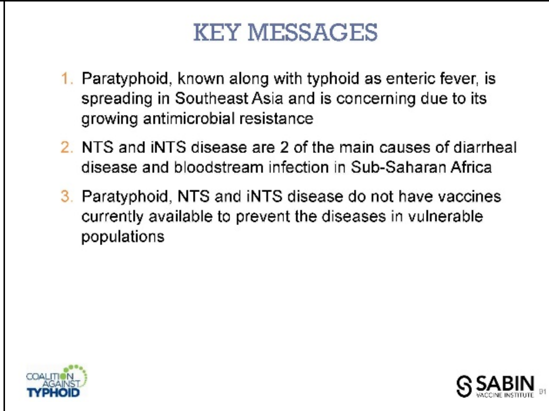
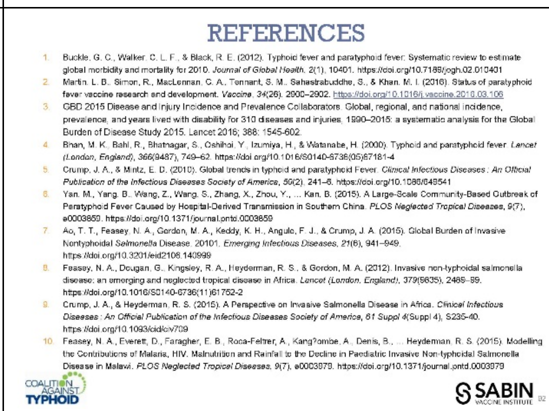
84		Paratyphoid can be prevented with the same WASH interventions discussed in the previous module, as it is spread through the fecal-oral pathway. The challenges for WASH interventions remain the same as we've discussed—namely, slow to implement and expensive. Currently, there's no licensed paratyphoid 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.
85		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?

		[*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.*]
86		We're now going to discuss nontyphoidal *Salmonella* (or NTS) and invasive nontyphoidal *Salmonella* (or iNTS) disease. NTS, caused by *Salmonella* bacteria that aren't *S.* Typhi or *S.* Paratyphi, 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. iNTS disease, which is when NTS invades the bloodstream, is a top cause of bloodstream infection and most commonly caused by *Salmonella enterica* serovars Typhimurium or Enteritidis. In 2010, there were an estimated 3.4 million iNTS disease infections, with a cast-fatality rate of 20-25%. However, estimates of iNTS disease incidence and mortality are not well documented. 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 non-typhoidal salmonella is just as common as the non-invasive.

87		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. 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.
88		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. 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. 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.
89		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. The symptoms of iNTS disease are nonspecific and easily confused for those of malaria and pneumonia, so laboratory tests are needed to confirm diagnosis. Treatment for iNTS disease is done with antimicrobials. However, like in typhoid and paratyphoid, growing antimicrobial resistance is

		a problem in iNTS disease leading to the need for more expensive treatments. 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.
90		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. 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. Non-vaccine prevention efforts would require more understanding of sources and modes of transmission.
91		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. 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. 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

<table>
<tr><td></td><td></td><td>estimated 50% is explained by changes in the local epidemiology of HIV—both directly and through its impact on malnutrition.</td></tr>
<tr><td>92</td><td>
</td><td> In this module, you should have learned the following key messages.
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.
Second, NTS and iNTS disease are two of the main causes of diarrheal disease and bloodstream infection in Sub-Saharan Africa.
Third, paratyphoid, NTS and iNTS disease do not have vaccines currently available to prevent the diseases in vulnerable populations.
This is the final module of this program. Are there any questions? </td></tr>
<tr><td>93</td><td>
</td><td>“References”</td></tr>
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