

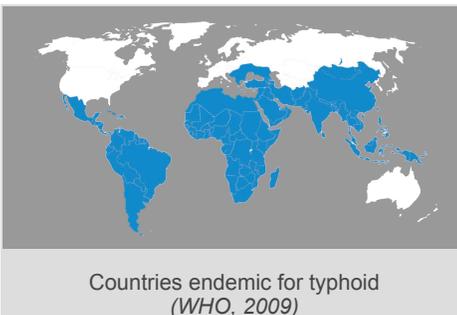
## Background

Global Burden | Causative Agent & Transmission | Pathogenesis | Current Control Strategy | Existing Products | Get Involved

### What is Typhoid Fever?

Typhoid fever, or enteric fever, is a bacterial infection caused by *Salmonella enterica* subspecies *enterica* serovar Typhi (abbreviated *Salmonella* Typhi). The disease is spread by ingestion of contaminated food or water. Typhoid commonly presents with a sudden onset of fever, headache, abdominal pain, and diarrhea and can quickly progress to a variety of potentially fatal complications, including gastrointestinal hemorrhage, intestinal perforation, and neurological dullness or delirium. Although infection is often curable with antibiotic treatment, the growing prevalence of resistance makes vaccination of at risk groups an increasingly urgent priority.

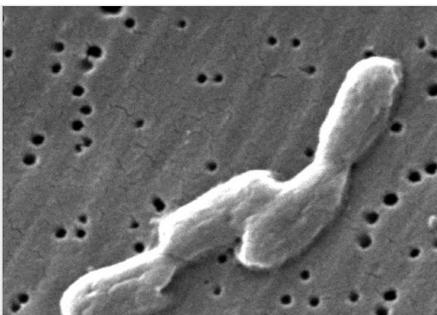
### Global Burden



Worldwide, there are an estimated 17-22 million cases of typhoid each year, leading to 200,000-600,000 deaths.<sup>1,2</sup> While improved public sanitation systems and the availability of antibiotics have virtually eradicated the disease in the industrialized world, typhoid continues to be endemic in regions with inadequate sewage treatment, crowded or chaotic conditions, and poor hygiene. Areas of Southeast Asia and India have the highest prevalence, followed by sub-Saharan Africa and South America. In addition to endemic disease, outbreaks of typhoid fever have recently occurred in regions such as Tajikistan and Haiti.<sup>3</sup> School-aged children are particularly susceptible to infection.

The economic burden of typhoid has been calculated by several cost-of-illness surveys. The average typhoid case in an urban slum in Delhi, India was found to generate health system costs equaling twice a family's monthly income.<sup>4</sup> Similar costs of approximately \$100 per case were estimated in areas of Indonesia, Pakistan, Vietnam, and China. Hospitalization can increase the cost up to \$500 per patient. Rapidly rising rates of antibiotic resistance are increasing the duration and expense of treatment.

### Causative Agent and Transmission



*Salmonella* bacteria that cause typhoid fever. (photo: CDC/Janice Carr)

*Salmonella* Typhi is a Gram negative bacterium of the species *Salmonella enterica*, which is divided into six subspecies, 50 serogroups (based on the O antigen), and >2500 serovars (based on the H antigen). *S. enterica* serovar Paratyphi A can also cause enteric fever. Close relatives of *Salmonella* Typhi, such as *S. enterica* serovar Typhimurium are responsible for outbreaks of food poisoning often associated with eggs and poultry. *Salmonella* Typhi is a pathogen exclusive to humans, and has no animal reservoir or vector.

Transmission of *Salmonella* Typhi occurs by ingestion of food or water contaminated with feces or urine. Shellfish harvested from polluted regions or raw vegetables fertilized with human manure (night soil) may also harbor the bacterium. Diligent hand washing is important to prevent hand to mouth transmission. In addition, flies may passively carry the bacteria to food. Typhoid symptoms generally appear 1-2 weeks after infection.

## Pathogenesis

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After ingestion, *Salmonella* Typhi bacteria attach to and penetrate specialized regions of the small intestine, called Peyer's patches. The pathogens are then taken up by macrophages and carried to the lymph nodes, spleen, bone marrow, and liver. Although macrophages are immune cells that typically destroy engulfed bacteria, *Salmonella* Typhi avoids this fate by expressing a number of virulence factors that block the function of the phagocytic vacuoles. Instead, the typhoid bacteria are protected from the immune system as they multiply within the macrophage. Infection eventually ruptures the host cell and *Salmonella* Typhi spreads throughout the body, potentially leading to life-threatening complications such as internal bleeding, intestinal perforation, and hypotensive shock. Severe neurological symptoms may occur and can persist even after the infection has been cleared. *Salmonella* Typhi has a strong affinity for the gallbladder, and the presence of the bacteria in the bile leads to fecal shedding.

While the majority of patients will stop excreting *Salmonella* Typhi bacteria within three months after infection, ~2-5% of patients will go on to become chronic carriers. Persistently infected individuals are at risk for a relapse of the disease and may experience biliary tract abnormalities, such as gallstones. While chronic carriers may not feel sick, they can still spread the disease to others and must be barred from food handling. Chronic *Salmonella* Typhi infection was made infamous in the case of an early 20<sup>th</sup> century New York City cook named Mary Mallon (Typhoid Mary), who was placed under quarantine for over two decades after her refusal to give up work in the food industry led to multiple outbreaks of the disease.

## Current Control Strategy

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Typhoid fever can be effectively treated with appropriate antibiotics, reducing case fatality rates from 10-30% to <4%.<sup>2</sup> However, *Salmonella* Typhi isolates showing resistance to first and second-line antibiotics are widespread, and third-generation drugs are also becoming less effective.<sup>5</sup> This leaves patients and physicians with alarmingly few options.

In the face of antibiotic resistance, control of typhoid fever is now focused on improved sanitation and expanding vaccine coverage. Safe water, proper food handling, diligent hand washing, and control of flies are particularly important to stem typhoid outbreaks. Case reporting of the disease is mandatory in most countries. Unfortunately, a diagnosis of typhoid can only be confirmed by analysis of blood or stool in a laboratory. The lack of simple, rapid, point-of-care diagnostics suitable for use in developing countries means that cases often go unreported and the true typhoid burden is underestimated.<sup>2</sup> Failure to recognize the extent of typhoid has also limited enthusiasm for widespread vaccination campaigns; while the World Health Organization has recommended immunization in endemic areas since 1998, only Vietnam, China, and Delhi State, India have begun routine vaccination.

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## Existing Products

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### ► Drugs

In resource-poor settings of the developing world, oral rehydration therapy is the standard of care for diarrheal diseases. While this is sufficient to reduce mortality for many enteric diseases, antibiotics are important for the treatment of typhoid to prevent complications from the infection and to reduce the risk of a person becoming an asymptomatic carrier.

Geographic patterns are used for predicting the sensitivity of *Salmonella* Typhi to particular drugs, but resistance is a moving target.<sup>5</sup>

- First-line antibiotics (ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole) have been rendered largely ineffective by widespread multi-drug resistance. In some regions where these antibiotics have been absent for long periods, however, *Salmonella* Typhi strains have reverted to wild type and the drugs can again be effective.
- Fluoroquinolones have become the new standard of treatment, but resistance to these drugs is common, especially in Asia.
- Third-generation cephalosporins are now in use in regions of high multi-drug resistance, but these too are becoming less

effective.

## ▶ Vaccines

A typhoid vaccine is recommended for those living in or travelling to endemic regions, those at risk of occupational exposure, and individuals living in the same household as a chronic carrier. As the vaccines lose their efficacy over time, boosters are recommended every 2-5 years for those at continued risk. Vaccine protection is not complete, so individuals should also practice good hygiene and avoid potentially unsafe foods. There is no vaccine approved for use in children under 2 years old.

- Vi capsular polysaccharide antigen (Typhim Vi, Sanofi-Pasteur): An injectable, single dose vaccine with an excellent safety profile and efficacies ranging from 55% to 65 – 72%.<sup>3</sup> The vaccine, which was first licensed in 1994, is now in the public domain and is produced by a number of manufacturers. The vaccine has good heat stability, high yields, and low production costs. Unfortunately, like other polysaccharide antigens, it is poorly immunogenic in infants.<sup>3</sup>
- Ty21a live-attenuated vaccine (Vivotif, Crucell): An oral vaccine given in 3-4 doses, two days apart. It is a live-attenuated bacterium that was derived from the *S. Typhi* Ty2 strain by chemical mutagenesis. The vaccine is safe, has been shown to have 51% -77% efficacy, and provides protection for 5-7 years.<sup>3,4</sup> Ty21a was first licensed in the 1980s and is now available in 56 countries. The vaccine requires a strict cold chain and is not recommended for use in children under six years of age.
- Inactivated whole-cell vaccines: A heat-killed phenol-preserved, whole-cell vaccine was used for the prevention of typhoid in Europe as far back as 1896.<sup>2</sup> This vaccine has been largely discontinued due to high reactogenicity. An acetone-inactivated vaccine, currently available only to members of the U.S. military, provides efficacy rates of 75%-94% and protection for up to 3 years.<sup>5</sup>

## ▶ Diagnostics

Typhoid fever is a multi-symptomatic illness that presents a diagnostic challenge for physicians. Broad-spectrum antibiotic therapy is usually begun before a confirmatory diagnosis is made, as delaying treatment can increase the chances of severe complications. Diagnostic tests for *Salmonella* Typhi are important to narrow the spectrum of appropriate antibiotics and to identify chronic carriers. Unfortunately, available tests require sophisticated laboratory infrastructure and have widely variable sensitivities.

- Culture of the bacterium from patient samples is the current gold standard diagnostic criterion. Blood, bone marrow, stool, urine, or other samples can be used. This test generally takes 2-3 days to give a result, and has varying success depending on the type of sample and when in the disease course it was taken.<sup>5</sup>
- Serological tests measure antibodies directed at *Salmonella* Typhi, and include the hemagglutination test and enzyme-linked immunosorbent assay (ELISA). These tests are limited in sensitivity and specificity. The Widal test, which measures agglutinating antibodies against the *Salmonella* Typhi H and O antigens, was the diagnostic standard for many years, but is no longer accepted due to very poor sensitivity and specificity.<sup>5</sup>

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1. Control of Communicable Diseases Manual (CCDM) 19th edition, An Official Report of the American Public Health Association, 2008.
2. WHO (2009) "Diarrhoeal Diseases".
3. Foudation Merieux (2007) "Report of the Meeting on Typhoid Fever, a Neglected Disease: Towards a Vaccine Introduction Policy".
4. Bahl R et al. (2004) "Costs of illness due to typhoid fever in an Indian urban slum community: implications for vaccination policy." *J Health Popul Nutr* 22: 304-10.
5. Bruschi, JL et al (2010) "Typhoid Fever" *eMedicine*.

## Get Involved

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# Pipeline & Analysis

Drugs | Vaccines | Diagnostics | Get Involved

## Drugs

Although drug resistance to common antibiotics is a serious concern, numerous antibiotics are available for the treatment of typhoid. Vaccines are the primary focus of new product development for typhoid fever.

## Vaccines

### ▶ PIPELINE

Product/Research Program	Developers	Discovery	Pre-clinical	Phase I	Phase II	Phase III
Ty800	Celldex Therapeutics Inc.					
Vi-CRM197	Novartis Vaccines Institute for Global Health					
CVD 909	Crucell Sanofi Pasteur University of Maryland Center for Vaccine Development					
Vi-DT conjugate vaccine	International Vaccine Institute National Institutes of Health Shantha Biotech					
OmpC-Vi conjugate vaccine	All India Institute of Medical Sciences					
FB-1811	Folia Biotech					
Typhella	Emergent BioSolutions				On Hold	
Vi-rEPA Conjugate Vaccine	Eunice Kennedy Shriver National Institute of Child Health & Human Development				On Hold	

### ▶ ANALYSIS

New vaccines for the prevention of typhoid focus on live attenuated and polysaccharide conjugate vaccines. The new live attenuated vaccines in development seem to be more immunogenic and require fewer doses than the existing Ty21a vaccine.<sup>1</sup> The ability of live attenuated *S. Typhi* vaccines to be delivered orally, to be taken up by phagocytic cells, and to elicit robust serum antibody, mucosal, and cell mediated immune response also makes them potential candidates for vectors to express heterologous antigens. For example, Emergent BioSolutions is developing an attenuated *Salmonella* Typhi vector to express other bacterial, viral, and cancer cell antigens. It may also be possible to engineer the *Salmonella* Typhi vector to express antigens from other related enteric pathogens, creating a single vaccine for multiple diarrheal diseases.

Because of the poor immunogenicity of the Vi antigen in infants, conjugation of the polysaccharide to a carrier protein is being pursued. Vaccines in development are exploring multiple possible protein conjugates such as an endotoxin of *Pseudomonas aeruginosa* and diphtheria toxin.<sup>2,3</sup> While polysaccharide protein conjugate vaccines are generally low cost and more stable than live vaccines, they

generally are not amenable to oral dosing. At this point it is unclear which vaccination approach will prove most effective.

	Strengths	Weaknesses	Opportunities	Risks
<b>Live attenuated vaccines</b>				
<p><b>Most advanced program:</b> On market (Most advanced new product, phase II)</p>	<p>One product already on market and in use</p> <p>Less reactogenic than inactivated vaccines</p> <p>Longer duration of protection than polysaccharide conjugate vaccines</p> <p>Oral dosing</p>	<p>Requires cold chain</p> <p>Requires multiple doses</p> <p>Some side effects due to live bacteria</p>	<p>High uptake of bacteria makes <i>Salmonella</i> a candidate as a heterologous vector for vaccination against other organisms</p>	<p>May not be practical for use in resource-poor settings due to cold chain requirement</p>
<b>Polysaccharide protein conjugate vaccines</b>				
<p><b>Most advanced program:</b> On market (Most advanced new product, phase II)</p>	<p>Less expensive and more stable than live attenuated vaccines</p>	<p>Existing vaccine has poor efficacy in infants</p> <p>Shorter duration of protection than live attenuated vaccine</p>	<p>Further exploration of carrier proteins</p>	<p>Improved efficacy in infant population will be required for integration into childhood vaccination regimens</p>

## Diagnosics

There are three approaches for improving typhoid diagnosis currently in development:<sup>4</sup>

- Enhanced culture-based diagnostics: Culture of *Salmonella* Typhi is limited by low levels of the bacterium in the blood, transient infection of any one tissue, unpredictable efficiency of culture, and the requirement for laboratory infrastructure. Improved understanding of *Salmonella* Typhi metabolism under different conditions is being used to identify more efficient culture media to enhance detection. This approach is unlikely to be practical in resource-poor settings.
- Next-generation serologic tests: Cross-reactive antibodies are a major limitation of serological tests for typhoid. Identifying new antigens that are highly specific for *Salmonella* Typhi or defining patterns of reactivity may be promising approaches.
- Nucleic acid based diagnostics: No PCR-based diagnostic test is yet available in the clinic. Nested PCR using primers directed at the flagellin gene has been shown to offer optimal sensitivity and specificity for detection of *Salmonella* Typhi in blood and urine.<sup>2</sup> Isolation of sufficient DNA, however, requires large amounts of patient samples.

Beyond individual diagnostics for typhoid, there is interest in diagnostics that can differentially diagnose typhoid from other causes of fever with non-specific symptoms and from other enteric infections associated with diarrhea. Panel diagnostics that include typhoid are likely to be more valuable than individual tests for this disease in resource poor settings with minimally trained health workers.

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## References

1. WHO (2009) "Diarrhoeal Diseases".
2. Bruschi, JL et al (2010) "Typhoid Fever" eMedicine.
3. Micoli F et al (2011) "Vi-CRM 197 as a new conjugate vaccine against *Salmonella* Typhi." *Vaccine* 29: 712-20.
4. Baker S et al. (2010) "Searching for the elusive typhoid diagnostic." *BMC Infectious Diseases* 10: 45.

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# Tools

Drugs | Vaccines | Diagnostics | Get Involved

The following series of tables describe the availability of tools for research, discovery, and development of novel drugs, vaccines, and diagnostics for typhoid. The tools listed in the following tables are not intended to be an all-inclusive list but rather capture the most common tools used for drug, vaccine, and diagnostic development. The tools for typhoid are quite advanced.

## Drug Development Tools

Basic Research: Target Identification	Target Validation	Screening: Hit/Lead Identification Optimization	Pre-clinical Validation	Clinical Validation
<p><b>Genome:</b> Sequenced</p> <p><b>Key databases:</b> NCBI Genome Project</p> <p>Wellcome Trust   Sanger Institute</p> <p>SIB ExpASY Proteomics Server</p> <p><b>In vitro culture:</b> Yes, in media and in cultures of human cells, e.g., macrophages</p>	<p><b>Gene knock-outs:</b> Yes</p> <p><b>Conditional gene knock-outs:</b> Yes</p> <p><b>Transposon mutagenesis:</b> Yes</p> <p><b>RNAi:</b> No</p> <p><b>Other antisense technology:</b> Yes, possible. E.g., phosphorodiamidate morpholino oligonucleotides (PMOs) have activity against <i>S. Typhimurium</i></p> <p><b>Viability assays:</b> Yes, colony forming on agar</p> <p><b>Transcription microarrays:</b> Yes, use purification/enrichment schemes to isolate bacterial RNA from host contamination</p> <p><b>Proteomics:</b> Yes, possible and ongoing under different conditions</p> <p><b>Crystal structures:</b> Yes</p>	<p><b>Whole-cell screening assays:</b> Yes, assay of infected cell monolayers or pure bacterial culture</p> <p><b>Enzymatic screening assays:</b> Yes</p>	<p><b>Animal models:</b> <i>S. Typhi</i> only infects humans.</p> <p><i>S. Typhimurium</i> is used as a mouse model of systemic infection (in <i>Nramp1</i><sup>-/-</sup> animals) or the chronic carrier state (in <i>Nramp1</i><sup>+/+</sup> mice).</p>	<p><b>Monitoring treatment efficacy:</b> Yes, bacterial culture of blood or stool</p> <p><b>Availability of endpoints:</b> Yes, bacterial clearance</p> <p><b>Availability of surrogate endpoints:</b> No</p> <p><b>Access to clinical trial patients/sites:</b> Yes</p>

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## Vaccine Development Tools

Basic Research: Antigen Identification	Immune Response Characterization	Clinical Validation
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<p><i>See drug development tools above</i></p>	<p><b>Predictive animal models:</b> No, <i>S. Typhimurium</i> infection of mice produces typhoid-like illness, but differences exist between the serovars.</p> <p><b>Detection of endogenous antigen specific response in clinical samples:</b> Yes, antibodies</p> <p><b>Natural immunity well characterized:</b> Prior infection does not confer immunity. Immunity after vaccination shows that anti-Vi and anti-H antibodies and cell mediated immunity are important.</p>	<p><b>Surrogate markers of protection:</b> Currently licensed vaccines elicit humoral and mucosal antibody responses. Live attenuated vaccines also elicit cellular responses.</p> <p><b>Challenge studies possible:</b> Not anymore, data available from human volunteer studies in the 1960s.</p>
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## Diagnostic Development Tools

Basic Research: Biomarker Identification	Biomarker Validation	Clinical Validation
<p><i>See drug development tools above</i></p>	<p><b>Biomarkers known:</b> No</p> <p><b>Access to clinical samples:</b> Yes</p> <p><b>Possible sample types:</b> Blood, feces, urine, bone marrow</p>	<p><b>Access to clinical trial patients/sites:</b> Yes</p> <p><b>Treatment available if diagnosed:</b> Yes, antibiotics</p>

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# Product Details

## CVD 909

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**Synonyms:**  
CVD 909

**Disease:**  
Typhoid fever

**Target/Technology:**  
Live attenuated vaccines

**Specific Indication:**  
Preventative

**Mechanism of Action:**

**Product Type:**  
Vaccine

**Molecule Class:**

**PRV Eligible?**  
No

**Administration Route:**  
Oral

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**Notes:**

Designed following previous vaccines CVD 908 and CVD 908-htrA (both discontinued). CVD 909 is the CVD 908-htrA strain with a constitutively active promoter driving Vi expression.

**Clinical Trials:**

NCT00326443

**Publications:**

17582563

## FB-1811

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**Synonyms:**  
FB-1811

**Disease:**  
Typhoid fever

**Target/Technology:**  
Recombinant/purified protein vaccines

**Specific Indication:**

**Mechanism of Action:**

**Product Type:**  
Vaccine

**Molecule Class:**

**PRV Eligible?**  
No

**Administration Route:**

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**Notes:**

**Clinical Trials:**

**Publications:**

## OmpC-Vi conjugate vaccine

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**Synonyms:**  
OmpC-Vi conjugate vaccine

**Disease:**  
Typhoid fever

**Target/Technology:**  
Polysaccharide protein conjugate vaccines

**Specific Indication:**  
Preventative

**Mechanism of Action:**

**Product Type:**  
Vaccine

**Molecule Class:**

**PRV Eligible?**  
No

**Administration Route:**

**Notes:****Clinical Trials:****Publications:****Ty800**

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**Synonyms:**

Ty800

**Disease:**

Typhoid fever

**Target/Technology:**

Live attenuated vaccines

**Specific Indication:**

Preventative

**Mechanism of Action:**

phoP/phoQ deletion variant of S. Typhi strain Ty2

**Product Type:**

Vaccine

**Molecule Class:****Administration Route:**

Oral

**PRV Eligible?**

No

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**Notes:**

Vaccine strain is a phoP/phoQ deletion variant of S. Typhi strain Ty2.

**Clinical Trials:**NCT00498654  
NCT00269295**Publications:**

8648213

**Typhella**

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**Synonyms:**Typhella  
M-01ZH09**Disease:**

Typhoid fever

**Target/Technology:**

Live attenuated vaccines

**Specific Indication:**

Preventative

**Mechanism of Action:****Molecule Class:****Administration Route:**

Oral

**Product Type:**

Vaccine

**PRV Eligible?**

No

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**Notes:**

Despite positive results in a Phase II clinical trial, this product is on hold pending partnering.

**Clinical Trials:**

NCT00679172

**Publications:**

19806505

**Vi-CRM197**

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**Synonyms:**

Vi-CRM197

**Disease:**

Typhoid fever

**Target/Technology:**

Polysaccharide protein conjugate vaccines

**Specific Indication:**

Preventative

**Mechanism of Action:****Molecule Class:****Administration Route:****Product Type:**

Vaccine

**PRV Eligible?**

No

**Notes:**

As an alternative to the Vi antigen from *S. Typhi*, Vi-CRM197 contains Vi from a BSL1 organism, *Citrobacter freundii*, strain WR7011, conjugated to CRM(197), a non-toxic mutant of diphtheria toxin.

**Clinical Trials:**

NCT01123941  
NCT01193907  
NCT01229176

**Publications:**

21115057  
21248155

## Vi-DT conjugate vaccine

**Synonyms:**

Vi-DT conjugate vaccine  
Vi-diphtheria toxoid (DT) conjugate vaccine

**Disease:**

Typhoid fever

**Target/Technology:**

Polysaccharide protein conjugate vaccines

**Specific Indication:**

Preventative

**Mechanism of Action:****Molecule Class:****Administration Route:****Product Type:**

Vaccine

**PRV Eligible?**

No

**Notes:****Clinical Trials:****Publications:**

## Vi-rEPA Conjugate Vaccine

**Synonyms:**

Vi-rEPA Conjugate Vaccine

**Disease:**

Typhoid fever

**Target/Technology:**

Polysaccharide protein conjugate vaccines

**Specific Indication:**

Preventative

**Mechanism of Action:****Molecule Class:****Administration Route:****Product Type:**

Vaccine

**PRV Eligible?**

No

**Notes:**

Polysaccharide Vi antigen from *S. Typhi* is conjugated to recombinant exotoxin A of *Pseudomonas aeruginosa* (Vi-rEPA). Currently not being commercially developed due to complexity of producing exotoxin carrier protein.

**Clinical Trials:**

NCT00342628  
NCT00386789

**Publications:**

10531232  
11320385

## Developer Details

### Celldex Therapeutics Inc. (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Typhoid fever	Ty800	Phase II

### **Sanofi Pasteur (France)**

Type	Disease	Product/Research Program	Current Phase
Vaccine	Typhoid fever	CVD 909	Phase I

### **Sanofi Pasteur (France)**

Type	Disease	Product/Research Program	Current Phase
Vaccine	Typhoid fever	Typhim Vi	Approved

### **University of Maryland Center for Vaccine Development (United States)**

Type	Disease	Product/Research Program	Current Phase
Vaccine	Typhoid fever	CVD 909	Phase I

### **Crucell (Netherlands)**

Type	Disease	Product/Research Program	Current Phase
Vaccine	Typhoid fever	CVD 909	Phase I

### **Crucell (Netherlands)**

Type	Disease	Product/Research Program	Current Phase
Vaccine	Typhoid fever	Vivotif	Approved

### **Emergent BioSolutions (United States)**

Type	Disease	Product/Research Program	Current Phase
Vaccine	Typhoid fever	Typhella	Phase II

### **Eunice Kennedy Shriver National Institute of Child Health & Human Development (United States)**

Type	Disease	Product/Research Program	Current Phase
Vaccine	Typhoid fever	Vi-rEPA Conjugate Vaccine	Phase II

### **International Vaccine Institute (South Korea)**

Type	Disease	Product/Research Program	Current Phase
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Vaccine	Typhoid fever	Vi-DT conjugate vaccine	Pre-clinical
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### **National Institutes of Health (United States)**

Type	Disease	Product/Research Program	Current Phase
Vaccine	Typhoid fever	Vi-DT conjugate vaccine	Pre-clinical

### **Shantha Biotech (India)**

Type	Disease	Product/Research Program	Current Phase
Vaccine	Typhoid fever	Vi-DT conjugate vaccine	Pre-clinical

### **All India Institute of Medical Sciences (India)**

Type	Disease	Product/Research Program	Current Phase
Vaccine	Typhoid fever	OmpC-Vi conjugate vaccine	Pre-clinical

### **Novartis Vaccines Institute for Global Health (Italy)**

Type	Disease	Product/Research Program	Current Phase
Vaccine	Typhoid fever	Vi-CRM197	Phase II

### **Folia Biotech (Canada)**

Type	Disease	Product/Research Program	Current Phase
Vaccine	Typhoid fever	FB-1811	Pre-clinical

### **Berna Biotech (Netherlands)**

Type	Disease	Product/Research Program	Current Phase
Vaccine	Typhoid fever	Vivotif	Approved