

Diarrhoea

What is diarrhoea?

Diarrhoea is the passing of increased amounts of loose stools. Literally, the noun has the meaning of excessive flow being a composition of the Greek words *dia* "through" and *rhoia* "flow". Diarrhoea can be acute (short term) or chronic (long term) – lasting more than two weeks. It is a symptom of other conditions or diseases and not a disease in itself.



Diarrhoea is often accompanied by stomach pains, feeling sick and vomiting. The disorder is most commonly caused by a virus, a bacterium or a protozoon, which has made its way into ingested food or water. In the digestive tract, the microorganisms irritate the mucous membrane of the small or large intestine resulting in an abnormally large quantity of water in the stools. Certain bacteria (usually *staphylococci sp.*) irritate the intestine by producing toxins. These toxins also affect the mucous membrane. The irritated gut becomes very active, contracting excessively and irregularly.

Other causes of diarrhoea include rich food, allergies to food such as intolerance to lactose or gluten (wheat protein), alcoholism, emotional upheaval, or reaction to medicines, e.g. certain antibiotics or laxatives. Chronic diarrhoea can be a symptom of diseases such as irritable bowel syndrome (IBS), acute, or chronic intestinal infections, chronic inflammatory bowel diseases such as ulcerative colitis and Crohn's disease, HIV/AIDS and chronic pancreatitis, which produces fatty stools.

Who does diarrhoea affect?

Most people are affected by diarrhoea at some time in their lives. Generally, the disorder is a rare occurrence for individuals who live in countries where sanitation is widely available, where there is access to clean water and personal and domestic hygiene is good. Worldwide around 1.1 billion people lack access to reliable water sources and 2.4 billion have no basic sanitation. Diarrhoea due to infection is widespread throughout these populations. In Southeast Asia and Africa, diarrhoea is responsible for as much as eight per cent of all deaths.

A particular bacterium, enterotoxigenic *Escherichia coli* (ETEC) is endemic in many parts of the world, causing more than 400 million cases of diarrhoea each year and more than half a million deaths, mostly among children in developing countries. Seven children die of diarrhoea every minute, mainly due to poor quality drinking water and malnutrition. Each year, an estimated 50 million tourists and business people travel to areas where there is a high risk of ETEC.

Many tourists have experienced travellers' diarrhoea. Travellers' diarrhoea results in four to five loose or watery stools per day. The average duration of excessive passing

of loose stools is three or four days but about ten per cent of the disorder persists longer than a week. Ten per cent of people experience diarrhoea accompanied by fever or bloody stools, or both. The organisms most commonly associated with travellers' diarrhoea are the bacteria *Escherichia coli*, *Salmonella sp.*, *Campylobacter*, *Shigella sp.*, and *Rotavirus* and the protozoa *Entamoeba histolytica* and *Giardia lamblia*.

Rotaviruses are the most common cause of severe diarrhoea in children worldwide. In developing countries, rotavirus infection may cause up to one million deaths each year, accounting for an estimated 20 to 25 per cent of all deaths due to diarrhoea and six per cent of all deaths among children less than five years old.

Present treatments:

Preventing dehydration is the main treatment in the initial stages of diarrhoea. Dehydration can cause serious problems, especially in babies, children, older adults and patients with special health problems. Drinking plenty of clear lightly sweetened fluid in small amounts is recommended. For frail and elderly patients, sachets are available with a ready-mix powder to prepare an oral rehydration solution to replace lost salts and sugar.

To decrease the number of bowel movements, antidiarrhoeal (antimotility) agents, may be used. These medicines slow down the motility of the intestine and increase fluid absorption by normalising the transit through the digestive tract and restoring normal stools. They also diminish diarrhoea thereby reducing fluid loss at the same time. Antidiarrhoeal agents are best used when sanitary arrangements are difficult such as during a long journey. They should not be used in cases where the diarrhoea is accompanied by high fever.

Antibiotics such as gyrase-blockers or antiprotozoal agents are prescribed in cases of severe diarrhoea once the type of pathogen causing the disorder has been isolated. The products mostly used to treat amoebiasis are first and second generation 5-nitroimidazole molecules.

There is also an oral suspension of a newly developed antiprotozoal available for use in children aged between 1 and 11 years for the treatment of diarrhoea caused by *Cryptosporidium parvum* and *Giardia lamblia*, the two most common waterborne protozoa. In 2002, it was the first product to be approved for cryptosporidiosis diarrhoea and the first time in 40 years for diarrhoea caused by *Giardia lamblia*.

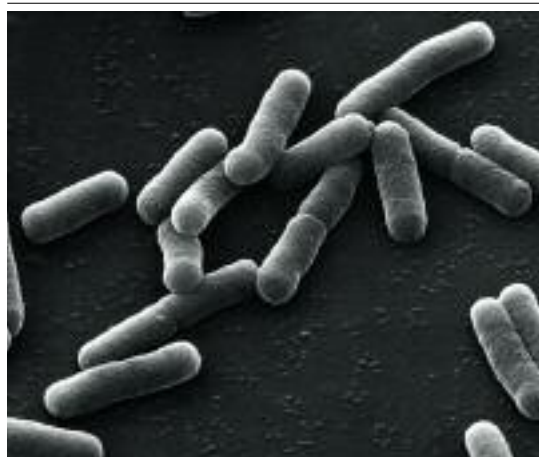
In May 2004, the US FDA has approved a medicine to help prevent travellers' diarrhoea. The antibiotic is given prophylactically. Its active principle is to stay in the gastrointestinal tract for a longer time period.

What's in the development pipeline?

In early 2004, researchers have reported interesting results from Phase 1 trials of an orally delivered ETEC vaccine, designed to protect travellers from diarrhoea. The study showed a 50 per cent immune response rate after a single dose, rising to 70 per cent after two doses. Investigators said this level of immune response was better than expected, and is the best achieved to date. The anti-diarrhoea vaccine is made from attenuated *Salmonella sp.* bacteria that have been modified to carry the ETEC antigen.

Clinical Phase 2 data from June 2004 for an investigational rotavirus vaccine suggest it could have complete efficacy against severe rotavirus infection and around 75 per cent efficacy against any rotavirus gastroenteritis. The product contains the five human serotypes that account for at least 75 per cent of rotavirus strains

Diarrhoea is the frequent passing of increased amounts of loose stools. Seven children a minute die of diarrhoea in areas where clean water and good hygiene are absent. Not only is the pharmaceutical industry continuing to develop medicines that treat dehydration and diarrhoea, it is also researching vaccines to help prevent it.



Scanning electron micrograph of the rod-shaped bacterium *E. coli* typical of many found in the human colon

worldwide – G1, G2, G3, G4 and P1. It is now in Phase 3 clinical trials which have enrolled more than 65,000 infants to date. The large number of participants became necessary to rule out the vaccine's association with the risk of intussusception (a type of intestinal blockage) which has led to the market withdrawal of an earlier developed rotavirus vaccine.

Another rotavirus vaccine is also in Phase 3 and was due to be filed in 2004 in Latin America for preventing rotavirus gastroenteritis in young children.

The longer-term future:

Future developments are varied. Researchers succeeded in further refining anti-diarrhoeal molecules to obtain compounds with even greater selectivity. The principle is to have activation only when they reach the intestinal cells. Such medicines may play a role in the treatment of diarrhoea in the future.

Rotavirus must breach the membrane of a target host cell to gain access to its cytoplasm. In August 2004, research groups have reported on the molecular mechanism of this membrane penetration step. The virus uses the spike protein VP4 as a principal component in its penetration into the cell. The researchers were able to determine the crystal structure of the main part of VP4.

The human pathogenic viruses such as astroviruses, caliciviruses and reoviruses (rotaviruses) have been poorly studied in the past since for the most part, researchers were not able to grow them in culture. Only recently has molecular information on the nature of their genomes become available. The full catalogue of genes and the molecular structure of their modes of entry will give a clearer route to therapies both for prevention and treatment of diarrhoea.



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