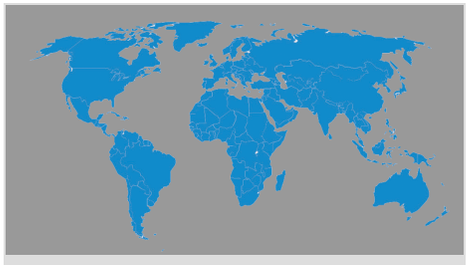
Background

What is Shigellosis?

Shigellosis is an infection by bacteria of the genus *Shigella* that causes severe abdominal symptoms, including diarrhea, dysentery, abdominal cramps, fever, and rectal pain. Shigellosis can result in death. The disease is more dangerous than other gut pathogens because it can penetrate the lining of the intestine and cause severe inflammation of the intestine and systemic complications.

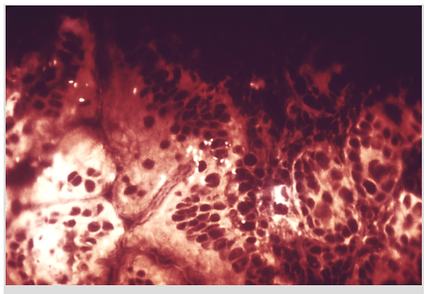
Global Burden



Prevalent Shigella species vary by geographic area *(WHO)*

Diarrheal disease is the second leading cause of death in children under 5 years old (after lower respiratory tract infections). It is estimated that shigellosis accounts for 5-10% of all diarrheal episodes and 75% of all diarrheal deaths.[1] Worldwide there are approximately 165 million cases of shigellosis per year (99% of cases occurring in the developing world), causing over 1.1 million deaths.[2] Nearly 70% of all episodes and approximately 60% of all deaths occur in children under 5 years old.[1]

Causative Agent and Transmission



Shigella bacteria may penetrate the intestinal mucosa. (photo: CDC/Sam Formal/WRAIR)

Shigella are Gram-negative bacteria transmitted in food or water contaminated with feces from an infected person. Consumption of as little as 10 bacteria can cause disease.

There are four species of *Shigella* that encompass more than 20 serotypes. These species vary in their geographic distribution.

Shigella species	Geographic location
S. sonnei	U.S. and other industrialized countries

S. flexneri	Developing world
S. boydii	Limited foci in India
S. dysentariae type 1	Epidemic outbreaks

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Pathogenesis

Shigella bacteria multiply within the epithelial cells of the colon, cause cell death, and spread laterally to infect and kill adjacent epithelial cells, resulting in mucosal ulceration, inflammation, and bleeding. *S. dysenteriae* type 1 produces severe disease and may be associated with life-threatening complications.

In some children, shigellosis causes seizures. In adults, Reiter's Syndrome can develop, leading to inflammation of the eye and joints as well as reactive arthritis.

Control Strategy

The primary control strategy for shigellosis is prevention of oral-fecal transmission through education and building sanitation infrastructure. Secondary to prevention, management of the disease using oral rehydration therapy is used to reduce morbidity and mortality associated with the disease.

Existing Products

Drugs

Although antibiotics can be used to shorten the length of infection, oral, or IV rehydration therapy is the standard of care of the treatment of shigellosis.

Vaccines

No vaccine for shigellosis is widely available. In China, a recombinant, live, oral, bivalent vaccine, produced by the Lanzhou Institute of Vaccines and Biological Products, is available for adults. The vaccine has approximately 60% efficacy for both *S. flexinari* and *S. sonnei*.[3] The vaccine has never been evaluated or approved for use outside of China.

Diagnostics

Bacterial culture from stool is the only method of diagnosis in widespread use for shigellosis.

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References

1. Kotloff KL. (1999) "Global burden of Shigella infections: implications for vaccine development and implementation of control strategies." *Bulletin of the World Health Organization* **77**: 651-666.
2. Kweon, M. (2008) "Shigellosis: the current status of vaccine development." *Current Opinion in Infectious Diseases* **21**: 313-318.

Get Involved

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Pipeline & Analysis

Drugs | Vaccines | Diagnostics | Get Involved

Drugs

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

Vaccines

PIPELINE

Product/Research Program	Developers	Discovery	Pre-clinical	Phase I	Phase II	Phase III
S. sonnei-rEPA	Eunice Kennedy Shriver National Institute of Child Health & Human Development					
S. flexneri type 2a-rEPAsucc	Eunice Kennedy Shriver National Institute of Child Health & Human Development					
Invaplex 50	Walter Reed Army Institute of Research					
SC599	Institut Pasteur					
GVXN SD133	GlycoVaxyn					
Mimopath-based Shigellosis vaccine	Mucosis B.V. PATH					
CVD 1208S	PATH University of Maryland				On Hold	

ANALYSIS

Vaccines for the prevention of shigellosis are a key focus of research and development efforts for this disease. The only existing vaccine is a live attenuated vaccine that is administered orally. Live attenuated bacteria delivered by the natural route in infection have a high likelihood of producing an effective immune response, but the balance between attenuation to prevent disease and retaining immunity is difficult to achieve.

Additional clinical stage vaccines include polysaccharide protein conjugate vaccinesand combinations of polysaccharide protein conjugates with killed whole bacteria. The polysaccharides on the surface of bacteria are highly immunogenic but also highly variable. Because the exact composition of polysaccharides can vary widely across bacterial serotypes, this strategy does not always provide enough breadth of protection. Combination of these conjugates with inactivated whole cells may compliment the narrow range of protection provided by polysaccharide protein conjugates alone.

	Strengths	Weaknesses	Opportunities	Risks
Polysaccharide protein conjugate				
Most advanced program: *S. flexnari 2a*	Immune response to polysaccharides from	Protection will most likely be limited to single	Combination with other vaccine technologies	If serotype coverage is too narrow, may not be

and *S. sonnei* –rEPA, Phase III	bacterial surface is well characterized and known to be protective	serotype (over 20 serotypes of Shigella spp. exist)	Combination with vaccines that cause other diarrheal diseases Expand to other serotypes	widely useful
Live attenuated				
Most advanced program: SC999 and CVD 1208S, Phase II	Same technology as used for vaccines for other bacteria that cause diarrhea (i.e., cholera and ETEC)	Difficult to achieve balance between immunogenicity and attenuation of virulence	Combination with vaccines that cause other diarrheal diseases	May cause symptoms
Combination: Polysaccharide protein conjugate and inactivated whole cell				
Most advanced program: Invaplex 50 (intranasal), Phase II	Combination of technologies provides improved chance for protection against multiple serogroups and serotypes with one vaccine	Complex vaccine with multiple conjugates and inactivated whole cells which may be difficult to produce in consistent batches	Potential demonstration of intranasal vaccination as viable route of delivery for diarrheal disease vaccination	Intranasal administration is not the natural route of infection, so may not be as effective as oral vaccines

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Diagnostics

There are currently both nucleic acid amplification and rapid diagnostic tests (for use at the point of care) in development for shigellosis.

As the treatment for all forms of diarrhea focuses on supportive therapy, including rehydration, diagnostics are not necessarily essential for diarrheal management. The key needs for diarrheal disease diagnosis are point of care tests that can determine the origin of the illness (i.e., viral, bacterial, or protozoan) thus directing patient treatment with antibacterial or anti-parasitic medications in conjunction with rehydration.

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Tools

The following series of tables describe the availability of tools for research, discovery, and development of novel drugs, vaccines, and diagnostics for shigellosis. 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 shigellosis are generally well developed.

Drug Development Tools

Basic Research: Target Identification	Target Validation	Screening: Hit/Lead Identification Optimization	Pre-clinical Validation	Clinical Validation
Genome: *S. flexnari* 2a sequenced **Key databases:** GenBank AE014073 ***In vitro* culture:** Yes	**Gene knock-outs:** Yes **Conditional gene knock-outs:** Yes **Transposon mutagenesis:** Yes **RNAi:** Host cell only **Other antisense technology:** Host cell only **Viability assays:** Yes **Transcription microarrays:** Yes **Proteomics:** Yes **Crystal structures:** Yes	**Whole-cell screening assays:** Yes **Enzymatic screening assays:** Yes	**Animal models:** Yes, mouse and guinea pig	**Monitoring treatment efficacy:** Yes **Availability of endpoints:** Yes, clearance of bacteremia **Availability of surrogate endpoints:** End of symptoms **Access to clinical trial patients/sites:** Yes

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Vaccine Development Tools

Basic Research: Antigen Identification	Immune Response Characterization	Clinical Validation
See drug development tools above	**Predictive animal models:** Yes, guinea pig inoculated intra-rectally **Detection of endogenous antigen specific response in clinical samples:** Yes	**Surrogate markers of protection:** No **Challenge studies possible:** Yes

	Natural immunity well characterized: Yes	

Diagnostic Development Tools

Basic Research: Biomarker Identification	Biomarker Validation	Clinical Validation
See drug development tools above	**Biomarkers known:** Yes, but most biomarkers are species or serotype specific **Access to clinical samples:** Yes **Possible sample types:** Stool	**Access to clinical trial patients/sites:** Yes **Treatment available if diagnosed:** Yes

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Product Details

Antibacterial discovery program

Synonyms:
Antibacterial discovery program

Disease:
Shigellosis

Specific Indication:
Shigellosis

Product Type:
Drug

PRV Elegible?
No

Target/Technology:
Unknown

Mechanism of Action:

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

CVD 1208S

Synonyms:
CVD 1208S

Disease:
Shigellosis

Specific Indication:
Preventive, Shigella flexneri 2a

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Live attenuated vaccines

Mechanism of Action:

Molecule Class:

Administration Route:
Oral

Notes:

Clinical Trials:

NCT00866476
NCT00866242

Publications:

GVXN SD133

Synonyms:
GVXN SD133

Disease:
Shigellosis

Specific Indication:
Preventive, Shigella dysenteriae

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Polysaccharide protein conjugate vaccines

Mechanism of Action:

Molecule Class:

Administration Route:
IM

Notes:

Clinical Trials:

NCT01069471

Publications:

Invaplex 50

Synonyms:
Invaplex 50

Disease:
Shigellosis

Specific Indication:
Preventive, Shigella flexneri 2a

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Combination: Polysaccharide protein conjugate and Inactivated whole cell

Mechanism of Action:

Molecule Class:

Administration Route:
Intranasal

Notes:

Clinical Trials:

NCT00485134
NCT00082069

Publications:

20619378

Mimopath-based Shigellosis vaccine

Synonyms:
Mimopath-based Shigellosis vaccine

Disease:
Shigellosis

Specific Indication:

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Recombinant/purified protein vaccines

Mechanism of Action:

Molecule Class:

Administration Route:
Oral

Notes:

Recombinant protein carried by bacterium-like particles (BLPs).

Clinical Trials:

Publications:

S. flexneri type 2a-rEPAsucc

Synonyms:
S. flexneri type 2a-rEPAsucc

Disease:
Shigellosis

Specific Indication:
Preventive, Shigella flexneri 2a

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Polysaccharide protein conjugate vaccines

Mechanism of Action:

Molecule Class:

Administration Route:

Notes:

Clinical Trials:
NCT00368316

Publications:
18448978

S. sonnei-rEPA

Synonyms:
S. sonnei-rEPA

Disease:
Shigellosis

Specific Indication:
Preventive, Shigella sonnei

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Polysaccharide protein conjugate vaccines

Mechanism of Action:

Molecule Class:

Administration Route:

Notes:

Clinical Trials:
NCT00368316

Publications:
18448978

SC599

Synonyms:
SC599

Disease:
Shigellosis

Specific Indication:
Preventive, Shigella dysenteriae 1

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Live attenuated vaccines

Mechanism of Action:

Molecule Class:

Administration Route:

Notes:

Clinical Trials:
NCT00210288

Publications:

Developer Details

Walter Reed Army Institute of Research (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Shigellosis	Invaplex 50	Phase II

Eunice Kennedy Shriver National Institute of Child Health & Human Development (United

States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Shigellosis	S. flexneri type 2a-rEPAsucc	Phase III

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

Type	Disease	Product/Research Program	Current Phase
Vaccine	Shigellosis	S. sonnei-rEPA	Phase III

Institut Pasteur (France)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Shigellosis	SC599	Phase II

PATH (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Shigellosis	CVD 1208S	Phase II

PATH (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Shigellosis	Mimopath-based Shigellosis vaccine	Discovery

University of Maryland (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Shigellosis	CVD 1208S	Phase II

GlycoVaxyn (Switzerland)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Shigellosis	GVXN SD133	Phase I

Department for International Development (United Kingdom)

Type	Disease	Product/Research Program	Current Phase

Drug	Shigellosis	Antibacterial discovery program	Discovery

Institute for OneWorld Health (United States)

Type	Disease	Product/Research Program	Current Phase
Drug	Shigellosis	Antibacterial discovery program	Discovery

Anacor Pharmaceuticals, Inc. (United States)

Type	Disease	Product/Research Program	Current Phase
Drug	Shigellosis	Antibacterial discovery program	Discovery

Lanzhou Institute

Type	Disease	Product/Research Program	Current Phase
Vaccine	Shigellosis	FS vaccine	Approved

Mucosis B.V. (Netherlands)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Shigellosis	Mimopath-based Shigellosis vaccine	Discovery