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NASAL PASSAGE IS THE COMMON ROUTE FOR RHINOVIRUS: A SILENT PATHOGENIC ALLERGEN READY TO HARM ANYTIME IS A CONTAGIOUS ONE

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ABSTRACT

The rhinovirus (from the Greek ῥίς rhis "nose", GEN ῥινός rhinos "of the nose", and the Latin virus) is the most common viral infectious agent in humans and is the predominant cause of the common cold. Rhinovirus infection proliferates in temperatures of 33–35°C (91–95°F), the temperatures found in the nose. Rhinoviruses belong to the genus Enterovirus in the family Picornaviridae. The three species of rhinovirus (A, B, and C) include around 160 recognized types of human rhinovirus that differ according to their surface proteins (serotypes). They are lyric in nature and are among the smallest viruses, with diameters of about 30 nanometers. By comparison, other viruses, such as smallpox and vaccines, are around ten times larger at about 300 nanometers, while flu viruses are around 80–120 nm. In 1953, when a cluster of nurses developed a mild respiratory illness, Winston Price, from the Johns Hopkins University, took nasal passage samples and isolated the first rhinovirus, which he called the JH virus, named after Johns Hopkins. His findings were published in 1956. Rhinoviruses have single–stranded positive sense RNA genomes of between 7200 and 8500 nt in length. At the 5' end of the genome is a virus–encoded protein and, as in mammalian mRNA, there is a 3' poly–A tail. Structural proteins are encoded in the 5' region of the genome and non–structural at the 3' end. This is the same for all picornaviruses. The viral particles themselves are not enveloped and are icosahedral in structure.

KEYWORDS: COPD, Cough, Sneeze, Runny nose, Sore throat, Nasal congestion, Cough, Aches, Fatigue, Malaise, Headache, muscle weakness, or loss of appetite, Virion, Genome, PCR.

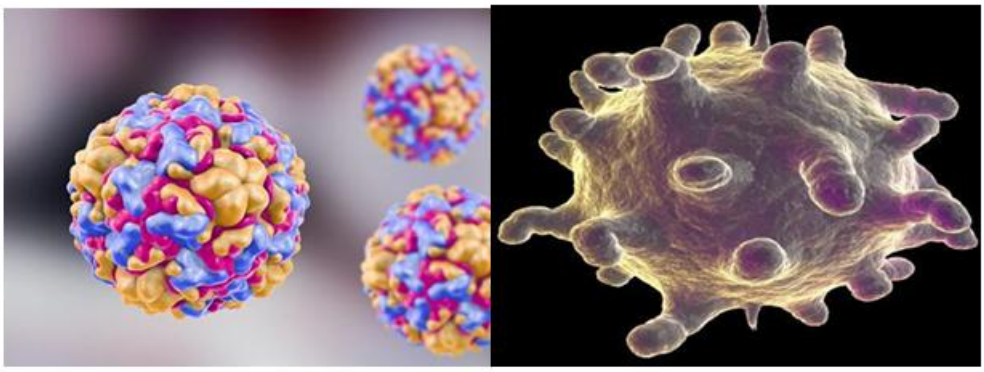
INTRODUCTION

Rhinovirus (*rhin means "nose")* **infections cause the common cold.** Rhinoviruses may also cause some sore throats, ear infections, and infections of the sinuses (openings in the bone near the nose and eyes). They may also cause pneumonia and bronchiolitis, but this is less common.

In children: Rhinoviruses easily pass from one person to another. When a child with a rhinovirus infection has a runny nose, the liquid from her nose gets on to her hands and from there on to tables, toys, and other places. Your child might touch the hands or skin of another child or toys that have the virus on it and then touch her own eyes or nose, infecting herself. She might also breathe in viruses that are in the air when a sick child sneezes or coughs.[1]

In adults: Rhinovirus (RV) is a major cause of acute respiratory disease in both children and adults. The clinical spectrum of rhinovirus infection can range from asymptomatic to more severe lower respiratory tract illness such as obliterative bronchiolitis and pneumonia. Rhinovirus is recognized as a major trigger of asthma and chronic obstructive pulmonary disease (COPD) exacerbations. It is also a commonly detected co–pathogen identified in 24% and 30% of mixed viral and

bacterial infections, respectively. Rhinovirus infection might contribute to serious complications such as obliterative bronchiolitis and acute graft rejection in lung and stem–cell transplant recipients.



Figure–1: Rhinovirus (Normal Picture & Scanned Electron Micrograph).

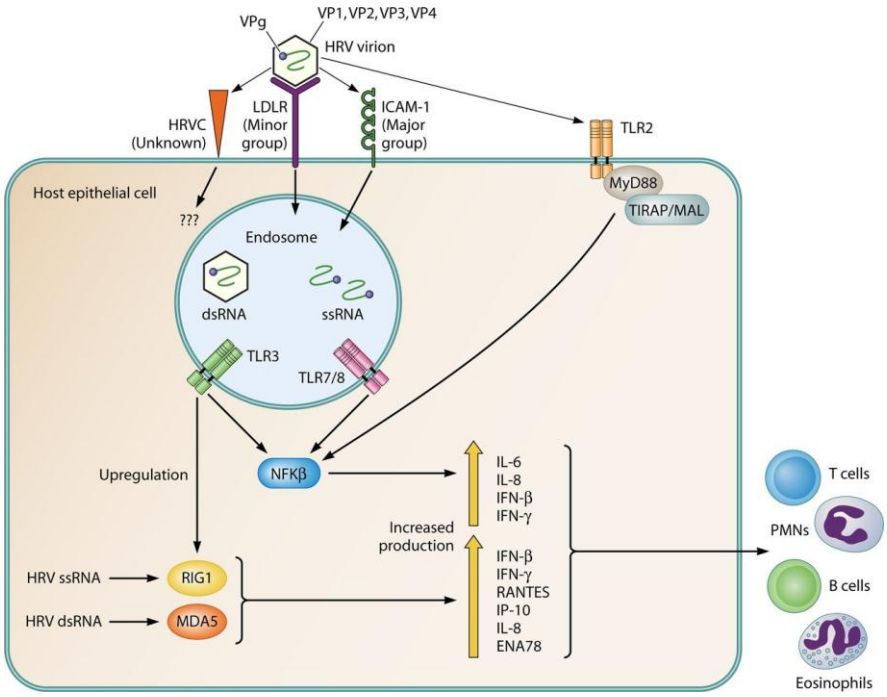
Transmission and epidemiology: There are two modes of transmission: via aerosols of respiratory droplets and from fomites (contaminated surfaces), including direct person–to–person contact. Rhinoviruses are spread worldwide and are the primary cause of the common cold. Symptoms include sore throat, runny nose, nasal congestion, sneezing and cough; sometimes accompanied by muscle aches, fatigue, malaise, headache, muscle weakness, or loss of appetite. Most sinus findings are reversible consistent with a self–limited viral process typical of rhinovirus colds. Fever and extreme exhaustion are more usual in influenza.

Figure–2: Sneezing without tissue is a prior reason of rhinovirus spreading.

Children may have six to twelve colds a year. In the United States, the incidence of colds is higher in the autumn and winter, with most infections occurring between September to April. The seasonality may be due to the start of the school year and to people spending more time indoors thereby increasing the chance of transmission of the virus. Lower ambient temperatures, especially outdoors, may also be factor given that rhinoviruses preferentially replicate at 32°C (89°F) as opposed to 37°C (98°F). Variant pollens, grasses, hays and agricultural practices may be factors in the seasonality as well as the use of chemical controls of lawn, paddock and sports fields in schools and communities. The changes in temperature, humidity and wind patterns seem to be factors. It is also postulated that poor housing, overcrowding and unsanitary conditions related to poverty are relevant factors in the transmission of 'common cold'. Those most affected by rhinoviruses are infants, the elderly, and immunocompromised people.[2]

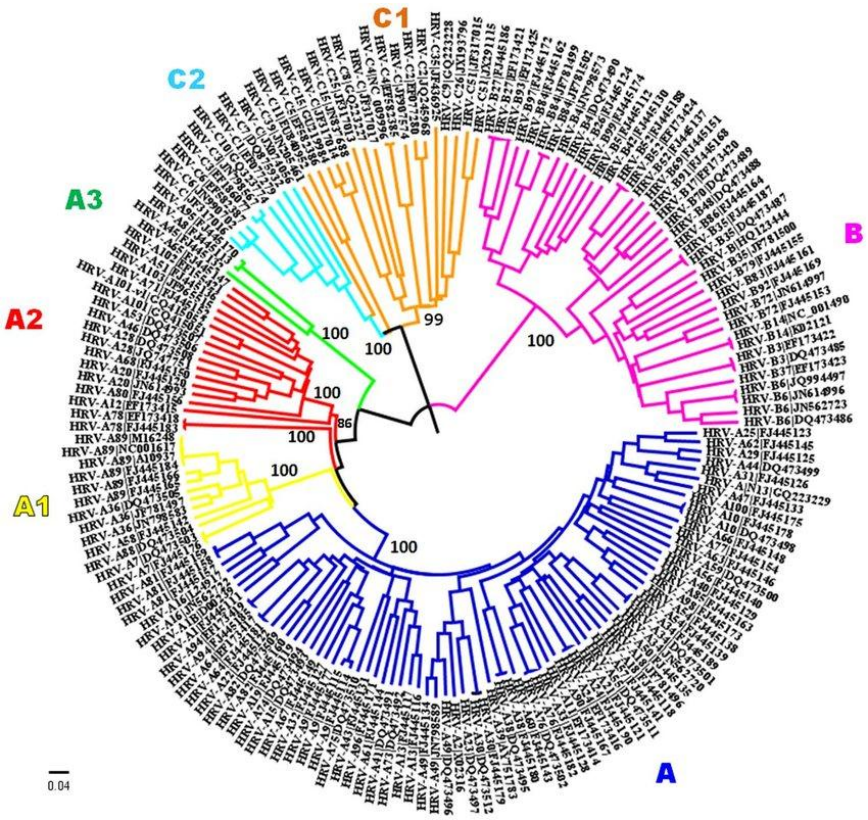
Pathogenesis: The primary route of entry for human rhinoviruses is the upper respiratory tract (mouth and nose). Rhinovirus A and B use "major" ICAM–1 (Inter–Cellular Adhesion Molecule 1), also known as CD54 (Cluster of Differentiation 54), on respiratory epithelial cells, as receptors to bind to. Some subgroups under A and B uses the "minor" LDL receptor instead. Rhinovirus C uses cadherin–related family member 3 (CDHR3) to mediate cellular entry. As the virus replicates and spreads, infected cells release distress signals known as chemokines and cytokines (which in turn activate inflammatory mediators). Cell lysis occurs at the upper respiratory epithelium. Infection occurs rapidly, with the virus adhering to surface receptors within 15 minutes of entering the respiratory tract. Just over 50% of individuals will experience symptoms within 2 days of infection. Only about 5% of cases will have an incubation period of less than 20 hours, and, at the other extreme, it is expected that 5% of cases would have an incubation period of greater than four and a half

days. Human rhinoviruses preferentially grow at 32°C (89°F), notably colder than the average human body temperature of 37°C (98°F); hence the virus's tendency to infect the upper respiratory tract, where respiratory airflow is in continual contact with the (colder) extrasomatic environment. Rhinovirus C, unlike the A and B species, may be able to cause severe infections. This association disappears after controlling for confounders. Duly, amongst infants infected with symptomatic respiratory illness in low–resource areas, there appears to be no association between rhinovirus species and disease severity.



Figure–3: Genetical spreading technique of Rhinovirus.

Taxonomy



Figure–4: Phylogenetic Tree of Rhinovirus.

Rhinovirus was formerly a genus from the family *Picornaviridae*. The 39th Executive Committee (EC39) of the International Committee on Taxonomy of Viruses (ICTV) met in Canada during June 2007 with new taxonomic proposals. In April 2008, the International Committee on Taxonomy of Viruses voted and ratified the following changes:

- 2005.264V.04 To **remove the following species** from the existing genus *Rhinovirus* in the family *Picornaviridae*:
  - Human rhinovirus A
  - Human rhinovirus B
- 2005.265V.04 To **assign the following species** to the genus *Enterovirus* in the family *Picornaviridae*:
  - Human rhinovirus A
  - Human rhinovirus B
- 2005.266V.04 To **remove the existing genus** *Rhinovirus* from the family *Picornaviridae*. Note: The genus *Rhinovirus* hereby disappears.

The merge is based on the grounds that the two "genera" of viruses are not significantly different in a virological sense. They have identical genome organizations and particle structures, and the phylogeny is not always monophyletic.

In July 2009, the ICTV voted and ratified a proposal to add a third species, *Human rhinovirus C* to the genus *Enterovirus*.

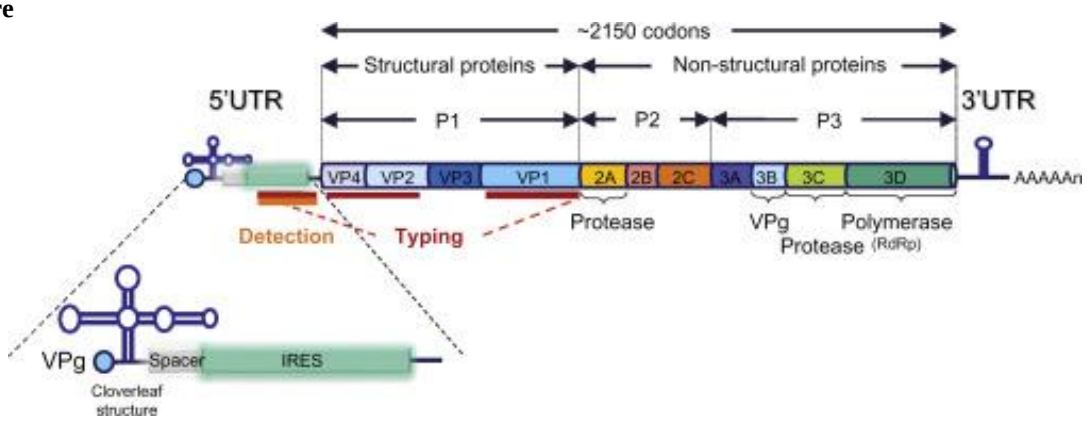
- 2008.084V.A.HRV–C–Sp 2008.084V To **create a new species** named Human rhinovirus C in the genus *Enterovirus*, family *Picornaviridae*.

There has been a total of 215 taxonomic proposals, which have been approved and ratified since the 8th ICTV Report of 2005.

Serotypes: Human rhinovirus serotype names are of the form HRV–*Xn* where *X* is the rhinovirus species (A, B, or C) and *n* is an index number. Species A and B have used the same index, while Species C has a separate index. Valid index numbers are as follows:

- Rhinovirus A: 1, 2, 7–13, 15, 16, 18–25, 28–34, 36, 38–41, 43–47, 49–51, 53–68, 71, 73–78, 80–82, 85, 88–90, 94–96, 98, 100–103
- Rhinovirus B: 3–6, 14, 17, 26, 27, 35, 37, 42, 48, 52, 69, 70, 72, 79, 83, 84, 86, 91–93, 97, 99
- Rhinovirus C: 1–51

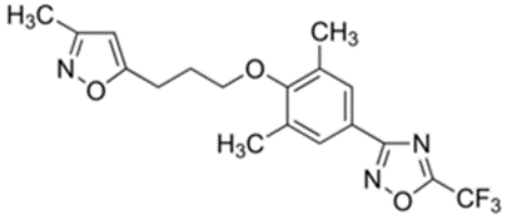
Structure



Figure–5: Human rhinovirus genome, virion structure.

Rhinoviruses have single–stranded positive sense RNA genomes of between 7200 and 8500 nt in length. At the 5' end of the genome is a virus–encoded protein and, as in mammalian mRNA, there is a 3' poly–A tail. Structural proteins are encoded in the 5' region of the genome and non–structural at the 3' end. This is the same for all picornaviruses. The viral particles themselves are not enveloped and are icosahedral in structure. The viral proteins are translated as a single, long polypeptide, which is cleaved into the structural and nonstructural viral proteins. Human rhinoviruses are composed of a capsid that contains four viral proteins, VP1, VP2, VP3 and VP4. VP1, VP2, and VP3 form the major part of the protein capsid. The much smaller VP4 protein has a more extended structure, and lies at the interface between the capsid and the RNA genome. There are 60 copies of each of these proteins assembled as an icosahedron. Antibodies are a major defense against infection with the epitopes lying on the exterior regions of VP1–VP3.

Novel antiviral drugs: Interferon–alpha used intranasally was shown to be effective against human rhinovirus infections. However, volunteers treated with this drug experienced some side effects, such as nasal bleeding, and began developing tolerance to the drug. Subsequently, research into the treatment was abandoned.[3]



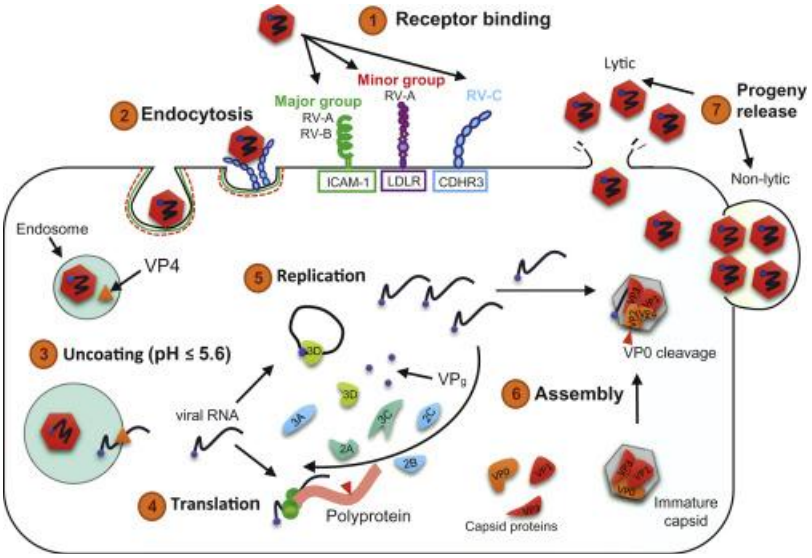
Figure–6: Pleconaril chemical structure.

Pleconaril is an orally bioavailable antiviral drug being developed for the treatment of infections caused by picornaviruses. This drug acts by binding to a hydrophobic pocket in VP1, and stabilizes the protein capsid to such an extent that the virus cannot release its RNA genome into the target cell. When tested in volunteers, during the clinical trials, this drug caused a significant decrease in mucus secretions and illness–associated symptoms. Pleconaril is not currently available for treatment of human rhinoviral infections, as its efficacy in treating these infections is under further evaluation. Other substances such as Iota–Carrageenan may form a basis for the creation of drugs to combat the human rhinovirus. In asthma, human rhinoviruses have been recently associated with the majority of asthma exacerbations for which current therapy is inadequate. Intercellular adhesion molecule 1 (ICAM–1) has a central role in airway inflammation in asthma, and it is the receptor for 90% of Human rhinoviruses. Human rhinovirus infection of airway epithelium induces ICAM–1. Desloratadine and loratadine are compounds belonging to the new class of H1–receptor blockers. Anti–inflammatory properties of antihistamines have been recently documented, although the underlying molecular mechanisms are not completely defined. These effects are unlikely to be mediated by H1–receptor antagonism and suggest a novel mechanism of action that may be important for the therapeutic control of virus–induced asthma exacerbations. In 2018, a new series of anti–rhinoviral compounds were reported by researchers at Imperial College London and colleagues at the University of York and the Pirbright Institute. These molecules target human *N*–myristoyltransferase, an enzyme in the host cell which picornavirus requires in order to assemble its viral capsid, and thus generate an infectious virion. The lead compound in this series, IMP–1088, very potently inhibited host myristoylation of viral capsid protein and prevented infectious virus formation, rescuing the viability of cells in culture which had been exposed to a variety of rhinovirus serotypes, or to related picornaviruses including poliovirus and foot–and–mouth–disease virus. Because these compounds target a host factor, they are broadly active against all serotypes, and it is thought to be unlikely that they can be overcome by resistance mutations in the virus.[4]

Vaccine: There are no vaccines against these viruses as there is little–to–no cross–protection between serotypes. At least 99 serotypes of human rhinoviruses affecting humans have been sequenced. However, a study of the VP4 protein has shown it to be highly conserved among many serotypes of human rhinovirus, opening up the potential for a future pan–serotype human rhinovirus vaccine. A similar result was obtained with the VP1 protein. Like VP4, VP1 also occasionally "pokes" out of the viral particle, making it available to neutralizing antibodies. Both peptides have been tested on rabbits, resulting in successful generation of cross–serotype antibodies. The successful introduction of human ICAM–1 into mice has removed a major roadblock in creating an animal model for RV vaccination.

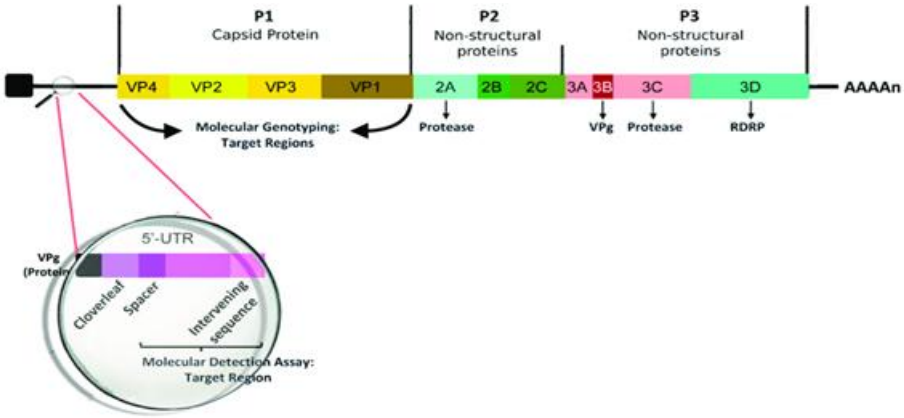
Methods of Recognition: Study design, subjects and specimens: Study subjects were enrolled as part of the GRACE (Genomics to combat Resistance against Antibiotics in Community–acquired lower respiratory tract infection in Europe) European Network of Excellence focusing on improving the management of community–acquired lower respiratory tract infections. 16 primary care networks from 12 European countries (Belgium, England, France, Germany, Italy, the Netherlands, Poland, Slovakia, Slovenia, Spain, Sweden and Wales) participated in a prospective recruitment of patients within the winter seasons between October 2007 and June 2010. Eligible patients were aged 18 years or older and consulting their general practitioner (GP) for the first time with a respiratory illness presenting with an acute or worsened cough (≤28 days duration) as the main symptom, or any clinical presentation that suggested a lower respiratory tract infection. Exclusion criteria were pregnancy, breast–feeding and any condition associated with severe impaired immune status. Patients with previous diagnoses of asthma, COPD and other co morbid disorders, such as diabetes; respiratory, cardiovascular and allergic diseases were not excluded and thus acute infective exacerbations were included as well. The study was approved by the medical ethics committees of the participating countries. Following written informed consent, a sputum (if available) and nasopharyngeal swab sample were collected from each patient during their first visit (V1) to the GP. A follow–up nasopharyngeal swab sample was obtained at the second visit (V2) to the GP approximately 28 days later.[5]

Clinical characteristics and disease severity: Clinical data, including past medical history, co morbidities and their management/treatment, and days the patient felt unwell were recorded by the GP on a case report form at the time of the first consultation. Following the first visit at the primary care centre, patients were requested to complete a daily symptom diary for the duration of illness (to a maximum of 28 days). The presence or absence of 13 symptoms were documented: cough, sputum production, shortness of breath, wheeze, coryza, fever, chest pain, muscle aching, headache, disturbed sleep, feeling generally unwell, interference with normal activities and confusion/disorientation. If present, the severity of each symptom was rated on a 7–point scale from 0 to 6. 0: “normal/not affected”; 1: “very little problem”; 2: “slight problem”; 3: “moderately bad”; 4: “bad”; 5: “very bad”; and 6: “as bad as it could be”. Disease severity was assessed from the following clinical outcomes: 1) duration of illness; 2) maximal symptom score; and 3) duration of higher symptom score.



Figure–7: Method of recognition of Rhinovirus.

The duration of illness was measured as the sum of days unwell before the first GP consultation and days the patient experienced any of the 13 symptoms over the 28–day follow–up period. The maximal symptom score was estimated as the highest mean daily symptom score based on the 13 symptoms evaluated in the patient diary during the 28–day follow–up period. The duration of higher symptom score was measured as the number of days the patient had a mean daily symptom score ≥2 corresponding to severity ranging from "slight problem" to "as bad as it could be".



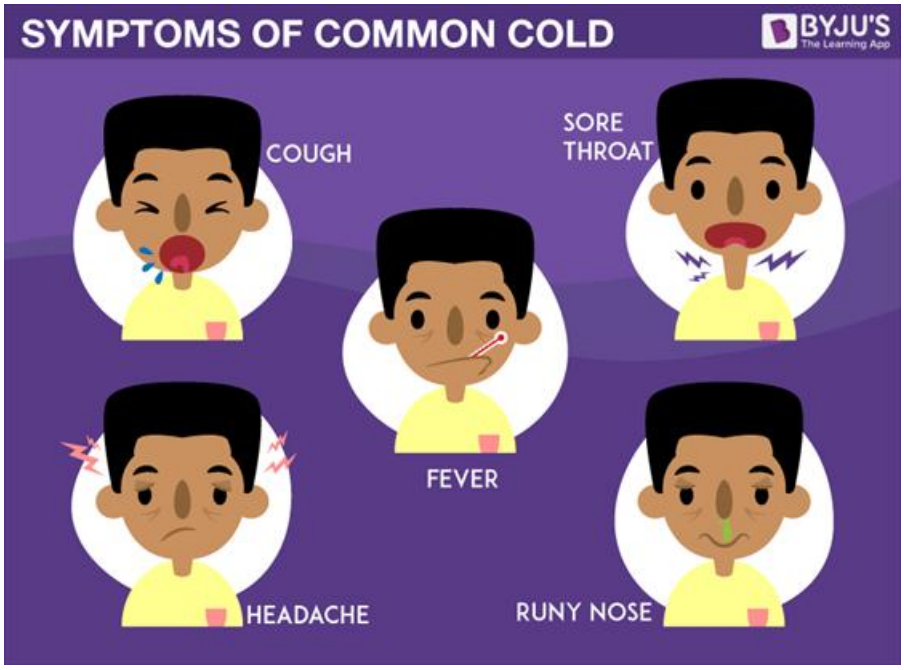
Figure–8: Analysis of Blueprint of human Rhinovirus.

Rhinovirus detection and molecular typing: Total nucleic acids were isolated from nasopharyngeal specimens with the NucliSens EasyMag system (bioMerieux, Grenoble, France) and stored at –70°C until further testing. Rhinovirus–positive samples were detected with an internally controlled real–time reverse transcriptase PCR assay amplifying a 142–bp fragment of the 5'–UTR region using primers, probes and conditions previously described. Threshold cycle (Ct) values were normalized using the same fluorescence threshold and were used as an approximate measure of viral load. Molecular typing of rhinoviruses was performed by amplification and sequencing of fragments in the VP3/VP1, VP4/VP2 or the 5'–UTR genome regions. Further information regarding the molecular typing assays and rhinovirus genotype assignment is provided in the online supplementary material.[6]

Detection of respiratory viral and bacterial co–pathogens: Nasopharyngeal swab samples were tested by real–time PCR assays for the following viruses: human metapneumovirus (hMPV), respiratory syncytial virus (RSV), influenza viruses A and B (IFA and IFB), parainfluenza virus types 1 to 4 (PIV–1 to –4), human coronavirus (HCoV stains 229E, OC43, and NL63), adenovirus (AdV), human bocavirus (HBoV), polyomavirus WU (WUPyV) and KI (KIPyV). Bacterial and fungal co–infections were detected in the nasopharyngeal swab specimens by using conventional culture and/or molecular methods for *Chlamydophila pneumoniae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Streptococcus* spp. *Haemophilus* spp., Gram–negative *Enterobacteriaceae*, *Candida* sp., *Aspergillus* sp. And *Pseudomonas aeruginosa*. Sputum samples were used for culture of *Streptococcus*

pneumoniae and *Haemophilus* spp. Most colds result from coronaviruses or rhinoviruses. The coronavirus that causes a cold is different from SARS–CoV–2, which causes COVID–19. COVID–19 and a cold are different diseases. Many types of virus can cause a cold, and the human body can never build up resistance to them all. This is why colds are so common and often return. According to the Centers for Disease Control and Prevention (CDC), adults on average get 2–3 colds per year, and children may have more. They usually last around 7–10 days. Colds spread through droplets in the air and on surfaces.[7]

Symptoms: When a person has a cold virus, their immune system tries to fight it off. This causes the symptoms that we recognize as a cold**.** People with a weakened immune system may develop more severe symptoms or a secondary infection, such as pneumonia. If a person develops more serious symptoms, they should seek medical help. The symptoms of a cold develop in stages. Here, get more detail about the stages of a cold. Symptoms can vary, but common ones include:



Figure–9: Symptoms of common cold.

- A sore throat
- A cough
- Sneezing
- A blocked or runny nose
- A headache

Rarer symptoms include:

- Muscle aches
- Shivering
- Pinkeye
- Weakness
- Low appetite
- Fatigue

Anyone who has the following symptoms should stay away from other people and seek medical advice:

Figure–10: Effect of Rhinovirus Attack.

- A high temperature
- A new, continuous cough
- A loss or change to the senses of smell or taste

Risk factors

Colds can affect anyone at any time of year, but some factors can increase the risk:

- Being a young child or an older adult
- Having a weak immune system
- Seasonal factors, as colds are more common in winter
- Having close contact with someone who has a cold

Complications: A cold is not usually serious, and colds mostly disappear after 7–10 days. Sometimes, however, complications can occur. These are most likely to affect those with a weakened immune system. A cold can worsen the symptoms of asthma and chronic obstructive pulmonary disease (COPD) — which includes emphysema and chronic bronchitis.[8] They include:

- Pneumonia
- Acute bronchitis
- Bronchiolitis
- Croup
- Otitis Media (middle ear infection)
- Strep Throat
- Top of Form
- Bottom of Form

Treatment: Rhinovirus (RV) infections are predominantly mild and self–limited; thus, treatment is generally focused on symptomatic relief and prevention of person–to–person spread and complications. The mainstays of therapy include rest, hydration, first–generation antihistamines, and nasal decongestants. The common cold is a viral infectious disease that affects the upper respiratory system. It is the most common infectious disease among humans. In adults, evidence has shown that zinc decreases the duration of symptoms and severity. Antibacterial agents are not effective unless bacterial superinfection occurs. No antiviral agents are available to treat infections. Development of a vaccine is nearly impossible, because of the large number of rhinovirus serotypes.[9]

Inpatient care is rarely required. Persons with rhinovirus infections are almost universally treated as outpatients. There is no cure for a cold, but treatment can help manage symptoms. Here are some tips:

- Drink plenty of fluids to prevent dehydration.
- Get plenty of rest.
- Use over–the–counter medications to manage pain and discomfort.
- Inhale steam, which may help relieve nasal congestion.
- Gargle saltwater for a sore throat.

Prevention: As so many viruses can cause a cold, it is difficult to develop a vaccine. However, people can take precautions to help prevent catching a cold. These include:

- Avoiding close contact with anyone who has a cold.
- Following a healthful and varied diet with plenty of fresh fruits and vegetables.
- Always sneezing or coughing into a tissue, then discarding the tissue carefully and washing your hands at once.
- If there is no tissue available, coughing or sneezing into the upper shirt sleeve, covering the nose and mouth completely.
- Washing hands regularly with soapy water for at least 20 seconds.
- Keeping surfaces at work and in the home.
- Avoiding touching the face, especially the eyes, nose, and mouth.

CONCLUSION

This group of viruses — of which there are more than 100 types — is by far the most common identified cause of colds. The viruses grow best at the temperature inside the human nose. Human rhinoviruses (HRVs) are highly contagious. However, they rarely lead to serious health consequences. Recent research has found that HRVs manipulate genes and it is this manipulation that brings about an overblown immune response. The response causes some of the most troublesome cold symptoms. This information could lead scientists to important breakthroughs in the treatment of the common cold. Over 200 different viruses can cause cold symptoms, and rhinoviruses are responsible for most of them. When a virus enters the body, the immune system tries to fight it. In a person with a strong immune system, symptoms may not develop. However, if the immune system cannot fight off the virus, symptoms of infection will appear.

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