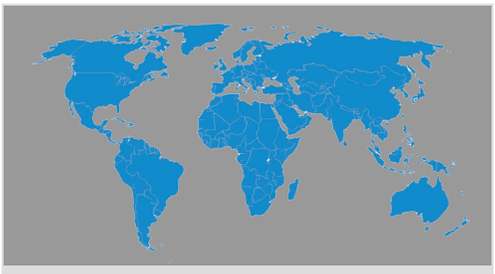
Background

What is Rotavirus?

Rotavirus is the most common cause of severe diarrhea among infants and young children worldwide. In developing nations, this virus is responsible for the large majority of diarrhea-related childhood deaths. Infection causes abdominal pain, watery diarrhea, vomiting, and fever. These symptoms can result in rapid dehydration, which can be fatal. Rotavirus spreads via a fecal-oral route and is easily transmitted person-to-person and through contact with contaminated objects, water, and food. Outbreaks can rapidly take hold in institutional settings, such as daycares, schools, and hospitals.

Global Burden



Rotavirus infects nearly all young children and infants worldwide, but mortality rates vary widely. *(WHO, 2009)*

Rotavirus is distributed worldwide, and nearly all children in both the developed and developing worlds have been infected by the time they are three years old.[1] Complicating factors, such as poverty and low birth weight, increase the risk for hospitalization irrespective of geographic location. Each year, rotavirus is responsible for an estimated 527,000 deaths,[1] with India, Southeast Asia, and sub-Saharan Africa bearing the greatest mortality rates.

In the United States alone, rotavirus infection leads to over 200,000 emergency room visits and 55,000 - 70,000 hospitalizations each year, translating into an economic impact of approximately US$1 billion annually.[2] Globally, rotavirus is estimated to result in 25 million doctors visits and 2 million hospitalizations each year.[3]

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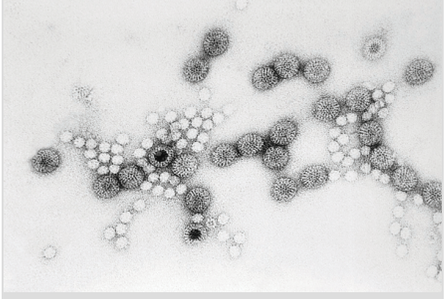
Causative Agent and Transmission



Scanning electron micrograph of rotavirus particles and a number of small, unknown particles. (photo: CDC/Eskine Palmer)

Rotaviruses are non-enveloped, double-stranded RNA viruses belonging to the family *Reoviridae*. Rotavirus particles are made up of three concentric layers of capsid proteins, giving them a wheel-like (latin, *rota*) appearance under the electronmicroscope.

Rotaviruses are classified into seven groups (A-G), which infect different species including humans, other mammals, and birds.[4] Group A rotaviruses cause the majority of human infections. Rotaviruses are further divided into multiple serotypes. Primary infection leads to the generation of antibodies that can protect against the initial serotype, and can give partial protection against other serotypes. Although primary infection does not provide full immunity against the many strains of rotavirus, subsequent infections are generally less severe.

Transmission of rotavirus occurs by ingestion of feces from an infected individual. The high numbers of virus particles shed from an acutely infected patient, combined with the low number of viruses required to cause infection, lead to rapid spread of the virus. Rotavirus can be found in the stool of both symptomatic and asymptomatic children. Rotavirus particles are highly stable and can remain infectious for months at room temperature, further facilitating transmission. Rotavirus is so infectious that good hygiene and hand washing are not enough to prevent its spread.[5] In temperate climates, rotavirus infections are seasonal, with the highest incidence from December to June; in the tropics, infections occur year-round.

Pathogenesis

Rotavirus is taken into the body by ingestion, and infects epithelial cells lining the small intestine. Viral replication in the cytoplasm causes cellular damage and fluid secretion, which result in profuse, watery diarrhea. The appearance of symptoms generally occurs suddenly after an incubation period of 1-2 days. Diarrhea, vomiting, and fever can last between 4-7 days, during which time very large numbers of virus particles are shed in the feces.

Control Strategy

Control of rotavirus focuses on improving sanitation and promoting vaccination. Two recently approved rotavirus vaccines have been beneficial at reducing infection rates in the developed world; safety, efficacy, and availability of the vaccines in poorer countries are still under investigation.[1]

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Existing Products

Drugs

There are no specific antiviral drugs available to treat rotavirus infection. Symptoms are managed by oral or intravenous rehydration therapy.

Vaccines

There are currently two vaccines available for the prevention of rotavirus:

1. **RotaTeq, developed by Merck:** Contains five types of rotaviruses, each based on an attenuated bovine strain (WC3) expressing VP7 (glycoprotein, G) and VP4 (protease-sensitive protein, P) from human rotaviruses.
2. **Rotarix, developed by GlaxoSmithKline:** Contains a single strain of rotavirus, which is derived from a human isolate and was attenuated by multiple passages in cell culture.

Both vaccines are administered orally and are based on live attenuated viruses. Although vaccination does not completely protect against the many rotavirus strains, it is effective at preventing severe infection. These vaccines have been highly beneficial in the United States, reducing rotavirus infections by 50% in the 2007-2008 season as immunization became widespread.[1] In the developing world, additional studies are underway to evaluate the safety and efficacy of these vaccines in the context of complicating factors, such as malnutrition, preexisting infections, and the need for cross-protection against additional rotavirus strains.

Country	Vaccine	Impact[1,6]
Australia	Rotateq and Rotarix	89-94% vaccine efficacy; 68-93% reduction in hospital admissions for rotavirus in children <1 year old
Belgium	Rotarix	65-83% reduction in rotavirus hospitalizations
El Salvador	Rotarix	35-48% decrease in all diarrhea events; 69-81% decrease in

		rotavirus hospitalizations in children <5 years old
Mexico	Rotarix	11-40% reduction in all cause diarrhea hospitalization in children <5 years old
Panama	Rotarix	22-37% reduction in all cause diarrhea hospitalizations in children <5 years old
United States	Rotateq	~50% decrease in rotavirus infections; no rotavirus epidemic detected in 2010 (first time in 19 years no epidemic occurred)

Diagnostics

Immune-based, nucleic acid amplification-based, and culture-based diagnostic techniques are available for rotavirus. All of these diagnostics require access to sophisticated laboratory facilities.

As diarrhea due to rotavirus, like other diarrheal disease, is primarily treated by supportive rehydration therapy rather than medications, specific diagnosis of rotavirus is not considered essential.

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References

1. WHO, Initiative for Vaccine Research: Diarrheal Diseases.
2. Parashar UD et al. (2006) “Prevention of Rotavirus Gastroenteritis Among Infants and Children.” *MMWR* **55**: 1-13.
3. Parashar UD et al. (2003) “Global illness and deaths caused by rotavirus disease in children.” *Emerg Infect Dis* **9**: 565-72.
4. Desselberger U et al. (2009) “Rotaviruses and rotavirus vaccines.” *Br Med Bull* **90**: 37-51.
5. CDC: About Rotavirus.
6. Patel MM et al (2010) “Real-world Impact of Rotavirus Vaccination.” *The Pediatric Infectious Disease Journal* **30**: S1-S5

Get Involved

To learn how you can get involved in neglected disease drug, vaccine or diagnostic research and development, or to provide updates, changes, or corrections to the Global Health Primer website, please view our FAQs or contact us at globalhealthprimer@bvgh.org.

Pipeline & Analysis

Drugs | Vaccines | Diagnostics | Get Involved

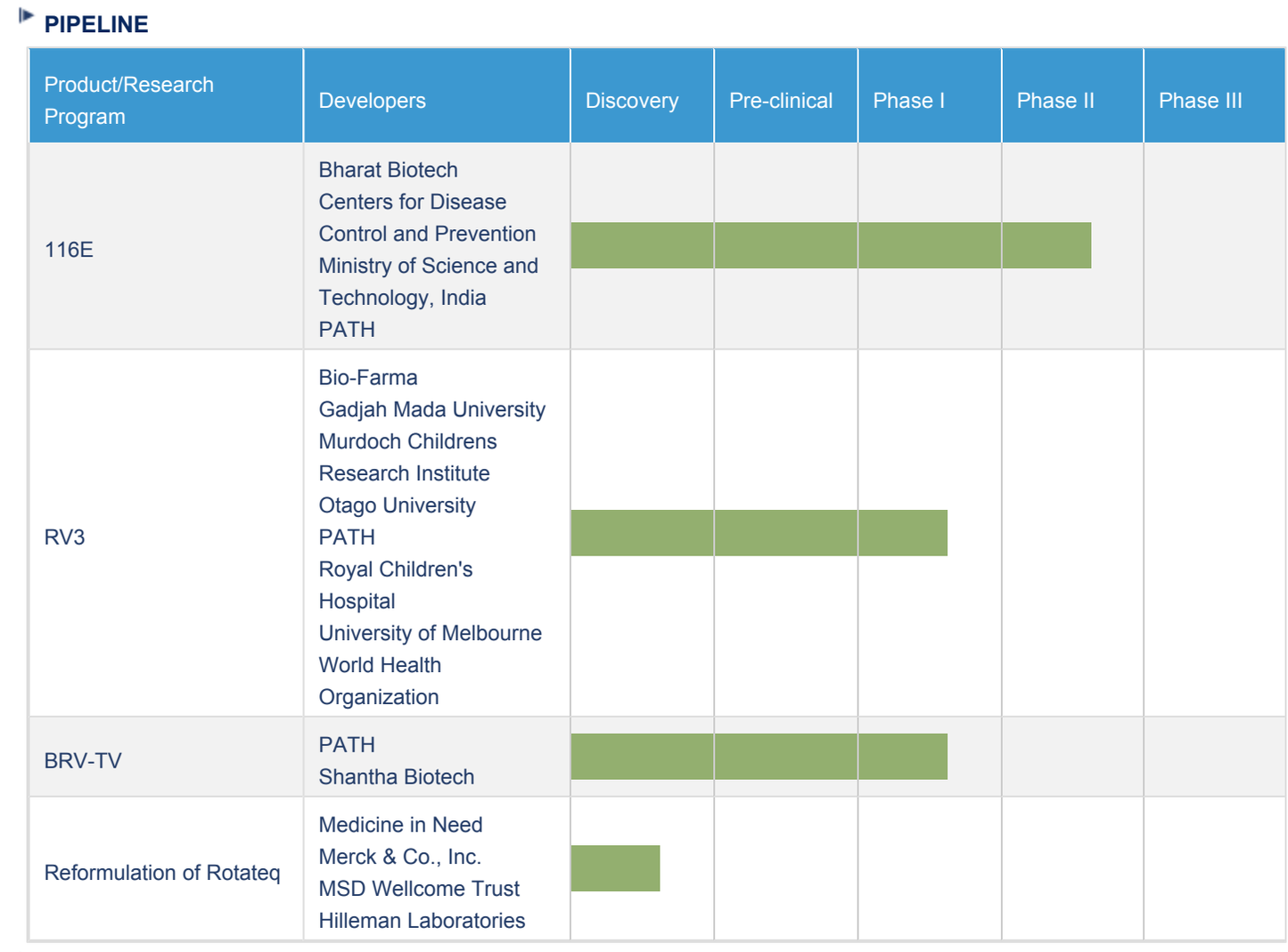
Drugs

Rotavirus, like other diarrheal diseases, is effectively managed by oral or intravenous rehydration therapy. Therefore, development of specific antiviral agents for rotavirus is not considered a priority.

Vaccines

PIPELINE

Product/Research Program	Developers	Discovery	Pre-clinical	Phase I	Phase II	Phase III
116E	Bharat Biotech Centers for Disease Control and Prevention Ministry of Science and Technology, India PATH					
RV3	Bio-Farma Gadjah Mada University Murdoch Childrens Research Institute Otago University PATH Royal Children's Hospital University of Melbourne World Health Organization					
BRV-TV	PATH Shantha Biotech					
Reformulation of Rotateq	Medicine in Need Merck & Co., Inc. MSD Wellcome Trust Hilleman Laboratories					



ANALYSIS

As there are already two vaccines commercially available for rotavirus, the primary focus for vaccine development includes:

1. Expanding clinical research on existing vaccines to more fully characterize their safety and efficacy in developing world populations
2. Increasing access to existing vaccines, including lowering the vaccine cost

New vaccine development is relatively limited for rotavirus, but includes two clinical phase vaccines. These vaccines are focusing on improving efficacy and allowing for at birth dosing. The value and best strategies for new vaccine development should be guided by limitations identified in the current vaccines as they are studied in more detail in developing world populations.

	Strengths	Weaknesses	Opportunities	Risks

Live attenuated				
Most advanced program: On market (New vaccines*: RV3,* phase I, and 116E, phase II)	Proven vaccine approach for rotavirus	Requires cold chain for delivery Efficacy and safety in developing world populations still unknown	Reduced number of doses At birth dosing Optimization for efficacy and safety in developing world	Two vaccines are already on market so may be difficult to improve upon those

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Diagnostics

As disease specific treatment is not available for rotavirus, the development of new diagnostics is not a high priority for this disease.

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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 rotavirus. 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.

Drug Development Tools

Basic Research: Target Identification	Target Validation	Screening: Hit/Lead Identification Optimization	Pre-clinical Validation	Clinical Validation
Genome: Sequenced **Key databases:** Virus Sequence Database ***In vitro* culture:** Yes, need to activate virus by trypsin proteolysis; reverse genetics system is available but limited by low efficiency and requirement for wild-type helper rotavirus	**Gene knock-outs:** Yes, but subject to limitations of reverse genetics system **Conditional gene knock-outs:** Yes, temperature sensitive mutants **Transposon mutagenesis:** Possible, but subject to limitations of reverse genetics system **RNAi:** Yes, using host cell machinery **Other antisense technology:** Host cell only **Viability assays:** Yes, virus causes cytopathic effect to infected cells **Transcription microarrays:** Yes, of infected cells **Proteomics:** Yes **Crystal structures:** Yes, cryoelectron microscopy structures of whole viral particles also available	**Whole-cell screening assays:** Yes, using virus infected cells or cells expressing viral proteins **Enzymatic screening assays:** Yes	**Animal models:** Yes, mice infected with rotavirus are useful for immunity studies, but only mimic human pathogenesis during first two weeks of life Gnotobiotic newborn pigs mimic human symptoms of rotavirus infection Rabbits and calves are also used	**Monitoring treatment efficacy:** Yes **Availability of endpoints:** Yes, clearance of virus **Availability of surrogate endpoints:** No **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, gnotobiotic newborn pig mimics human disease most closely, but time window for vaccination and challenge is short; adult mouse model is useful for studying immunity, but does not mimic human pathogenesis **Detection of endogenous antigen specific response in clinical samples:** Yes **Natural immunity well characterized:** Yes, virus-specific IgA is important	**Surrogate markers of protection:** Yes, serum IgA and neutralizing antibodies **Challenge studies possible:** Used in adults in the 1980s and 1990s but most likely not possible in children, the target population for a vaccine

Diagnostic Development Tools

Basic Research: Biomarker Identification	Biomarker Validation	Clinical Validation
See drug development tools above	**Biomarkers known:** Yes, viral RNA and proteins **Access to clinical samples:** Yes **Possible sample types:** Stool, serum	**Access to clinical trial patients/sites:** Yes **Treatment available if diagnosed:** Oral rehydration therapy available but no specific antivirals

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Product Details

116E

Synonyms:
116E

Disease:
Rotavirus

Specific Indication:
Preventive

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Live attenuated vaccines

Mechanism of Action:

Molecule Class:

Administration Route:
Oral

Notes:

Clinical Trials:

NCT00439660

Publications:

19545211

BRV-TV

Synonyms:
BRV-TV
tetravalent bovine-human reassortant rotavirus vaccine

Disease:
Rotavirus

Specific Indication:

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Live attenuated vaccines

Mechanism of Action:

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

NCT01091298

Publications:

Reformulation of Rotateq

Synonyms:
Reformulation of Rotateq

Disease:
Rotavirus

Specific Indication:

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Live attenuated vaccines

Mechanism of Action:

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

Reformulation of Merck's on market Rotateq product onto dissolvable strips that do not require refrigeration.

RV3

Synonyms:
RV3

Disease:
Rotavirus

Specific Indication:
Preventive

Product Type:
Vaccine

PRV Elegible?
No

Target/Technology:
Live attenuated vaccines

Mechanism of Action:
Neonatal human rotavirus

Molecule Class:

Administration Route:
Oral

Notes:

Clinical Trials:

Publications:

19907040

Developer Details

MSD Wellcome Trust Hilleman Laboratories (India)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	Reformulation of Rotateq	Discovery

Medicine in Need (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	Reformulation of Rotateq	Discovery

Merck & Co., Inc. (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	RotaTeq	Approved

Merck & Co., Inc. (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	Reformulation of Rotateq	Discovery

GlaxoSmithKline (United Kingdom)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	Rotarix	Approved

PATH (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	RV3	Phase I

PATH (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	116E	Phase II

PATH (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	BRV-TV	Phase I

Ministry of Science and Technology, India (India)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	116E	Phase II

Bharat Biotech (India)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	116E	Phase II

Centers for Disease Control and Prevention (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	116E	Phase II

World Health Organization (Switzerland)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	RV3	Phase I

Murdoch Childrens Research Institute (Australia)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	RV3	Phase I

University of Melbourne (Australia)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	RV3	Phase I

Royal Children's Hospital (Australia)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	RV3	Phase I

Otago University (New Zealand (Aotearoa))

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	RV3	Phase I

Gadjah Mada University (Indonesia)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	RV3	Phase I

Bio-Farma (United Kingdom)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	RV3	Phase I

Shantha Biotech (India)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Rotavirus	BRV-TV	Phase I