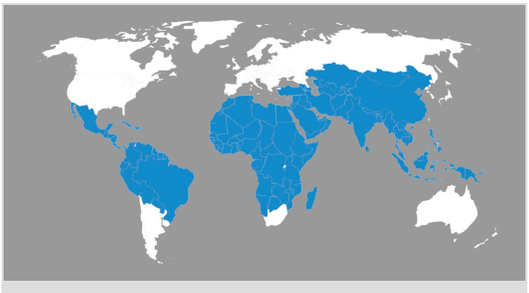
Background

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

What is Enterotoxigenic E. coli (ETEC)?

ETEC are bacteria that colonize the small intestine and cause severe diarrhea, dysentery, abdominal cramps, and fever. ETEC can be life threatening due to significant fluid loss and severe dehydration. Beyond its burden in endemic countries, ETEC is the leading cause of diarrhea in travelers from developed regions returning from vacation in low resource countries.

Global Burden



Countries at high risk for traveler's diarrhea
(CDC, 2007)

Diarrheal disease is currently the most common illness in the world.[1] There are many causes of diarrhea, including bacterial, viral, and parasitic pathogens. However, ETEC is estimated to cause 280-400 million diarrheal episodes per year in children under 5 years of age, resulting in 300,000 to 500,000 deaths.[2] Due to difficulty in culturing the bacterium and the similarity of symptoms to other diarrheal diseases, these numbers are believed to be significantly underestimated.

ETEC is the second leading cause of death in children less than 5 years of age. Often ETEC is the first enteric infection experienced by infants in low resource countries, and in endemic areas almost all children will have had 1 ETEC diarrhea episode in their first year of life. In Bangladesh and Egypt, the majority of cases of ETEC occur in children less than 2 years of age, and between 15 and 18% of children 3 years and younger experience ETEC-associated diarrhea episodes. ETEC is less prevalent in children 5 years and older, as well as in adults, because of natural immunity that develops following several episodes of the disease.[3] However, older adults are quite vulnerable and ETEC, along with cholera, is likely to be responsible for approximately half of the hospitalizations due to diarrheal disease in this age group in endemic areas.

As with other types of diarrheal disease, ETEC infection is associated with malnutrition, growth stunting, and cognitive deficits in children. It is not uncommon for children in the developing world to experience 10 severe episodes of diarrhea in a year, with several due to ETEC. The malnutrition and dehydration that results translates into productivity loss of 15 to 20% in adult life.[4]

ETEC is also an important cause of disease in travelers. It is the leading cause of diarrhea in travelers from the developed world returning from vacation in low resource countries. The incidence of ETEC in travelers from industrialized regions to developing countries is projected to be in the 30 to 45% range.[5] One out of every six travelers to endemic areas has been observed to be infected with ETEC.[6]

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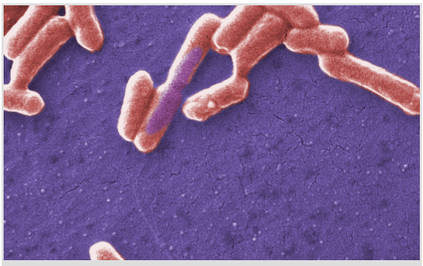
Causative Agent and Transmission



Escherichia coli (photo: CDC/Janice Carr)

E. coli is a bacterium with numerous serotypes, most of which normally inhabit the human intestinal tract with little ill effect. Several strains, however, secrete toxins that act on the intestinal lining and cause disease. *E. coli* that cause diarrheal illness can be broken down into four categories based on virulence mechanism: enterotoxigenic (ETEC), enteropathogenic (EPEC), enteroinvasive (EIEC), and enteroaggregative (EAggEC). ETEC differs from the other *E. coli* serotypes in that it produces two toxins that induce extreme fluid secretion from the small intestine.

ETEC is transmitted when a person eats food, or drinks water or ice contaminated with ETEC bacteria. Human or animal wastes (e.g., feces) are the main source of ETEC contamination.

Pathogenesis

ETEC bacteria colonize the mucosal surface of the small intestine. The bacteria use fimbrial adhesins (projections from the bacterial cell surface) to bind enterocyte cells in the small intestine. Adhesion to the mucosal epithelial cells allows for transfer of enterotoxins produced by ETEC bacteria which stimulate the release of liquid from the cells lining the intestinal walls. ETEC make two toxins, heat-labile (LT) and heat-stable (ST), that cause intestinal epithelial cells to secrete excess fluid. Some strains produce only one of the toxins while others produce both.

ETEC infection results in the production of abundant watery diarrhea and abdominal cramping. Other symptoms such as fever, vomiting, chills, headache, muscle aches, and bloating can also occur but are less common. Illness usually lasts 3-4 days following exposure to the bacteria but can persist for up to 3 weeks. Supportive measures including rehydration tend to be sufficient for recovery, and hospitalization or antibiotics are usually not required.

Control Strategy

The primary control strategy for ETEC is prevention of oral-fecal transmission through building sanitation infrastructure. Other measures can be taken to control infection, these include cooking food and keeping it hot, peeling fruits and vegetables, and using water that has been boiled or chemically treated with iodine, chlorine, or another disinfectant. Bismuth subsalicylate preparations (essentially an antidiarrheal agent) can reduce ETEC and other common bacterial infections that cause diarrhea. Before taking bismuth subsalicylate, individuals with kidney disease should consult a physician. Secondary to prevention, management of the disease using oral rehydration therapy reduces morbidity and mortality associated with the disease.

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Existing Products

Drugs

Individuals with diarrhea are treated with clear liquids to prevent dehydration and loss of electrolytes. Oral rehydration salts or premixed oral rehydration solutions are often used to treat dehydration. Zinc treatment can speed recovery time.

Fluoroquinolones have been found to be effective in treating ETEC infection. Although antibiotics can shorten the length of diarrheal disease, especially if given early, ETEC is frequently resistant to common antibiotics, including trimethoprim-sulfamethoxazole and ampicillin. Since antibiotic resistance is on the increase worldwide, the decision to treat ETEC with an antibiotic should be carefully considered with regards to the severity of the illness.

Vaccines

No vaccines directed against ETEC bacteria are on market at this time. Dukoral, an oral whole-cell/recombinant B-subunit vaccine directed against cholera, has been found to provide short term efficacy against ETEC diarrhea. Protective efficacy against cholera is 85 percent, while protection against the heat-labile toxin of ETEC reaches 67 percent.

Diagnostics

ETEC detection relies on the identification of the two enterotoxins. Several immunoassays have been developed for detection of the heat-stable toxin (ST), including a radioimmunoassay and an enzyme-linked immunosorbent assay (ELISA). Two commercial agglutination tests are available for detecting ETEC heat-labile enterotoxin (LT).

ETEC strains were among the first pathogenic microorganisms for which molecular diagnostic techniques were developed. DNA probes are found to be useful in the detection of LT- and ST-encoding genes in stool and environmental samples. Several PCR assays exist for ETEC that are quite sensitive and specific when used directly on clinical samples or on isolated bacterial colonies.

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References

1. WHO (2008). The World Health Report 2008: Primary HealthCrae-Now More Than Ever.
2. WHO (2006) “Future directions for research on enterotoxigenic *Escherichia coli* vaccines for developing countries.” Weekly Epidemiological Record. 81:97-104.
3. Fisher-Walker CL and Black RE (2010) “Diarrheoa morbidity and mortality in older children, adolescents and adults.” *Epidemiology and Infection* **138**:1215-1226.
4. Qadri F et al. (2005) “Enterotoxigenic *Escherichia coli* in developing countries: epidemiology, microbiology, clinical features, treatment, and prevention.” *Clinical Microbiology Reviews* **18**: 465-483.
5. Subekti DS et al. (2003) “Prevalence of enterotoxigenic *Escherichia coli* (ETEC) in hospitalized acute diarrhea patients in Denpasar, Bali, Indonesia.” *Diagnostic Microbiology and Infectious Disease* **47**: 399-405.
6. Steffen R et al. (2005) “Vaccination against enterotoxigenic *Escherichia coli*, a cause of travelers’ diarrhea”. *Journal of Travel Medicine* **12**: 102-107.

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 ETEC. Vaccines are the primary focus of new product development for ETEC.

Vaccines

PIPELINE

Product/Research Program	Developers	Discovery	Pre-clinical	Phase I	Phase II	Phase III
ACE527	Johns Hopkins Bloomberg School of Public Health PATH Pierrel Research USA TD Vaccines A/S					
dmLT	National Institute of Allergy and Infectious Diseases PATH Tulane University					
SBL 109	Crucell PATH					
Peru-15 pCTB (ETEC)	National Institute of Allergy and Infectious Diseases					
FTL-LTB chimera protein	Naval Medical Research Center Sanofi Pasteur University of Colorado					
LT/ST fusion proteins	International Enteric Vaccine Consortium PATH Research Council of Norway					
EtpA glycoprotein	University of Tennesee					
ACE920	TD Vaccines A/S					
SRP	Syntiron					
Mucosal immunobiology and vaccines discovery	Mucosal Immunobiology and Vaccine Center					
Mimopath-based ETEC	Mucosis B.V.					

vaccine	PATH					
Traveler's diarrhea vaccine	Intercell AG					On Hold

ANALYSIS

Vaccines for the prevention of ETEC are a key focus of research and development efforts for this disease. The only existing vaccine for ETEC is a cholera vaccine (Dukoral) that provides partial protection due to cross protection between the cholera B toxin and the ETEC toxins. Clinical stage vaccines include live attenuated, recombinant protein and inactivated whole cell vaccine technologies. However, clinical efficacy is not yet available to determine which of these technology strategies will be most successful.

A recombinant protein vaccine for ETEC (traveler's diarrhea vaccine, Intercell) was recently put on hold after it failed to meet efficacy endpoints in phase II and III trials.[1] Interestingly, antibodies to the ETEC heat-labile toxin (LT) were detected in vaccinated individuals. This failure raises questions as to whether recombinant LT produces a sufficient immune response to protect against disease. Other recombinant protein vaccines in development are exploring LT and other protein antigens.

The discontinued recombinant protein vaccine was delivered by intradermal patch. The detection of antibodies to LT suggests this vaccine delivery technology was working, despite the endpoint failure of the study. This technology might have applications for other NTD vaccines.

	Strengths	Weaknesses	Opportunities	Risks
Live attenuated				
Most advanced program: ACE527, Phase II Additional product in phase I	Live, deletion attenuated strain that mimics natural infection	Difficult to achieve balance between immunogenicity and attenuation of virulence	Combination with vaccines that cause other diarrheal diseases by expression of additional protein antigens in the modified live vaccine strain	May cause symptoms if attenuation is incomplete
Recombinant/purified protein				
Most advanced program: dmLT, Phase I Product formerly in phase III on hold as of December 2010 Additional products in pre-clinical development	As it is the ETEC secreted toxins that cause the majority of disease, protection against the toxin is likely to be important Based on concept that cross protection against ETEC with Dukoral (cholera vaccine) is due to cross protection between cholera and ETEC toxin proteins	Previous phase III study failed to meet endpoints of preventing ETEC/diarrhea Previous phase II vaccine and dmLT vaccine target the heat labile toxin (LT) but not the heat stable toxin (ST)	Although on hold at the phase III development stage, transdermal patch technology may be applicable to other recombinant protein vaccines in development	Unlikely to be delivered via the oral route of natural infection which may affect efficacy
Inactivated				
Most advanced program: SBL 109, Phase I	Can use virulent disease strain to generate vaccine Can be delivered orally via the natural route of infection	Inactivated whole cell vaccine for cholera not fully effective, clinical data for ETEC not yet available	Potential for combination with recombinant protein vaccines as was done for Dukoral for cholera	May not generate as strong an immune response as the live attenuated vaccine in phase II development

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Diagnostics

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.

References

1. Intercell press release.

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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 ETEC. 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 ETEC are generally well developed.

Drug Development Tools

Basic Research: Target Identification	Target Validation	Screening: Hit/Lead Identification Optimization	Pre-clinical Validation	Clinical Validation
Genome: ETEC strain H10407 sequenced and annotated; ETEC strain E1392/75 sequenced **Key databases:** EB-Eye Search: Strain H10407 Accession no. FN649414 EB-Eye Search: Strain E1392/75 Plasmid accession nos. FN822745, FN822746, FN822747, FN822748, FN822749 ***In vitro* culture:** Yes	**Gene knock-outs:** Yes **Conditional gene knock-outs:** Yes **Transposon mutagenesis:** Yes **RNAi:** No **Other antisense technology:** Yes **Transcription microarrays:** Yes **Proteomics:** Yes **Crystal structures:** Yes, several crystal structures of ETEC proteins exist including fimbrial adhesion F17-G, heat-labile enterotoxin, and type 2 secretion system GspK-GspI-Gsp-J complex.	**Whole-cell screening assays:** Yes, can be done in liquid culture and on culture plates, heat-labile toxin is often used as the assay readout **Enzymatic screening assays:** Yes	**Animal models:** Several models exist, including Balb/c mice; infant mouse strain Swiss 0F1; infant rabbit; infant piglet; rabbit ileal loop; and dog-jejunal Thiry-Vella loops	**Monitoring treatment efficacy:** Immunoassays to detect ST toxin and agglutination tests for detection of LT produced by bacterial cultures can be used for disease monitoring PCR to detect ST and LT from clinical samples or isolated cultures **Availability of endpoints:** Yes **Availability of surrogate endpoints:** Yes, watery diarrhea **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, most commonly mouse and pig **Detection of endogenous antigen specific response in clinical samples:** Yes to LT not to ST; serum titers to LT do not last long **Natural immunity well characterized:** Yes	**Surrogate markers of protection:** Yes **Challenge studies possible:** Yes

Diagnostic Development Tools

Basic Research: Biomarker Identification	Biomarker Validation	Clinical Validation
See drug development tools above	**Biomarkers known:** Yes **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

ACE527

Synonyms:
ACE527

Disease:
Enterotoxigenic E. coli (ETEC)

Specific Indication:
Anti-toxin, LT

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Live attenuated vaccines

Mechanism of Action:

Molecule Class:

Administration Route:
Oral

Notes:

Clinical Trials:

NCT01060748
NCT00901654

Publications:

ACE920

Synonyms:
ACE920

Disease:
Enterotoxigenic E. coli (ETEC)

Specific Indication:
Preventive, cross protection for Campylobacter

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Unknown

Mechanism of Action:

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

dmLT

Synonyms:
dmLT

Disease:
Enterotoxigenic E. coli (ETEC)

Specific Indication:
Anti-toxin, LT

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Recombinant/purified protein vaccines

Mechanism of Action:

Molecule Class:

Administration Route:
Oral

Notes:

Clinical Trials:

NCT01147445

Publications:

EtpA glycoprotein

Synonyms:
EtpA glycoprotein

Disease:
Enterotoxigenic E. coli (ETEC)

Specific Indication:

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Recombinant/purified protein vaccines

Mechanism of Action:

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

FTL-LTB chimera protein

Synonyms:
FTL-LTB chimera protein

Disease:
Enterotoxigenic E. coli (ETEC)

Specific Indication:

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Recombinant/purified protein vaccines

Mechanism of Action:

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

LT/ST fusion proteins

Synonyms:
LT/ST fusion proteins

Disease:
Enterotoxigenic E. coli (ETEC)

Specific Indication:

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Recombinant/purified protein vaccines

Mechanism of Action:

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

Mimopath-based ETEC vaccine

Synonyms:
Mimopath-based ETEC vaccine

Disease:
Enterotoxigenic E. coli (ETEC)

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:

Mucosal immunobiology and vaccines discovery

Synonyms:
Mucosal immunobiology and vaccines discovery

Disease:
Enterotoxigenic E. coli (ETEC)

Specific Indication:
Preventive

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Unknown

Mechanism of Action:

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

Peru-15 pCTB (ETEC)

Synonyms:
Peru-15 pCTB (ETEC)

Disease:
Enterotoxigenic E. coli (ETEC)

Specific Indication:
Preventive, cholera vaccine with ETEC cross protection

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Live attenuated vaccines

Mechanism of Action:

Molecule Class:

Administration Route:
Oral

Notes:

In development for cholera but has potential ETEC cross protection.

Clinical Trials:

NCT00654108

Publications:

SBL 109

Synonyms:
SBL 109

Disease:
Enterotoxigenic E. coli (ETEC)

Specific Indication:

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Inactivated vaccines

Mechanism of Action:

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

SRP

Synonyms:
SRP

Disease:
Enterotoxigenic E. coli (ETEC)

Specific Indication:

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Unknown

Mechanism of Action:

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

Traveler's diarrhea vaccine

Synonyms:
Traveler's diarrhea vaccine

Disease:
Enterotoxigenic E. coli (ETEC)

Specific Indication:
Preventive, developed for use in travelers

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Recombinant/purified protein vaccines

Mechanism of Action:

Molecule Class:

Administration Route:
Transcutaneous

Notes:

Clinical Trials:

NCT00993681
NCT01040325
NCT00516659

Publications:

Developer Details

International Vaccine Institute (South Korea)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	Dukoral (ETEC)	Approved

Intercell AG (Austria)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	Traveler's diarrhea vaccine	Phase III

PATH (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	ACE527	Phase II

PATH (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	SBL 109	Phase I

PATH (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	LT/ST fusion proteins	Pre-clinical

PATH (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	dmLT	Phase I

PATH (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	Mimopath-based ETEC vaccine	Discovery

Tulane University (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	dmLT	Phase I

National Institute of Allergy and Infectious Diseases (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	Peru-15 pCTB (ETEC)	Phase I

National Institute of Allergy and Infectious Diseases (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	dmLT	Phase I

TD Vaccines A/S (Denmark)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	ACE527	Phase II

TD Vaccines A/S (Denmark)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	ACE920	Pre-clinical

Pierrel Research USA (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	ACE527	Phase II

Johns Hopkins Bloomberg School of Public Health (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	ACE527	Phase II

Crucell (Netherlands)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	SBL 109	Phase I

University of Colorado (United States)

Type	Disease	Product/Research Program	Current Phase

Vaccine	Enterotoxigenic E. coli (ETEC)	FTL-LTB chimera protein	Pre-clinical

Sanofi Pasteur (France)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	FTL-LTB chimera protein	Pre-clinical

Naval Medical Research Center (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	FTL-LTB chimera protein	Pre-clinical

International Enteric Vaccine Consortium (Norway)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	LT/ST fusion proteins	Pre-clinical

Research Council of Norway (Norway)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	LT/ST fusion proteins	Pre-clinical

University of Tennesee (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	EtpA glycoprotein	Pre-clinical

Syntiron (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	SRP	Discovery

Mucosal Immunobiology and Vaccine Center (Sweden)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	Mucosal immunobiology and vaccines discovery	Discovery

Mucosis B.V. (Netherlands)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Enterotoxigenic E. coli (ETEC)	Mimopath-based ETEC vaccine	Discovery