= Rotavirus =

Rotavirus is the most common cause of severe vomiting and diarrhoea among infants and young children . It is a genus of double @-@ stranded RNA viruses in the family Reoviridae . Nearly every child in the world has been infected with rotavirus at least once by the age of five . Immunity develops with each infection , so subsequent infections are less severe ; adults are rarely affected . There are eight species of this virus , referred to as A , B , C , D , E , F , G and H. Rotavirus A , the most common species , causes more than 90 % of rotavirus infections in humans .

The virus is transmitted by the faecal @-@ oral route . It infects and damages the cells that line the small intestine and causes gastroenteritis (which is often called " stomach flu " despite having no relation to influenza) . Although rotavirus was discovered in 1973 by Ruth Bishop and her colleagues by electron micrograph images and accounts for up to 50 % of hospitalisations for severe diarrhoea in infants and children , its importance has been underestimated within the public health community , particularly in developing countries . In addition to its impact on human health , rotavirus also infects animals , and is a pathogen of livestock .

Rotavirus is usually an easily managed disease of childhood , but worldwide more than 450 @,@ 000 children under five years of age still die from rotavirus infection each year , most of whom live in developing countries , and almost two million more become severely ill . In the United States , before initiation of the rotavirus vaccination programme , rotavirus caused about 2 @.@ 7 million cases of severe gastroenteritis in children , almost 60 @,@ 000 hospitalizations , and around 37 deaths each year . Public health campaigns to combat rotavirus focus on providing oral rehydration therapy for infected children and vaccination to prevent the disease . The incidence and severity of rotavirus infections has declined significantly in countries that have added rotavirus vaccine to their routine childhood immunisation policies .

= = Signs and symptoms = =

Rotaviral enteritis is a mild to severe disease characterised by nausea , vomiting , watery diarrhoea and low @-@ grade fever . Once a child is infected by the virus , there is an incubation period of about two days before symptoms appear . The period of illness is acute . Symptoms often start with vomiting followed by four to eight days of profuse diarrhoea . Dehydration is more common in rotavirus infection than in most of those caused by bacterial pathogens , and is the most common cause of death related to rotavirus infection .

Rotavirus A infections can occur throughout life : the first usually produces symptoms , but subsequent infections are typically mild or asymptomatic , as the immune system provides some protection . Consequently , symptomatic infection rates are highest in children under two years of age and decrease progressively towards 45 years of age . Infection in newborn children , although common , is often associated with mild or asymptomatic disease ; the most severe symptoms tend to occur in children six months to two years of age , the elderly , and those with immunodeficiency . Due to immunity acquired in childhood , most adults are not susceptible to rotavirus ; gastroenteritis in adults usually has a cause other than rotavirus , but asymptomatic infections in adults may maintain the transmission of infection in the community .

= = Transmission = =

Rotavirus is transmitted by the fæcal @-@ oral route , via contact with contaminated hands , surfaces and objects , and possibly by the respiratory route . Viral diarrhea is highly contagious . The faeces of an infected person can contain more than 10 trillion infectious particles per gram ; fewer than 100 of these are required to transmit infection to another person .

Rotaviruses are stable in the environment and have been found in estuary samples at levels up to 1 ? 5 infectious particles per US gallon , the viruses survive between 9 and 19 days . Sanitary measures adequate for eliminating bacteria and parasites seem to be ineffective in control of rotavirus , as the incidence of rotavirus infection in countries with high and low health standards is

similar .

= = Disease mechanisms = =

The diarrhoea is caused by multiple activities of the virus . Malabsorption occurs because of the destruction of gut cells called enterocytes . The toxic rotavirus protein NSP4 induces age- and calcium ion @-@ dependent chloride secretion , disrupts SGLT1 transporter @-@ mediated reabsorption of water , apparently reduces activity of brush @-@ border membrane disaccharidases , and possibly activates the calcium ion @-@ dependent secretory reflexes of the enteric nervous system . Healthy enterocytes secrete lactase into the small intestine ; milk intolerance due to lactase deficiency is a symptom of rotavirus infection , which can persist for weeks . A recurrence of mild diarrhoea often follows the reintroduction of milk into the child 's diet , due to bacterial fermentation of the disaccharide lactose in the gut .

= = Diagnosis and detection = =

Diagnosis of infection with rotavirus normally follows diagnosis of gastroenteritis as the cause of severe diarrhoea . Most children admitted to hospital with gastroenteritis are tested for rotavirus A. Specific diagnosis of infection with rotavirus A is made by finding the virus in the child 's stool by enzyme immunoassay . There are several licensed test kits on the market which are sensitive , specific and detect all serotypes of rotavirus A. Other methods , such as electron microscopy and PCR , are used in research laboratories . Reverse transcription @-@ polymerase chain reaction (RT @-@ PCR) can detect and identify all species and serotypes of human rotavirus .

= = Treatment and prognosis = =

Treatment of acute rotavirus infection is nonspecific and involves management of symptoms and , most importantly , management of dehydration . If untreated , children can die from the resulting severe dehydration . Depending on the severity of diarrhoea , treatment consists of oral rehydration therapy , during which the child is given extra water to drink that contains small amounts of salt and sugar . In 2004 , the WHO and UNICEF recommended the use of low @-@ osmolarity oral rehydration solution and zinc supplementation as a two @-@ pronged treatment of acute diarrhoea . Some infections are serious enough to warrant hospitalization where fluids are given by intravenous therapy or nasogastric intubation , and the child 's electrolytes and blood sugar are monitored . Probiotics have been shown to reduce the duration of rotavirus diarrhoea , and according to the European Society for Pediatric Gastroenterology " effective interventions include administration of specific probiotics such as Lactobacillus rhamnosus or Saccharomyces boulardii , diosmectite or racecadotril . " Rotavirus infections rarely cause other complications and for a well managed child the prognosis is excellent .

= = Epidemiology = =

Rotavirus A , which accounts for more than 90 % of rotavirus gastroenteritis in humans , is endemic worldwide . Each year rotavirus causes millions of cases of diarrhoea in developing countries , almost 2 million resulting in hospitalization and an estimated 453 @,@ 000 resulting in the death of a child younger than five , 85 percent of whom live in developing countries . In the United States alone ? before initiation of the rotavirus vaccination programme ? over 2 @.@ 7 million cases of rotavirus gastroenteritis occurred annually , 60 @,@ 000 children were hospitalised and around 37 died from the results of the infection . The major role of rotavirus in causing diarrhoea is not widely recognised within the public health community , particularly in developing countries . Almost every child has been infected with rotavirus by age five . It is the leading single cause of severe diarrhoea among infants and children , being responsible for about 20 % of cases , and accounts for 50 % of the cases requiring hospitalization . Rotavirus causes 37 % of deaths attributable to diarrhoea and 5

% of all deaths in children younger than five . Boys are twice as likely as girls to be admitted to hospital . Rotavirus infections occur primarily during cool , dry seasons . The number attributable to food contamination is unknown .

Outbreaks of rotavirus A diarrhoea are common among hospitalised infants , young children attending day care centres , and elderly people in nursing homes . An outbreak caused by contaminated municipal water occurred in Colorado in 1981 . During 2005 , the largest recorded epidemic of diarrhoea occurred in Nicaragua . This unusually large and severe outbreak was associated with mutations in the rotavirus A genome , possibly helping the virus escape the prevalent immunity in the population . A similar large outbreak occurred in Brazil in 1977 .

Rotavirus B , also called adult diarrhoea rotavirus or ADRV , has caused major epidemics of severe diarrhoea affecting thousands of people of all ages in China . These epidemics occurred as a result of sewage contamination of drinking water . Rotavirus B infections also occurred in India in 1998 ; the causative strain was named CAL . Unlike ADRV , the CAL strain is endemic . To date , epidemics caused by rotavirus B have been confined to mainland China , and surveys indicate a lack of immunity to this species in the United States .

Rotavirus C has been associated with rare and sporadic cases of diarrhoea in children , and small outbreaks have occurred in families .

= = Prevention = =

Because improved sanitation does not decrease the prevalence of rotaviral disease , and the rate of hospitalizations remains high despite the use of oral rehydrating medicines , the primary public health intervention is vaccination . Two vaccines against Rotavirus A infection are safe and effective in children : Rotarix by GlaxoSmithKline and RotaTeq by Merck . Both are taken orally and contain attenuated live virus . In 2009 , the World Health Organization (WHO) recommended that rotavirus vaccine be included in all national immunisation programmes . The incidence and severity of rotavirus infections has declined significantly in countries that have acted on this recommendation . In Mexico , which in 2006 was among the first countries in the world to introduce rotavirus vaccine , diarrhoeal disease death rates dropped during the 2009 rotavirus season by more than 65 percent among children age two and under . In Nicaragua , which in 2006 became the first developing country to introduce a rotavirus vaccine , severe rotavirus infections were reduced by 40 percent and emergency room visits by a half . In the United States , rotavirus vaccination since 2006 has led to drops in rotavirus @-@ related hospitalizations by as much as 86 percent . The vaccines may also have prevented illness in non @-@ vaccinated children by limiting the number of circulating infections .

Rotavirus vaccines are licensed in more than 100 countries , but only 28 countries have introduced routine rotavirus vaccination . Following the introduction of routine rotavirus vaccination in the US in 2006 , the health burden of rotavirus gastroenteritis " rapidly and dramatically reduced " despite lower coverage levels compared to other routine infant immunizations . Clinical trials of the Rotarix rotavirus vaccine in South Africa and Malawi , found that the vaccine significantly reduced severe diarrhoea episodes caused by rotavirus , and that the infection was preventable by vaccination . Safety and efficacy trials of Rotarix and RotaTeq in Africa and Asia found that the vaccines dramatically reduced severe disease among infants in developing countries , where the majority of rotavirus deaths occur . A 2012 Cochrane review of 41 clinical trials that included 186 @,@ 263 participants concluded Rotarix and RotaTeq are effective vaccines . Additional rotavirus vaccines are under development . In September 2013 , the vaccine was offered to all children in the UK , aged between two and three months , and it is expected to halve the cases of severe infection and reduce the number of children admitted to hospital because of the infection by 70 percent .

International non @-@ governmental organization PATH , the WHO , the U.S. Centers for Disease Control and Prevention , and the GAVI Alliance are working to bring rotavirus vaccines to developing countries , where children face the greatest burden . Through the Rotavirus Vaccine Program and the Accelerating Vaccine Introduction initiative , these groups are partnering with research institutions and governments to reduce child morbidity and mortality from diarrhoeal disease by

making a vaccine against rotavirus available for use in developing countries .

= = Infections of other animals = =

Rotaviruses infect the young of many species of animals and they are a major cause of diarrhoea in wild and reared animals worldwide . As a pathogen of livestock , notably in young calves and piglets , rotaviruses cause economic loss to farmers because of costs of treatment associated with high morbidity and mortality rates . These rotaviruses are a potential reservoir for genetic exchange with human rotaviruses . There is evidence that animal rotaviruses can infect humans , either by direct transmission of the virus or by contributing one or several RNA segments to reassortants with human strains .

= = Virology = =

= = = Types of rotavirus = = =

There are eight species of rotavirus , referred to as A , B , C , D , E , F , G , and H. Humans are primarily infected by species A , B and C , most commonly by species A. A ? E species cause disease in other animals . Within rotavirus A there are different strains , called serotypes . As with influenza virus , a dual classification system is used based on two proteins on the surface of the virus . The glycoprotein VP7 defines the G serotypes and the protease @-@ sensitive protein VP4 defines P serotypes . Because the two genes that determine G @-@ types and P @-@ types can be passed on separately to progeny viruses , different combinations are found .

= = = Structure = = =

The genome of rotavirus consists of 11 unique double helix molecules of RNA which are 18 @,@ 555 nucleotides in total . Each helix , or segment , is a gene , numbered 1 to 11 by decreasing size . Each gene codes for one protein , except genes 9 , which codes for two . The RNA is surrounded by a three @-@ layered icosahedral protein capsid . Viral particles are up to 76 @.@ 5 nm in diameter and are not enveloped .

= = = Proteins = = =

There are six viral proteins (VPs) that form the virus particle (virion) . These structural proteins are called VP1 , VP2 , VP3 , VP4 , VP6 and VP7 . In addition to the VPs , there are six nonstructural proteins (NSPs) , that are only produced in cells infected by rotavirus . These are called NSP1 , NSP2 , NSP3 , NSP4 , NSP5 and NSP6 .

At least six of the twelve proteins encoded by the rotavirus genome bind RNA . The role of these proteins play in rotavirus replication is not entirely understood ; their functions are thought to be related to RNA synthesis and packaging in the virion , mRNA transport to the site of genome replication , and mRNA translation and regulation of gene expression .

= = = = Structural proteins = = = =

VP1 is located in the core of the virus particle and is an RNA polymerase enzyme . In an infected cell this enzyme produces mRNA transcripts for the synthesis of viral proteins and produces copies of the rotavirus genome RNA segments for newly produced virus particles .

VP2 forms the core layer of the virion and binds the RNA genome .

VP3 is part of the inner core of the virion and is an enzyme called guanylyl transferase . This is a capping enzyme that catalyses the formation of the 5 ' cap in the post @-@ transcriptional modification of mRNA . The cap stabilises viral mRNA by protecting it from nucleic acid degrading

enzymes called nucleases .

VP4 is on the surface of the virion that protrudes as a spike . It binds to molecules on the surface of cells called receptors and drives the entry of the virus into the cell . VP4 has to be modified by the protease enzyme trypsin , which is found in the gut , into VP5 * and VP8 * before the virus is infectious . VP4 determines how virulent the virus is and it determines the P @-@ type of the virus .

VP6 forms the bulk of the capsid . It is highly antigenic and can be used to identify rotavirus species . This protein is used in laboratory tests for rotavirus A infections .

VP7 is a glycoprotein that forms the outer surface of the virion . Apart from its structural functions , it determines the G @-@ type of the strain and , along with VP4 , is involved in immunity to infection .

= = = = Nonstructural viral proteins = = = =

NSP1 , the product of gene 5 , is a nonstructural RNA @-@ binding protein . NSP1 also blocks the interferon response , the part of the innate immune system that protects cells from viral infection . NSP1 causes the proteosome to degrade key signaling components required to stimulate production of interferon in an infected cell and to respond to interferon secreted by adjacent cells . Targets for degradation include several IRF transcription factors required for interferon gene transcription .

NSP2 is an RNA @-@ binding protein that accumulates in cytoplasmic inclusions (viroplasms) and is required for genome replication .

NSP3 is bound to viral mRNAs in infected cells and it is responsible for the shutdown of cellular protein synthesis . NSP3 inactivates two translation initiation factors essential for synthesis of proteins from host mRNA . First , NSP3 ejects poly (A) -binding protein (PABP) from the translation initiation factor eIF4F . PABP is required for efficient translation of transcripts with a 3 ' poly (A) tail , which is found on most host cell transcripts . Second , NSP3 inactivates eIF2 by stimulating its phosphorylation . Efficient translation of rotavirus mRNA , which lacks the 3 ' poly (A) tail , does not require either of these factors .

NSP4 is a viral enterotoxin that induces diarrhoea and was the first viral enterotoxin discovered .

NSP5 is encoded by genome segment 11 of rotavirus A. In virus @-@ infected cells NSP5 accumulates in the viroplasm .

NSP6 is a nucleic acid binding protein and is encoded by gene 11 from an out @-@ of @-@ phase open reading frame .

This table is based on the simian rotavirus strain SA11 . RNA @-@ protein coding assignments differ in some strains .

= = = Replication = = =

Rotaviruses replicate mainly in the gut , and infect enterocytes of the villi of the small intestine , leading to structural and functional changes of the epithelium . The triple protein coats make them resistant to the acidic pH of the stomach and the digestive enzymes in the gut .

The virus enter cells by receptor mediated endocytosis and form a vesicle known as an endosome . Proteins in the third layer (VP7 and the VP4 spike) disrupt the membrane of the endosome , creating a difference in the calcium concentration . This causes the breakdown of VP7 trimers into single protein subunits , leaving the VP2 and VP6 protein coats around the viral dsRNA , forming a double @-@ layered particle (DLP) .

The eleven dsRNA strands remain within the protection of the two protein shells and the viral RNA @-@ dependent RNA polymerase creates mRNA transcripts of the double @-@ stranded viral genome . By remaining in the core , the viral RNA evades innate host immune responses called RNA interference that are triggered by the presence of double @-@ stranded RNA .

During the infection , rotavirus produces mRNA for both protein biosynthesis and gene replication . Most of the rotavirus proteins accumulate in viroplasm , where the RNA is replicated and the DLPs are assembled . Viroplasm is formed around the cell nucleus as early as two hours after virus infection , and consists of viral factories thought to be made by two viral nonstructural proteins :

NSP5 and NSP2 . Inhibition of NSP5 by RNA interference results in a sharp decrease in rotavirus replication . The DLPs migrate to the endoplasmic reticulum where they obtain their third , outer layer (formed by VP7 and VP4) . The progeny viruses are released from the cell by lysis .

= = History = =

In 1943 , Jacob Light and Horace Hodes proved that a filterable agent in the faeces of children with infectious diarrhoea also caused scours (livestock diarrhoea) in cattle . Three decades later , preserved samples of the agent were shown to be rotavirus . In the intervening years , a virus in mice was shown to be related to the virus causing scours . In 1973 , Ruth Bishop and colleagues described related viruses found in children with gastroenteritis .

In 1974 , Thomas Henry Flewett suggested the name rotavirus after observing that , when viewed through an electron microscope , a rotavirus particle looks like a wheel (rota in Latin) ; the name was officially recognised by the International Committee on Taxonomy of Viruses four years later . In 1976 , related viruses were described in several other species of animals . These viruses , all causing acute gastroenteritis , were recognised as a collective pathogen affecting humans and animals worldwide . Rotavirus serotypes were first described in 1980 , and in the following year , rotavirus from humans was first grown in cell cultures derived from monkey kidneys , by adding trypsin (an enzyme found in the duodenum of mammals and now known to be essential for rotavirus to replicate) to the culture medium . The ability to grow rotavirus in culture accelerated the pace of research , and by the mid @-@ 1980s the first candidate vaccines were being evaluated .

In 1998 , a rotavirus vaccine was licensed for use in the United States . Clinical trials in the United States , Finland , and Venezuela had found it to be 80 to 100 % effective at preventing severe diarrhoea caused by rotavirus A , and researchers had detected no statistically significant serious adverse effects . The manufacturer , however , withdrew it from the market in 1999 , after it was discovered that the vaccine may have contributed to an increased risk for intussusception , a type of bowel obstruction , in one of every 12 @,@ 000 vaccinated infants . The experience provoked intense debate about the relative risks and benefits of a rotavirus vaccine . In 2006 , two new vaccines against rotavirus A infection were shown to be safe and effective in children , and in June 2009 the World Health Organization recommended that rotavirus vaccination be included in all national immunisation programmes to provide protection against this virus .

In 2015 , India unveiled a cheaper vaccine with support of US National Institute of Health .