Hidden in Plain Sight: The Impact of Human Rhinovirus Infection in Adults

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# Abstract

## Background

Human rhinovirus (HRV), an unencapsulated RNA virus, was first identified more than 70 years ago. It is highly infectious and easily transmitted through aerosols and direct contact. The advent of multiplex PCR has enhanced the detection of a diverse range of respiratory viruses, and HRV consistently ranks among the most prevalent respiratory pathogens globally. Circulation occurs throughout the year, with peak incidence in autumn and spring in temperate climates. Remarkably, during the SARS-CoV-2 pandemic, HRV transmission persisted, demonstrating its resilience against stringent public health measures aimed at curbing viral transmission.

## Main Body

HRV is characterized by its extensive genetic diversity, comprising three species and more than 170 genotypes. This diversity and large number of concurrently circulating strains allows HRV to frequently escape the adaptive immune system and poses formidable challenges for the development of effective vaccines and antiviral therapies. Subsequently, there is currently a lack of specific treatments.

Historically, HRV has been associated with self-limiting upper respiratory infection. However, there is now extensive evidence highlighting its significant role in severe lower respiratory disease in adults, including exacerbations of chronic airway diseases, such as asthma and chronic obstructive pulmonary disease (COPD), but importantly also pneumonia. These severe manifestations can occur even in immunocompetent individuals, broadening the clinical impact of this ubiquitous virus.

Consequently, the burden of rhinovirus infections extends across various healthcare settings, from primary care to general hospital wards and intensive care units. The impact of HRV in adults, in terms of morbidity and healthcare utilization, rivals that of the other major respiratory viruses, including influenza and respiratory syncytial virus. Recognition of this substantial burden underscores the critical need for novel treatment strategies and effective management protocols to mitigate the impact of HRV infections on public health.

## Conclusion

This review examines the epidemiology, clinical manifestations, and risk factors associated with severe HRV infection in adults. By drawing on contemporary literature, we aim to provide a comprehensive overview of the virus’s significant health implications. Understanding the scope of this impact is essential for developing new, targeted interventions and improving patient outcomes in the face of this persistent and adaptable pathogen.

Keywords: Rhinovirus, adults, pneumonia, asthma, COPD.

# Introduction

Since its initial identification by Winston Price in the 1950s, human rhinovirus (HRV) has become recognized as one of the most common agents responsible for respiratory infections(1) Despite this, there are no approved therapies for this pathogen. The significance of HRV infection in children is well established, with consistent associations found between infections during childhood and the development of wheezing, asthma, and severe lower respiratory complications(2). However, despite evidence pointing to substantial morbidity in adults, the impact of HRV infection in this population remains largely underestimated. This review aims to shed light on this impact by detailing HRVs epidemiology, transmission, and clinical manifestations. It aims to update clinicians on the role of HRV infection beyond childhood, inform ongoing research efforts, and underscore the urgent need for innovative therapeutic approaches.

# Background

## General structure and properties

HRVs are single-stranded, positive-sense RNA viruses belonging to the Enterovirus genus of the Picornaviridae family (Figure 1).

A diagram of a cell structure

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**Figure 1: Overview of the structure, taxonomy, diversity and infection targets of human rhinovirus (HRV). HRV is among the most diverse viral pathogens. The vast genetic diversity of circulating HRV strains hampers adaptive immunity, which is limited to homologous strains. Host defence is therefore largely dependent on innate responses. The co-circulation of these diverse strains also presents a challenge to the development of antiviral and vaccine therapies. Abbreviations: bp (Base-pairs), CHDR-3 (Cadherin Related Family Member 3), ICAM-1 (Intracellular Adhesion Molecule 1), LDL-R (Low Density Lipoprotein Receptor), RV (Rhinovirus), RNA (Ribonucleic Acid) VP (Viral Protein)**

Rhinoviruses (RVs) comprise three primary species, RV-A, RV-B, and RV-C, each of which are distinguished by characteristic genomic features and phylogenetic sequences(3-5). Notably, the discovery of RV-C in 2006 was delayed due to its inability to be cultured using traditional techniques(6-8).

HRVs exhibit remarkable diversity, primarily due to their high mutation frequency during replication. Initially, HRVs were classified based on antigenic properties (serotyping), but the current classification relies on genotyping, utilizing divergence in nucleotide sequences of viral protein (VP) genes(9-12). This genotyping approach has identified more than 170 RV genotypes, further subdivided into more than 27,000 strains based on precise genomic sequencing differences(13). Although historically considered human specific, rhinovirus has also been detected in wild chimpanzees in Uganda(14).

## Viral Capsid and Host Entry

HRV is unencapsulated, with an icosahedral capsid composed of four proteins (VP1-4). VPs 1-3 form the external surface of the capsid, which possesses antigenic properties, while VP4 is located on the internal surface and is in direct contact with the viral genome(3, 15). Intracellular adhesion molecule 1 (ICAM-1) is the viral receptor for all RV-B types and most RV-A types(3, 16). Twelve types of RV-A bind to low-density lipoprotein receptors (LDL-Rs), known as the minor RV-A group(17). Cadherin-related family member 3 (CHDR-3) acts as the glycoprotein viral receptor for RV-C(3, 18).

Upon binding to their respective receptors, HRV enters airway epithelial cells via endocytosis and micropinocytosis. The more acidic intracellular pH triggers uncoating of the capsid, facilitating translation of the viral positive-sense RNA. Newly formed virions packaged with RNA are then assembled and subsequently released from the host cell to continue the infection cycle(19-21).

## Host Response

Upon infection, pathogen-associated molecular patterns (PAMPs) present on HRVs, such as elements of the HRV capsid and HRV-RNA, engage host pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), retinoic acid inducible gene-1 (RIG-1) and melanoma differentiation associated gene 5 (MDA-5)(22). RIG-1 and MDA-5 play crucial roles in host defence against RNA viruses by recognizing HRV-RNA, leading to the induction of a type I/III interferon (IFN) response and the production of pro-inflammatory cytokines and chemokines. Subsequent recruitment of innate immune cells such as neutrophils, macrophages and dendritic cells precedes the slower mobilization of the adaptive immune response. The balance between pro-inflammatory and anti-inflammatory signals determines the severity of the host response, ultimately influencing clinical outcomes. While HRV infection itself has limited direct cytopathic effects, IFNs, along with pro-inflammatory chemo/cytokines such as RANTES, ENA-78 IP-10, IL-6, and IL-8, are responsible for symptom development and cytotoxicity(22-28). For instance, the level of IL-8 in nasal fluid correlates with nasal symptom severity, peaking 48-72 hours after infection(24).

The SARS-CoV-2 pandemic has underscored the importance of a sophisticated understanding of host-pathogen interactions to identify factors associated with severity and potential host-directed therapies(29-31). Transcriptomic approaches aimed at identifying host factors associated with severity in HRV cohorts with severe outcomes are needed and may unveil potential targets for novel host-modulating therapies(32-34). Furthermore, human experimental models will be key to further understanding the immunology of HRV as well as other respiratory viral infections(35, 36).

## HRV Transmission

HRV transmission occurs through airborne routes involving droplets and aerosols, as well as via contact through autoinoculation of the nasal or conjunctival mucosa (Figure 2).

A diagram of a person's body

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**Figure 2: Overview of Human Rhinovirus (HRV) Transmission. HRV is highly infectious and can be effectively transmitted through contact and airborne methods. While contact transmission has been accepted for some time, it now appears that spread via aerosols is likely the dominant method of transmission. HRV can be effectively transmitted during its asymptomatic incubation period.**

Traditionally, direct or indirect contact with HRV on surfaces (fomites) and subsequent self-inoculation have been considered the primary transmission modes. Gwaltney et al demonstrated that 11 out of 15 hand-to-hand HRV exposures and 20 out of 28 indirect contact exposures resulted in successful infection in adults(37). Winther et al. reported that 41% of surfaces in the homes of HRV-infected adults were contaminated with viral RNA, with fresh mucus (<24 hours old) being more likely to facilitate transmission(38). Turner et al reported that hand treatments with 2% citric acid and 2% malic acid in 62% ethanol were ineffective at preventing HRV transmission(39). Alcohol-based handwashing alone has been deemed insufficient to destroy HRV, and traditional soap and water have been suggested to reduce HRV transmission(40).

In the 1980s, Dick et al. suggested that, contrary to the popular opinion at the time, the chief method of HRV transmission was via inhalation of suspended HRV aerosols/microdroplets rather than contact-mediated self-inoculation(41). This view has gained support through research attention during the SARS-CoV-2 pandemic, highlighting the crucial role that airborne transmission plays in the transmission of respiratory viruses(42, 43). A recent systematic review suggested that indoor airborne transmission of large or small aerosols is likely the dominant method of HRV transmission(44). While the transfer of HRV via direct/indirect contact is possible, it is unlikely to be the most common transmission route(44). This is supported by previous observations that HRV infectivity decreases rapidly upon transfer to hands and surfaces(45).Factors influencing airborne HRV transmission include strain type, viral load, temperature, humidity, ventilation/filtration systems and ultraviolet radiation exposure(43, 46).

Thus, the most effective methods for reducing transmission are likely to include improving indoor ventilation, maintaining appropriate humidity and temperature levels, and increasing outdoor activities(47). Notably, surgical facemasks appear to be less effective at preventing HRV spread, although they are somewhat effective at reducing the transmission of encapsulated respiratory viruses such as influenza and coronaviruses(48). One study revealed RV in 8% of healthcare workers despite adherence to mask policies and contact precautions, highlighting the necessity for improvement in infection prevention measures(49).

Following infection, HRV has an incubation period of 0.42-5.5 days, an infectious period of 7-16 days and a basic reproduction number (R0) ranging from 1.2-2.6(50).

# Epidemiology, Clinical Syndromes

HRV is a ubiquitous perennial pathogen that circulates year-round, with a peak prevalence often observed during spring and autumn(51-55). This seasonal pattern is often demonstrated across studies focused on adults presenting with upper and lower respiratory illness and acute respiratory infection (ARI)(54-57). Interestingly, the peak incidences of different respiratory viruses typically do not overlap, which might be influenced by the short-term inhibitory effects of initial HRV infections on other viruses, such as influenza, possibly due to enhanced antiviral IFN responses(58-60). For instance, the prevalent circulation of HRV appeared to delay the onset of H1N1 influenza during the most recent influenza pandemic(58, 61-63).

RV-A and RV-C are in constant circulation throughout the year, while RV-B circulation is less consistent (53, 55). A single-centre study from 2013–2017, in which respiratory samples were collected from adult patients (65.8% inpatients, 34.2% outpatients), revealed that RV-A was the predominant species, being detected in 60.9% of patients, followed by RV-C in 26.4% and RV-B in 12.7%. RV-A and RV-C were detected year-round, whereas RV-B was not detected from June to August across the four-year period(55).

The diversity of concurrently circulating HRV genotypes is notable. Even within a single geographic location, a wide array of genotypes can be identified in adults(55), although no single genotype typically constitutes more than 20% of the detected strains(53). This genotype variability is lower in adults than in children aged 0-3 years(53). The predominance of any single HRV genotype among adults varies, ranging from 3.9%(55) to 21.4%(64). Despite differences in circulating genotypes, the proportion of HRV species in symptomatic adults is relatively stable, with RV-A and RV-C usually being the most common and RV-B being the least common species(55, 57, 65).

## Impact of the SARS-CoV-2 Pandemic on HRV

Despite widespread lockdowns, social distancing measures, and the use of facemasks during the SARS-CoV-2 pandemic, HRV continued to circulate, even maintaining circulation rates comparable to pre-pandemic HRV levels(66-68). This contrasts sharply with the incidence of encapsulated respiratory viruses such as influenza and respiratory syncytial virus (RSV), which significantly decreased during the SARS-CoV-2 pandemic(69).

A systematic review and meta-analysis explored the pooled prevalence of viruses other than SARS-CoV-2 in symptomatic adults and adolescents during the pandemic(70). This study suggested that HRVs were by far the most prevalent non-SARS-CoV-2 virus, despite being tested for less frequently than influenza, metapneumovirus (MPV), RSV and human coronavirus. During the first half of the pandemic, the prevalence of HRV was 4.69%, which increased to 9.52% during the second half(70).

A Japanese study during the SARS-CoV-2 pandemic revealed that among 191 patients with upper respiratory symptoms, HRV was the most common viral pathogen identified and was detected more frequently than SARS-CoV-2(71).

Additionally, a retrospective observational study conducted on Reunion Island among adults with severe community-acquired pneumonia (CAP) requiring intensive care from 2016 to 2021 observed that HRV was the only non-SARS-CoV-2 viral pathogen whose incidence did not decrease following the onset of the SARS-CoV-2 pandemic. This was noted despite a significant overall decrease in the incidence of non-SARS-CoV-2 CAP between the pre-pandemic period and the early pandemic(72).

## Clinical manifestations in adults

The clinical manifestations of HRV infection in adults are diverse. HRV infection can be asymptomatic or can manifest with upper respiratory, lower respiratory or systemic symptoms. Unlike influenza, RSV, or SARS-CoV-2, there are no validated patient-reported outcome measures specifically for adults with HRV infection beyond cold scores. The development of further instruments would be invaluable for objectively assessing patient experiences and serving as outcome measures in clinical trials(73-75). Furthermore, chronic respiratory symptoms in patients with respiratory comorbidities can confound the recognition of acute symptoms associated with HRV as well as other respiratory viral infections(76).

After discussion of asymptomatic infection, we will review pulmonary manifestations. It should be noted, however that non-pulmonary sequelae of HRV infection are emerging. For example, HRV infection has been described as a predictor of myocardial infarction admission in adults aged 65-74 and stroke admission in adults over 75 years(77), further demonstrating the diverse consequences of HRV infection.

### Asymptomatic infection

The detection of HRV in the absence of symptoms is a well-documented phenomenon. A longitudinal study of 2685 adults visiting a New York Tourist attraction across 2 years identified a positive respiratory virus PCR in 6.2% of the samples, with approximately half of the positive cases (50.6%) being positive for HRV(78). More than half of the positive cases were asymptomatic according to any of the 7 symptom definitions used. In another cohort study, 214 individuals—including children, teenagers, and adults—were tested weekly via nasopharyngeal PCR. The study found that 55% of the virus-positive specimens were from asymptomatic individuals, and HRV was responsible for more than half of the symptomatic episodes.

Asymptomatic infection is less prevalent in adults than in children(79). HRV infection is detected in 4-8% of asymptomatic adults; in contrast, the incidence of asymptomatic HRV infection in children under four years of age ranges from 12-33%(57, 80).

Analysis of gene expression patterns indicated that symptomatic HRV infection could be distinguished from asymptomatic infection by elevated expression of genes related to type I IFN, IL1, IL12, and IL6, and this elevated expression correlated with the overall severity of infection(81). Furthermore, the gene expression profiles of asymptomatic patients who test positive are markedly different from those of patients who test negative for respiratory viruses(81).

Asymptomatic detection of HRV may stem from several processes. These include detection during the incubation period-prior to the development of symptoms, detection during mild infections-where symptoms go unrecognized/perception is attenuated, and detection after the resolution of acute symptoms-where there is continued viral shedding. Clinicians should therefore take a careful history, carefully elucidate temporal aspects of any previously reported symptoms and use clinical judgement in the presence of a positive HRV PCR.

### Upper Respiratory Infection (URI)

HRV is the predominant pathogen associated with the common cold, arguably the most frequently occurring human ailment. This condition is often self-diagnosed and deeply ingrained in cultural folklore with numerous suggested origins and treatments(82, 83). Historically, according to Hippocratic humoral theory, the common cold was believed to stem from excessive cooling that disrupts bodily humours, leading to abnormal mucus production(83). Modern understanding defines it as a clinical syndrome marked by upper respiratory symptoms such as sore throat, rhinorrhoea, sneezing, nasal congestion, headache and cough. The term “flu-like illness” is used for more prominent systemic manifestations, including fever, myalgia, and fatigue(82). Typically, these symptoms often present as a mild prodrome, which becomes progressively worse before peaking and gradually resolving(82).

Research in the 1960s found HRVs are responsible for 10-30% of acute upper respiratory infections in adults(84). Later studies identified HRV much more frequently. Arruda et al. identified a Picornavirus in 82% of adults with self-diagnosed colds(56). The first symptom noted in these adults was sore throat, and the illness lasted 9.5-11 days on average(56). Similarly, Makela et al. identified rhinovirus in 52.5% of adults with clinical evidence of rhinorrhoea, nasal congestion, or sore throat(85).

Adults with the common cold often have sinus involvement. In a study of adults with the common cold who underwent computerized tomography (CT) imaging of the sinuses, 87% had radiological evidence of sinusitis(86). Acute rhinosinusitis presents with nasal congestion, obstruction, posterior rhinorrhoea anosmia and facial pain. Most acute rhinosinusitis resolves within 10 days, but approximately 3 in every 100 patients persist longer(87). Risk factors that modulate susceptibility to the common cold include psychological stress, smoking, disrupted sleep, poor nutrition and older age(82, 88-90).

Although the upper respiratory manifestations of HRV infection are usually self-limiting, they are however responsible for immense health, economic and societal costs due to the sheer scale of associated medical visits/prescriptions work and education(91-95). The frequency of HRV infection compounds this burden, as both children and adults may be infected by HRV multiple times per year(96-98). The common cold, for which HRV is primarily responsible, was estimated to cost 4 billion dollars per year, including 1.1 billion on antibiotic prescriptions alone in the US alone in 2003(94).

### HRV and Lower Respiratory Infection (LRI)

#### Background

The role of HRV in lower respiratory infections (LRIs) is frequently underestimated. The term LRI is often used imprecisely; however, LRIs can be classified as acute bronchitis in the absence of radiological infiltrates or pneumonia in the presence of infiltrates. Cough and dyspnoea are the most common symptoms of lower respiratory infection, and less than half of patients with HRV pneumonia may present with fever. Bilateral pulmonary infiltrates detectable on chest radiography are common in HRV-associated pneumonia patients(99, 100).

Traditionally, there has been scepticism regarding the viability of HRV infection of the lower respiratory tract. The optimal rhinovirus replication temperature is 33-35 °C(101), and previous dogma assumed that HRV replication within the warmer lower respiratory tract was unlikely. This assumption is incorrect.

Firstly, although parenchymal lung tissue reaches a temperature of approximately 37 °C(102), the temperature of large- and medium-sized airways is 33-35°C, which is suitable for HRV replication, and the ideal replication temperature varies between rhinovirus types(103). Furthermore, ex vivo experiments have suggested that HRV can replicate more efficiently in human bronchial epithelium than in human nasal epithelium(104). In addition, HRV infection in the lower respiratory epithelium and airway fluid in vivo can be readily demonstrated following experimental infection(105-107). In the context of natural infection, sputum obtained without contamination from tracheal samples often has a greater amount of HRV than does sputum obtained from secretions from the upper respiratory tract(108). Finally, it has been demonstrated that HRVs can migrate from the upper to the lower respiratory tract(109). In support of these observations, a wealth of studies have confirmed the commonality of HRV infection in adults who present with lower respiratory syndromes, which we discuss below.

#### HRV in adults with Lower Respiratory Infection (LRI)

CAP is associated with a massive healthcare burden. In the USA, 650 per 100 000 people are hospitalised with CAP every year, with an associated 100,000 deaths(110). Viruses are implicated in 30-40% of CAP in adults(111-113). Historically, the role of viruses in LRIs, including CAP, has generally been underappreciated due to previous reliance on less sensitive technologies.

For example, Templeton et al demonstrated that polymerase chain reaction (PCR) was more sensitive than traditional culture/serology for the detection of respiratory viruses in a cohort of adults with CAP, where HRV was the most commonly identified viral pathogen(114). Furthermore, Alimi et al. performed a meta-analysis of 21 European studies of adults with CAP(111). The proportion of adults with CAP with viral pathogens was 22%, but this percentage increased to 29.0% in studies where PCR was used(111). As expected, studies after 2010 had higher proportions of patients with detectable respiratory viruses. HRV was second only to influenza among the detected viral pathogens. Influenza virus was detected in 9% of adults with CAP, followed by HRV at 5% (111). Several meta-analyses prior to the SARS-CoV-2 pandemic also identified HRV as the first or second most common virus detected in adults with CAP along with influenza despite HRV being tested for less frequently(111, 115, 116). These meta-analyses revealed HRV in 5-9% of adults with CAP, but the true impact is likely underestimated(111, 115, 116).

It was often previously assumed that HRV pneumonia was largely associated with immunocompromised states(117, 118). However, the EPIC study, a multicentre prospective US surveillance study for CAP in immunocompetent adults, found respiratory viruses to be the most common pathogen detected(113). Patients were tested systematically for bacterial and viral pathogens, and among 2259 adults with CAP, viruses were found in 23% of adults, with HRV being the most frequently identified pathogen being found in 9% of cases of CAP(113). Similarly, a multicentre prospective cohort study of adults with CAP in China from 2014–2019 also detected HRV in 9% of cases(119).

Furthermore, HRV is associated with CAP in all adult age groups. An acute surveillance study in China from 2009–2019 identified HRV as the second most commonly detected respiratory virus. Among patients with pneumonia who tested positive for a respiratory virus, HRV was detected in 18% of those aged 18-60 and 17% of those aged >60 years. In adults with ARI without pneumonia, HRV was detected in 14% of adults aged 18-60 and 18% of those aged >60 years(120). HRV is also increasingly implicated in hospital-acquired lower respiratory infections(121).

While HRV is frequently detected via PCR using nasopharyngeal swabs in adults with lower respiratory symptoms(113), the detection of HRV using nasopharyngeal swabs does not in itself prove causation in lower respiratory infection. However, the fact that many such studies reporting HRV-associated lower respiratory infection have asymptomatic controls, in which HRV is identified infrequently, supports a causal role(113, 122, 123). Shi et al. conducted a meta-analysis of case–control studies of older adults with ARI and provided evidence that HRV is causally related to both ARI and CAP in older adults(123). HRV was significantly more common in adults aged over 65 years with ARI or pneumonia than in asymptomatic individuals/healthy controls (OR 7.1; 95% CI 3.7-13.6), with an HRV-specific attributable fraction among the exposed individuals of 86%, supporting causality(123). Furthermore, the frequent detection of HRV as the sole respiratory pathogen in lower respiratory samples of acutely unwell adults also provides reasonable circumstantial evidence that HRV may be the causative agent in lower respiratory disease(124-127).

The reliance on nasopharyngeal PCR alone may actually underestimate the true incidence of lower respiratory HRV infection(115). For example, in adults with CAP, a meta-analysis by Burk et al revealed that the pooled proportion of adults with CAP with a detectable respiratory virus was 24.5% using nasopharyngeal swabs (95% CI 21.5–27.5%). This proportion increased to 44.2% (95% CI 35.1-53.3%) when only studies that obtained lower respiratory samples from more than half of patients were included(115). Additionally, Hong et al. detected rhinovirus in 16.7% of nasopharyngeal sample patients but 29.3% of BAL fluid samples(128).

##### HRV and LRI Community Settings

LRIs in primary care settings are among the most common reasons for seeking medical attention, costing considerable resources and are associated with significant morbidity even in otherwise healthy working-age adults. This manifests with an average of 3.5 sick days per year, which has a large social and economic impact(129, 130). In community settings, HRV is among the most common aetiological agents associated with LRIs(95).

A prospective European primary care study of non-immunocompromised adults with symptoms of a lower respiratory infection across 11 countries evaluated the occurrence of respiratory viruses using nasopharyngeal PCR(131). The authors demonstrated that viruses were detected in 45.8% of adults with LRIs, with HRV being by far the most commonly detected viral pathogen (40% of patients with a positive respiratory virus PCR)(131). Adults who presented with LRIs to GPs with HRV, influenza, HMPV or RSV had a 2-8% higher symptom score than patents without these viruses, and HRV patients reported a median time to resolution of symptoms of 7 days (IQR 5-11). Notably, adults with HRV infection in the community frequently reported severe wheezing (OR 1.6, 95% CI 1.9-4.4)(131).

In primary care settings, HRV association with pneumonia in addition to acute bronchitis is also described frequently described. A case–control study in adults with acute cough/GP diagnosis of LRI across 16 primary care networks in Europe a respiratory virus in approximately half of adults, and HRV was the most frequently detected virus. HRV was detected in 20.4% of adults with lower respiratory infection without pneumonia and in 14.2% of those with pneumonia(132). Additionally, community HRV outbreaks are common in nursing home/residential care settings. Hicks et al described two rhinovirus outbreaks in the United States, half of cases in these outbreaks were associated with pneumonia(133)

Elderly patients represent a vulnerable group in the community. In a multicentre international study of adults >65 years of age with moderate-severe influenza-like illness (ILI­) in the community (severity defined by the authors as having pneumonia, requiring admission or having an influenza symptom score >2), Falsey et al. demonstrated that viruses were detected in 57.6% of cases. HRV was second only to influenza and was detected in 25.6% of cases(134).

Community lower respiratory infections are a leading cause of antibiotic prescription, despite their ineffectiveness in most cases. Unnecessary antibiotic prescriptions by clinicians are a key driver of the growth of antimicrobial-resistant organisms(135, 136). Clinicians need valid, cost-effective tools to distinguish between bacterial and viral infections.

##### HRV and Hospitalised adults

In hospitalised adults with ARI/LRI, HRV infection is prevalent worldwide. Zimmerman et al. calculated the population-based hospitalisation burden for respiratory viruses in adults in Pennsylvania from 2015–2019. HRV was the most frequently detected viral pathogen, accounting for 30.1% of viral infections, with an annual hospitalisation burden of 137-174 per 100,000 people. Among adults under the age of 65, there were more HRV-associated than influenza-associated hospitalisations(137).

Other studies corroborate the observation that HRV is among the most common viruses found in hospitalised adults with ARI globally. Grech et al. demonstrated that picornavirus was the most prevalent respiratory pathogen detected in a multicentre Australian observational study from 2014–2019. HRV was the leading pathogen, accounting for 32.8% of admissions to general medical wards and 40.2% of admissions to intensive care units (ICUs) with ARI and a detectable pathogen(54). In a Mexican observational study, 23.5% of adults with HRV infection required hospital admission(138). Similarly, Chiu et al reported HRV in 21.5% of adults admitted to Taiwanese hospitals with ARI(139). A Lebanese study across hospitals found that HRV was detected in 22% of community-acquired respiratory tract infections, making it the most commonly detected pathogen(140). Additionally, a recent Malaysian study identified a respiratory virus in 57% of adults with an ARI, 49% of which was HRV(141).

HRV infection has also been associated with severe pneumonia requiring intensive care admission, as well as acute respiratory distress syndrome (ARDS), in adults(126, 127, 142-149). Notably, HRV infection-induced ARDS has been described in immunosuppressed(150) and immunocompetent(143) adults in the absence of identifiable bacterial coinfection(144).

The prevalence of HRV in ICU settings rivals that of other viruses. In a retrospective study by Piralla et al., HRV was the 2nd most commonly detected virus in patients admitted to the ICU with severe respiratory syndromes(124). Similarly, another study showed that HRV was the second most prevalent virus identified in adults admitted with severe CAP(142). A recent national surveillance study by Liu et al. over 12 years in China revealed HRV to be the second most frequently detected virus among adults aged 18-60 and over 60 years requiring ICU care for CAP(151).

HRV is not only prevalent in hospitalised adults but also has clinical consequences comparable to those of other viruses. In a prospective 3-year cohort study, in adults admitted with ILI, Picornaviridae were the most common non-influenza virus detected (27%). Notably non-influenza viruses exhibited similar lengths of stay and in-hospital mortality to influenza patients, although specific analyses for Picornaviridae was lacking(152). Furthermore, a retrospective cohort study in a single centre found comparable adjusted 30-day mortality rates among adults hospitalised due to HRV, RSV or MPV infections compared to those hospitalised with influenza infection. HRV infections were associated with 8% 30-day mortality, and 60% of HRV-infected adults required hospital admission, a proportion similar to those admitted with influenza, RSV or MPV (67-71%). Notably, the median age of HRV patients was 69 years, which was lower than that of patients with influenza, RSV or MPV(153).

Another study focusing on elderly hospitalised adults with pneumonia highlighted that HRV infection was associated with significantly higher mortality rates at 30 days, 90 days, and 1 year, as well as prolonged hospital stays(154). Those infected with HRV were significantly more likely to require oxygen therapy than those infected with influenza. The study suggested that premorbid functional status might influence outcomes, as a greater proportion of HRV-infected patients resided in institutional or residential care settings prior to admission. Independent risk factors for 1-year mortality among HRV-infected adults included residence in a care home before admission, low haemoglobin levels (<13.3 g/dl), oxygen therapy requirement, and intensive care treatment during hospitalisation(154).

Adults with obstructive lung disease are particularly vulnerable to severe manifestations of lower respiratory tract infections associated with HRV, a topic we will explore further.

### HRV and Airways Disease in adults

#### HRV and Asthma Exacerbation

Theodore Minor associated HRV infection with asthma exacerbations in the early 1970s(155). HRV has also been implicated in the development of asthma as well as its exacerbation(156). Asthma exacerbations are marked by acute worsening of symptoms and a decline in pulmonary function and frequently result in emergency department admission, hospitalisation and death(157). In the United States, 43% of adults experienced at least one exacerbation annually in 2018, despite optimised asthma therapies(158). Globally, respiratory viruses are responsible for half of all asthma exacerbations in adults with HRV being the most common viral pathogen(159-162)

Recent meta-analyses have confirmed the significant role of HRVs, with findings showing that HRV was detected in 20-46% of asthma exacerbations in adults(158, 159). HRV is consistently identified as among the most common causes of asthma exacerbation in adults in both outpatient(160, 162-164) and inpatient settings(161, 165) (160, 161, 163, 165, 166). While patients with and without asthma have a similar frequency of HRV upper respiratory infections, patients with asthma have more frequent and severe lower respiratory symptoms following HRV infection(167).

HRV infection in asthmatic patients propagates airway hyperresponsiveness and eosinophilic inflammation. A recent meta-analysis demonstrated that adults with asthma exhibit significantly lower levels of IFN-β and IFN-γ than controls following HRV infection(168). Moreover, elevated levels of IL-4, IL-5, IL-8 and IL-13 correlate with respiratory symptoms in asthmatic patients with HRV infection(168).

Muehling et al. experimentally identified two distinct immunophenotypes among asthmatic adults infected with HRV using analysis of viral load and nasal cytokine profiles(27). One immunophenotype exhibited increased viral loads along with elevated IFN-α and IL-15. Conversely, patients with the other immunophenotype exhibits a lower viral load but more severe symptoms and a dysregulated immune state with increased IgE and IFN-γ(27). Additionally, excessive activation of RIG-I in asthmatic patients may impair type I/type III IFN responses, leading to impaired viral clearance and prolonged airway inflammation(169). HRV infection in asthmatic patients can also induce airway remodelling, highlighting the need for further research to identify potential therapeutic targets aimed at preventing viral-induced remodelling(170). Understanding these processes could pave the way for precision medicine approaches targeting specific endotypes of HRV-induced asthma exacerbation with host-directed biological therapies.

#### HRV and COPD exacerbations

Acute exacerbations of COPD (AECOPD) drive morbidity and mortality in patients with COPD, and viral infections are common triggers(171). These exacerbations are frequent causes of hospital admission(172).

A landmark prospective study in adults with chronic bronchitis in the 1960s demonstrated that HRV infection could cause acute exacerbations of chronic bronchitis, even in patients without typical upper respiratory symptoms(173). Seemungal et al. reported that HRV was the most frequently detected viral pathogen and was responsible for 58% of viral exacerbations of COPD(174). A meta-analysis from 2014 highlighted a prevalence of respiratory viruses in COPD exacerbations of 39.3% (95% CI 36.9-41.6), with a pooled risk ratio of 4.1 (95% CI 2.0-8.5) for AECOPD compared to stable COPD(175). HRV was identified as a predominant virus with a prevalence of 15%(175). Many other studies have consistently identified HRV as one of the most common pathogens in AECOPD(161, 172, 174, 176-183).

HRV infections contribute to seasonal peaks in COPD exacerbations, and interestingly, COPD patients colonised with *Haemophilus influenzae* may be particularly vulnerable to HRV-induced exacerbations(180)**.** Acute viral infection in the context of chronic bacterial colonisation can modulate the host inflammatory response in COPD, involving complex interactions of innate and adaptive responses that drive exacerbations and contribute to other clinical consequences of COPD, such as fixed airflow obstruction, lung remodelling and emphysema(170, 184). IFN deficiency in COPD, through unclear mechanisms, may increase the susceptibility of patients to a greater viral load and HRV-associated inflammation(171).

#### Other Pulmonary Diseases

The impact of HRV on chronic lung diseases extends beyond asthma and COPD and includes interstitial lung disease (ILD), bronchiectasis, and cystic fibrosis. However, these conditions have been less extensively studied. Evidence indicates that HRV, along with other respiratory viruses, plays a significant role in the exacerbation of these diseases.

Li et al. conducted a retrospective study in patients with viral infections and ILD and revealed that HRV accounted for 9.2% of viral infections in the non-immunocompromised group. Interestingly, non-influenza viral infections were associated with higher 30-day mortality than influenza infections(185).

In bronchiectasis, respiratory viruses are isolated in approximately a quarter of exacerbations, with HRV contributing to approximately one-fifth of virus-associated exacerbations, ranking second only to influenza in one study(186).

Regarding cystic fibrosis in adults, Flight et al. conducted a prospective study involving 100 adults and found that respiratory viruses were detected in 30.5% of visits. HRV accounted for 72.5% of the detected viruses, and viral infection was associated with a greater risk of exacerbation (OR 2.26), higher symptom scores, and elevated C-reactive protein (CRP) levels(187).

# Factors Modulating Severity of HRV Infection

## Viral Factors

A higher HRV viral load has been linked to greater symptom severity, although it does not appear to increase the likelihood of hospitalisation(131, 138). In adults, among the rhinovirus species, RV-A and RV-C are more likely to cause severe infections. Conversely, RV-B is associated with asymptomatic infections. Even in symptomatic patients with RV-B infection, RV-B may be milder than RV-A and RV-C(57). In a prospective observational study spanning two years, Chen et al. reported that among 62 healthy adults with ILI, 72.6% were infected with RV-A, 27.7% with RV-B, and 9.7% with RV-C. RV-A and RV-C infections were associated with numerically greater upper respiratory, lower respiratory, and systemic symptoms and overall symptom severity scores than RV-B infections. RV-A caused statistically significantly more severe upper respiratory symptoms than RV-B infection(188).

Furthermore, a multicentre prospective observational study conducted over four years indicated that 26% of participants tested positive for HRV, with 67.1% being adults. RV-B infections were significantly less likely to result in hospitalisation (p<0.001)(138). This aligns with in vitro findings showing that RV-B replicates more slowly and induces a more attenuated cytokine response than RV-A and RV-C(189).

Although one study revealed that RV-C is more common in adults with asthma and COPD(190), other research has not found convincing evidence that specific HRV species are associated with preexisting respiratory conditions such as asthma or COPD(55, 65).

## Host Factors

Hospitalised adults often present with multiple comorbidities, including prevalent conditions such as diabetes, hypertension, and cardiorespiratory diseases.(55, 99, 100, 138) Elderly individuals, immunocompromised patients, and those with multiple comorbidities are particularly at risk for severe HRV infections(99, 100, 191, 192).

In a retrospective cohort study involving adults with community-acquired pneumonia (CAP) and HRV infection, most patients were elderly with multiple comorbidities, with a median age of 71 years. Common comorbidities included diabetes and hypertension(99). Among these patients, 15.1% required ICU admission, and notably, there was no significant difference in pneumonia severity index between ICU and non-ICU patients(99). Chronic respiratory disease and male sex in particular may be associated with more severe infections requiring intensive care admission(141). Reduced functional status, such as being bedbound, is identified as a risk factor for hospitalisation due to HRV infection(99). Current tobacco smoking has also been implicated as a potential risk factor among adults attending the emergency department with HRV infection(193).

Elucidating how the diverse factors associated with multimorbidity drive impaired outcomes in patients with rhinovirus infection is crucial(194). Elderly patients may present atypically with attenuated symptoms, potentially due to altered host pathogen interactions associated with immunosenescence(194). Immunosenescence involves diminished B-cell production, dysregulated T-cell immunity, thymic involution, reduced naive T cells and a greater proportion of terminally differentiated, functionally impaired, exhausted T cells, thus impacting the response to respiratory viral infections(194, 195). IFNs play a crucial role in antiviral defence and given the diversity of HRV strains, HRVs can largely escape the protection normally provided by the adaptive immune response. Hence, a competent innate immune response is essential. Defective IFN expression has been demonstrated in both asthma and COPD patients, which may provide insight into the increased susceptibility of these patients to respiratory viral infection, including HRV(196-198). Both immunodeficient and dysregulated immune responses may drive disease severity(199).

# Viral and Bacterial Coinfection

Viral co-infection has been reported to be common in children; however, in adults, viral coinfection is less common(200-203). Viral co-infection in adults has been reported at around 1-5%(200, 201, 204-206).

Golke et al identified that in a hospital centre in Germany, 21% of HRV infections were associated with co-infection. Bacterial co-infection was by far the most common coinfection (71% of all co-infections)(55). Staphylococcus aureus, Pseudomonas aeruginosa, Haemophilus influenzae, Klebsiella pneumoniae, and Escherichia coli were the detected bacterial co-pathogens. The study identified associations between viral-bacterial co-infection and the development of lower respiratory infections. and pneumonia, prolonged length of stay and admission to the ICU(55). A positive bacterial blood culture has been associated with a greater risk of critical illness in adults with HRV infection(141).

Bidirectional interactions between bacteria and viruses may occur, whereby colonisation of the respiratory epithelium by bacteria may increase susceptibility to HRV infection. Conversely, HRV infection can disrupt epithelial integrity, potentially predisposing individuals to secondary bacterial infections(207). Notably, while HRV-associated CAP requiring ICU admission has been described without identifiable bacterial coinfection, high rates of antibiotic prescription may lead to negative culture results, masking the influence of bacterial pathogens(99).

Interestingly, a recent systematic review found that due to the limited number of studies, there is no evidence that pneumococcal conjugate vaccines provide protection against severe outcomes in adults with rhinovirus infection, which contrasts with some evidence for protection against influenza and coronavirus infections(208).

Identifying bacterial coinfection remains challenging, highlighting the need for novel biomarkers to guide appropriate antibiotic use. FebriDx is a rapid point-of-care immunoassay that measures mxyovirus resistance protein A (MxA) and C-reactive protein (CRP) from a finger-prick test(209). It has shown promising sensitivities of 92.2% for bacterial infection and 70.3% for viral infection, with specificities of 88.4% and 88.0%, respectively(209). Clinicians need objective, validated tools in the future to properly guide antibiotic prescription and combat emerging antimicrobial resistance. Transcriptomic profiling may also hold promise for identifying bacterial co-infection, particularly in acutely unwell patients where obtaining invasive lower respiratory samples for culture/PCR can be challenging(210-213).

# HRV Therapeutic Challenges

As mentioned above, HRV is frequently underrecognized. Rapid detection of HRV will be a prerequisite for timely delivery of HRV therapies in acutely unwell adults, although specific therapies are currently lacking(111, 115, 116).

Current treatments for HRV infection are supportive. Analgesics/antipyretics such as paracetamol, ibuprofen, and aspirin are used to alleviate symptoms such as fever, headache, muscle aches, and sore throat. Nasal congestion, although temporarily relieved with sympathomimetics such as xylometazoline and pseudoephedrine, often recurs upon cessation of treatment(82).

Several promising treatments are currently in development, including capsid binders, viral enzyme inhibitors, and host-targeted antivirals(214, 215).

Capsid binders act by preventing viral uncoating post-entry into host cells, binding to VP-1 and thereby inhibiting the release of HRV RNA into the cytoplasm(216). Pleconaril an oral capsid-binding antiviral, has shown efficacy in reducing viral RNA levels and culture positivity, as well as shortening illness duration by approximately one day. However, its effectiveness is influenced by viral susceptibility, and up to 10.7% of post-treatment virus isolates may exhibit partial or total resistance. Pleconaril is also associated with notable side effects, including interference with contraceptive efficacy and moderate gastrointestinal upset(216, 217). Pirodavir, another capsid binder administered intranasally, has been shown to reduce viral shedding but has no significant clinical benefit on symptom duration(218). A key limitation of capsid binders is their inability to effectively target RV-C species(219) and concerns regarding the induction of antiviral-resistant HRVs(220). Viral enzyme inhibitors, such as rupintrivir, which inhibits the picornavirus 3C protease, show potent activity against HRV, although their clinical efficacy remains uncertain(221). Additionally, gemcitabine, originally used in cancer therapy, exhibits viral enzyme inhibitor properties by inhibiting viral polymerase activity in enteroviruses when it is administered at lower doses(222).

Host-targeted antivirals represent another approach, with compounds such as 25/27-hydroxycholesterol reducing phosphatidylinositol 4-phosphate on the endoplasmic reticulum, thereby preventing the recruitment of viral RNA polymerase(223). These drugs show potential for broad-spectrum antiviral activity(224, 225). Other host-targeted antivirals include phosphatidylinositol 4-kinase IIIB (PI4KB) inhibitors, which also have potentially broad-spectrum antiviral activity. However, there have been concerns regarding their toxicity to the host(226, 227).

The use of IFNs to enhance host anti-viral defence has also been explored. Nebulised IFN-β has been studied for potential use in viral exacerbations of asthma and SARS-CoV-2 infection, and although not meeting primary endpoints, there is some evidence of a signal suggesting prevention of progression to more severe disease. However, further studies are required to investigate these findings(228, 229).

# Vaccine Challenges

Efforts to develop effective HRV vaccines have been ongoing since the 1960s, when it was established that deliberate inoculation could induce protective antibodies against specific HRV strains(230). Subsequent studies demonstrated that intramuscular administration of inactivated HRV could lead to antibody production capable of protecting against subsequent illness(231-233).

However, developing vaccines with prolonged and broad immunity has proven challenging due to the vast number of co-circulating HRV types and their associated antigenic diversity(234-236). Promisingly, a polyvalent vaccine targeting 50 HRV strains has been developed and tested in macaques(237). Practical strategies include regular surveillance of HRV in acutely ill populations and focusing vaccine efforts on the most prevalent and pathogenic HRV types. Additionally, vaccines that target common epitopes shared among HRV strains to induce cross-strain immune responses are in development(238). Such vaccines could mitigate the challenges posed by the antigenic diversity of HRVs. Vaccines are particularly crucial for at-risk groups such as patients with COPD, aiming to reduce the frequency of virus-induced exacerbations(239).

# Conclusion

HRV is not merely the ubiquitous agent of the common cold; it is a predominant pathogen in adults presenting with ARI in diverse healthcare settings—from primary care to intensive care units (Figure 3). This pathogen significantly influences morbidity, mortality, and hospital stay duration across a wide spectrum of adult populations. Elderly, immunocompromised, and individuals with cardiorespiratory comorbidities are particularly vulnerable to severe outcomes. HRV transmission through aerosolization contributes to its persistence and prevalence throughout the year. The dogma that HRV infection is confined to mild upper respiratory infections should be challenged, as HRV is frequently implicated in severe lower respiratory conditions, even in immunocompetent adults, including in pneumonia and exacerbations of asthma and COPD.

Given its extensive impact, it is important to improve our understanding of HRV epidemiology, comparable to SARS-CoV-2, to enhance our understanding of the strain-specific severity of infections. More prospective observational studies and continuous surveillance are needed, particularly among community care homes and among hospitalised adults. This approach would not only facilitate the identification of high-risk HRV strains to guide vaccine development but also aid in precisely determining factors that influence the severity of infections and host-pathogen. Such data are essential for developing effective intervention strategies, including targeted antiviral therapies and vaccines. Given the scale of HRV infection, the use of digital tools to assist with the design of future care pathways and clinical trials may be valuable(240). Moreover, improving methods for detecting bacterial coinfection is critical, as they could guide appropriate antibiotic prescriptions and potentially reduce the burden of severe infections.

By elevating HRV to a status comparable to that of other major viral pathogens, such as influenza, in research and public health priorities, we can better mobilize resources and direct efforts towards mitigating its substantial impact on public health. This comprehensive approach is essential for developing effective preventive and therapeutic measures that could lead to significant reductions in ARI cases associated with HRV.

A diagram of various diseases

Description automatically generated with medium confidence

**Figure 3: Impact of Rhinovirus Infection in Adults. HRV is a major global pathogen and is detected throughout the year. Upper respiratory manifestations, including the common cold, are the most common manifestation and while self-limiting are associated with a considerable societal cost. It is now increasingly apparent that HRV is a driver of severe lower respiratory manifestations in adults, including exacerbations of airway disease and pneumonia, on a scale comparable to that of other respiratory viruses. The severity of infection is determined by the complex interaction of host factors such as age, multimorbidity and immune dysfunction alongside other factors such as viral characteristics and the presence of bacterial co-infection. There is an urgent need for novel treatment options, as options currently available are merely supportive in nature.**

# List of Abbreviations

AECOPD: Acute Exacerbations of COPD

ARDS: Acute Respiratory Distress Syndrome

ARI: Acute Respiratory Infection

CAP: Community Acquired Pneumonia

COPD: Chronic Obstructive Pulmonary Disease

CI: Confidence Interval

CRP: C-Reactive Protein

CT: Computerized Tomography

CHDR-3: Cadherin Related Family Member 3

ENA-78: Epithelia Neutrophil Activating Peptide 78

MxA: Mxyovirus Resistance Protein A

H1N1: Haemagglutinin 1 Neuraminidase 1

HRV: Human Rhinovirus

ICU: Intensive Care Unit

IL: Interleukin

ILI: Influenza Like Illness

IFN: Interferon

IP-10: Interferon Gamma Inducible Protein 10

LDL-R: Low Density Lipoprotein Receptor

LRI: Lower Respiratory Infection

ICAM-1: Intracellular Adhesion Molecule 1

MDA-5: Melanoma Differentiation Associated Gene

OR: Odds Ratio

PAMP: Pathogen Associated Molecular Pattern

PI4KB: Phosphatidylinositol 4-Kinase IIIB

PCR: Polymerase Chain Reaction

PRR: Pattern Recognition Receptor

RANTES: Regulated Upon Activation, Normal T Cell Expressed and Secreted

RIG-1: Retinoic Acid Inducible Gene 1

RNA: Ribonucleic Acid

RSV: Respiratory Syncytial Virus

RV: Rhinovirus

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

TLR: Toll Like Receptor

URI: Upper Respiratory Infection

VP: Viral Protein

# Declarations

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Availability of data and materials

Not applicable.

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