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Review

Molecular Pathogenesis of Human Rhinovirus (HRV) Infection

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Abstract. Human Rhinovirus (HRV) is a RNA virus belonging to the Picornaviriade family that most often causes acute respiratory infections (ARI). This virus can cause dangerous infections in children, people with chronic respiratory disorders, and individuals with low immunity. This virus can infect newborns six to eight times and adults two to four times per year. In addition, HRV is the main cause of pneumonia and bronchiolitis which can worsen the symptoms of cystic fibrosis asthma. This article also discusses the development of the HRV replication process that occurs in the respiratory tract epithelium which takes place in several stages, starting with virus attachment and ending with the release of new virions. We also analyze the stages of neutralizing antibodies (nAbs) to prevent HRV infection. Currently, there are not any authorized antiviral drugs or HRV vaccination because this virus has highly variable antigenic sites. To develop a vaccine that can protect against various HRV serotypes, a consensus sequence that combines several strains is needed.

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1. Introduction

Human Rhinovirus (HRV) are one of the most pathogen cause of Acute Respiratory Infections (ARI), especially the common cold. As reported by the WHO, ARI are responsible for almost 20% of all deaths of children under 5 years globally [1]. According to the 2023 Indonesian Health Survey published by the Ministry of Health, there were 877,531 cases of ARI in Indonesia in 2023, with approximately 23.3-23.8% of patients exhibiting symptoms [2].

By the National Institute for Health and Care Excellence (NICE), a common cold is defined as a mild, self limiting upper respiratory tract infection signed by nasal congestion and discharge sneezing, sore throat and coughing.[3] With at least 100 serotypes, rhinoviruses lead to cause common cold in children and adults, which have a major financial impact on healthcare system and individual quality of life. At least 50% of colds in adults are caused by rhinoviruses [4-5].

Overall, the syndrome is moderate and self limited, but mainly in children and people with weakened immune systems or chronic respiratory disorders, they chiefly cause infection in upper and lower breathing tracts [6]. The most typical symptoms of upper infection are lower fever, headache, sore throat, rhinorrhea, cough, and malaise. However, in some cases, these symptoms can lead to rhinosinusitis and otitis media. While infection in lower respiratory tract are frequently linked with pneumonia and bronchiolitis, particularly in children [7]. This is strengthened by the results of the PERCH (The Pneumonia Etiology Research for Child Health) analysis which showed that HRV-positive children had a 13% higher risk of developing pneumonia [8]. In addition, HRV-induced bronchiolitis carries a very high risk of subsequent asthma progression and is a frequent precipitant of acute asthma exacerbations [9].

Advancements in molecular diagnostics have demonstrated the role of HRV in more severe clinical infections, especially in patients with long term pathologic conditions such as cystic fibrosis, asthma, and obstructive pulmonary disease (COPD), which may exacerbate lung disease in these patients [10-11]. In addition, HRV infection can be exacerbated by the lack of approved antiviral agents for prevention or treatment due to the high genetic diversity of the virus, as well as the vulnerability of the viral RNA polymerase to errors that can lead to spontaneous mutations and increased risk of drug resistance, hindering antiviral drug development efforts [12].

This review aims to present a current overview of RV molecular features as well as the related to infection's pathogenesis, the activation of host immunological response that contributed with other respiratory diseases, including the development of antivirals and vaccine for the prevention and treatment of these viral infections.

2. Experimental Section

In order to compile this review, from June until September 2024 the authors conducted various database of scientific literature and research to search utilizing keywords linked to human rhinovirus (HRV), pathogenesis, virology, and other relevant terms on PubMed, Elsevier, Google Scholar, and other official media channels which publication ranging from 2019 to 2023. The search included of terms (1) Morphology and Genome Structure, (2) Classification, (3) Transmission and Pathogenesis, (4) Replication, (5) Epidemiology, (6) Immune Response to HRV, (7) Mechanisms of Antibody-Mediated Neutralization of HRV, (8) Detection, (9) Theraphy and Prevention of HRV.

We analyzed recent research studies to understand the latest finding on molecular pathogenesis of HRV infection. Articles with screening potential were identified from abstract to full text publishing and 30 journals fullfil the criteria and were available for review. Figure 1 illustrates the workflow for article selection process.

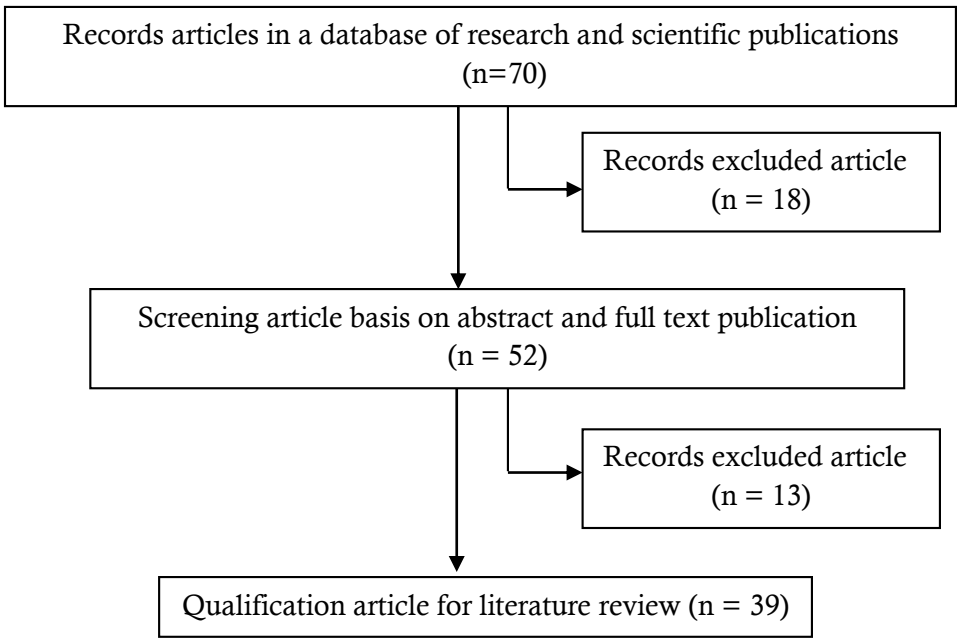

Figure 1. PRISMA workflow

3. Result and Disucssion

3.1 Morphology and Genome Structure

HRV is a small, naked viruses and a part of the Enterovirus genus in the Picornaviridae family. The virus include a single-stranded positive-sense RNA with a length of approximately 7200 kilobases. The RNA genome is sealed by an icosahedral capsid containing capsid proteins (VP1, VP2, VP3, and VP4) in 60 copies [13].

The complete sequence of HRV genome consist of single Open Reading Frame (ORF) clamped by the 5' and 3' untranslated regions (UTRs) and a poly-A tail [14]. The 5' UTR include an Internal Ribosome Entry Site (IRES) used to detect HRV in clinical samples and short Viral Protein genome (VPg). The ORF can encode polyproteins to be broken down by proteases into 11 proteins : 4 structural proteins and 7 non structural proteins [15].

The ORF composed by P1, P2, and P3 regions. The P1 region can encode viral structural proteins (VP4-VP1) forming a protective capsid and has an impact in the antigenic diversity of the virus as it is a primary target in the immunological system of the host [16]. The VP1, VP2 and VP3 proteins are located on the capsid exterior and participate in the antigenic diversity of the virus, while the VP4 protein is found on the capsid's inside and plays a role in binding the genome to the capsid. From the four capsid proteins, the VP1 protein is the biggest protein and function as an attachment site for viral receptors in host cells [17]. VP4/2 or VP1 is the part that is widely used to determine the genotype of this virus [15].

Besides containing 4 structural proteins, HRV also contains 7 non-structural proteins such as 2A, 2B, 2C, 3A, 3B, 3C and 3D. These non-structural proteins play a role in replication, translation and hijacking the host cell machinery. This type of protein belongs to the P2 and P3 regions. Region P2 have a part in viral replication and consists of proteins 2A, 2B and 2C [16]. Protein 2A acts as a cysteine protease that works between the P1 and P2 regions, while protein 2B participate in assisting the virus's discharge from contaminated host cells and protein 2C functioning in intracellular binding of host proteins. Region P3, apart from its role in viral replication, also participate in modulating the host immune response. This region consists of proteins 3A, 3B, 3C and 3D. The 3A protein can

interact with the PI4KB protein and facilitate replication. Protein 3B, also known as VPg, serve as a primer and is the only non-structural protein in the virion. Similar to protein 2A, protein 3C is a protease that can cleave and degrade Retinoic Acid Inducible Gene I (RIG-I) which can reduce type 1 interferon (IFN) production. Meanwhile, protein 3D acts as an RNA dependent RNA polymerase (RdRp) that helps synthesise new viral RNA during replication. The end of the HRV genome is a Tail Poly (A) found in the 3' UTR contributes to genome stability. (Figure 2) [14][16].

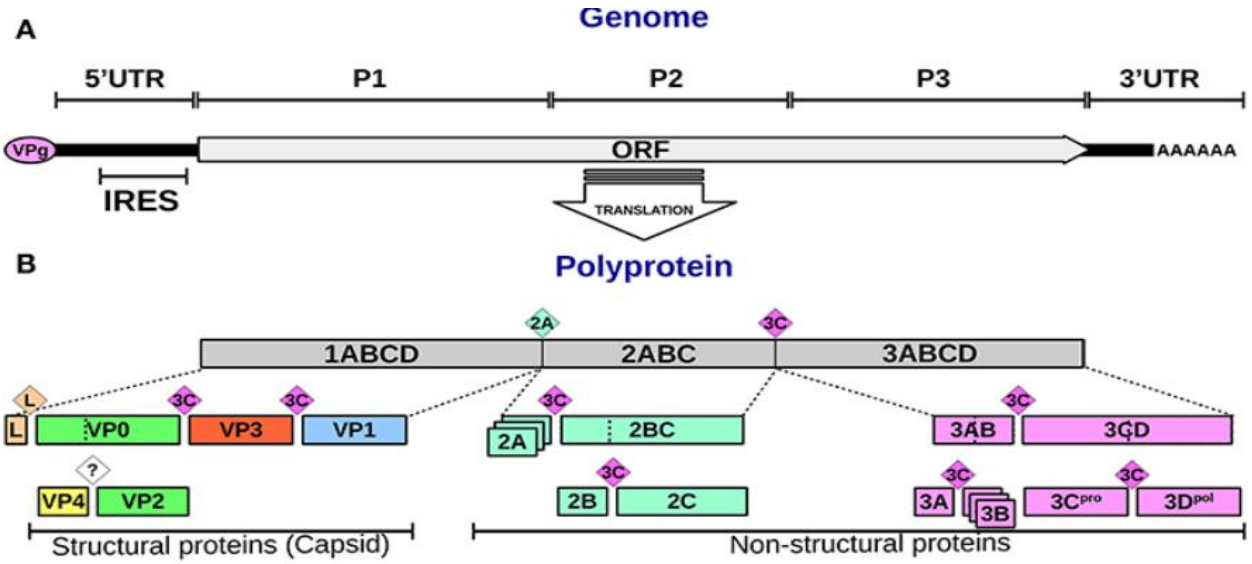

Figure 2. The Complete Structure of The HRV Genome. The viral RNA binds covalently to the VPg protein at the 5' end and the poly(A) tail at the 3' end. The genome of this virus has single ORF that can encode poly proteins and can be broken down by viral proteases (2A and 3C) into structural and non-structural proteins [16].

3.2 Classification

HRV is classified based on nucleotide sequence differences in VP4/VP2 and VP1 proteins into three species: HRV-A (80 serotypes), HRV-B (32 serotypes) and HRV-C (57 serotypes). This serotype distinction is based on nucleotide sequence differences of more than 11% between each other's nucleotide sequences consistently on the VP1 protein [15].

In the majority of HRV-A serotypes are uses Intercellular Adhesion Molecule-1 (ICAM-1) receptor, while in a minority proportion of HRV-A (about 12 serotypes) uses Low Density Lipoprotein Receptor (LDLR). In HRV-B serotypes are uses ICAM-1 receptor and has the lowest severity when compared to HRV-A and HRV-C. Conversely in HRV-C serotypes are uses Cadherin-3 (CDHR-3) as receptor which is only found in ciliated epithelial cells [18].

Studies have mentioned that HRV-A and HRV-C infect more individuals and have more severity than HRV-B. This is because the replication rate of HRV-A and HRV-C tends to be faster and cause a greter inflammatory response than HRV-B. In addition, HRV-C often leads to illness to cause disease severity in children, while HRV-A in mature individuals. In contrast, HRV-B generally causes mild symptoms but causes more severe exacerbations in asthma patients [19-20].

3.3 Transmission and Pathogenesis

HRV can transfer from one person to another person from respiratory secretions containing the virus through three different routes of transmission: exposure (direct or indirect) through the nasal mucosa or conjunctiva, large aerosols (droplets) and smaller aerosols.

Direct exposure can occur between and infected individual and susceptible host through touching or kissing, while indirect exposure is through hands or virus contaminated objects (fomites). Large aerosols (droplets) that come from the air due to gravity will settle on the surface and infect susceptible hosts. Similarly, in small aerosols, the virus can spread because the virus can extended periods for a long time in the air, then spread in a room and be inhaled by susceptible hosts [21]. The virus can survives because the virus has slight resistance to hand sanitizers, alcohol, and other common disinfectants [22].

HRV that spreads can infect the upper and lower breathing tract. In the top breathing tract, the virus can cause pharyngitis, laryngitis and sinusitis with symptoms such as rhinorrhoea, congestion in the nose, cough, sore throat, headache and low fever lasting about 7 to 14 days. In individuals with a good immune system, the infection may resolve on its own. Moreover, the virus can also cause inflammation of the sinus tissues [22-23]. If there is inflammation of the sinus tissue, the individual is more vulnerable to bacterial sinusitis, and in some cases if there is blockage of the eustachian tube, it can lead to bacterial otitis media [18]. While in the bottom breathing tract, viruses are pathogenic agents that cause CAP (Community Acquired Pneumonia) which can cause pneumonia, bronchiolitis and asthma exacerbations in children [22-23]. Wheezing caused by HRV during infancy may lead to recurrent wheezing and the onset of asthma, especially in patients infected with HRV-C and having allergies before the age of three [18].

In another study was mentioned that the virus has a co-infection rate of 78.9% with various bacteria, viruses or fungi. Co-infection with bacteria can be a primary factor in causing the severeness of infection with this virus, especially if infected with HRV-A and HRV-C. Co-infection with viruses is more common with other respiratory viruses, especially when infecting infant under two and can lead to an higher chance of being admitted to ICU compared to one infection [19].

3.4 Replication

Viral replication process occurs in the airway epithelial cells. This process begins with binding of the the virions to the host cell by plasma membrane's virally- specific receptors assisted to VP1**.** This causes the virion to be absorbed into the cell through a process of endocytosis depending on the type of receptor used. Consequently, the virus to undergo conformational changes in the endosome to generate particles of hydrophobic subvirals and the genome is released in the cytoplasm. When the RNA genome and VP4 are in the cytosol, the ribosomes of host cells will interpret the RNA genome into a single polyprotein form with the help of viral proteases (protease 2A, 2Apro and protease 3C, 3Cpro) through co-translation techniques in cis and trans forms to form 11 proteins.

The cleavage begins with the release of P1 from the protein facilitated by protease 2Apro causing P1 to cleave and produce the viral capsid protein, while protease 3Cpro facilitates the cleavage of other polyproteins to release P2 and P3 to form non-structural proteins such as 2Apro, 2B, 2C, 3A, 3B (VPg), 3Cpro, and 3D. During replication, single stranded RNA genomes form double RNAs that are used as design for the synthesis of new single RNA genomes. The replication process ends with the assembly of new infectious virions and the release of virions out the cell through cell lysis. (Figure 3) [24].

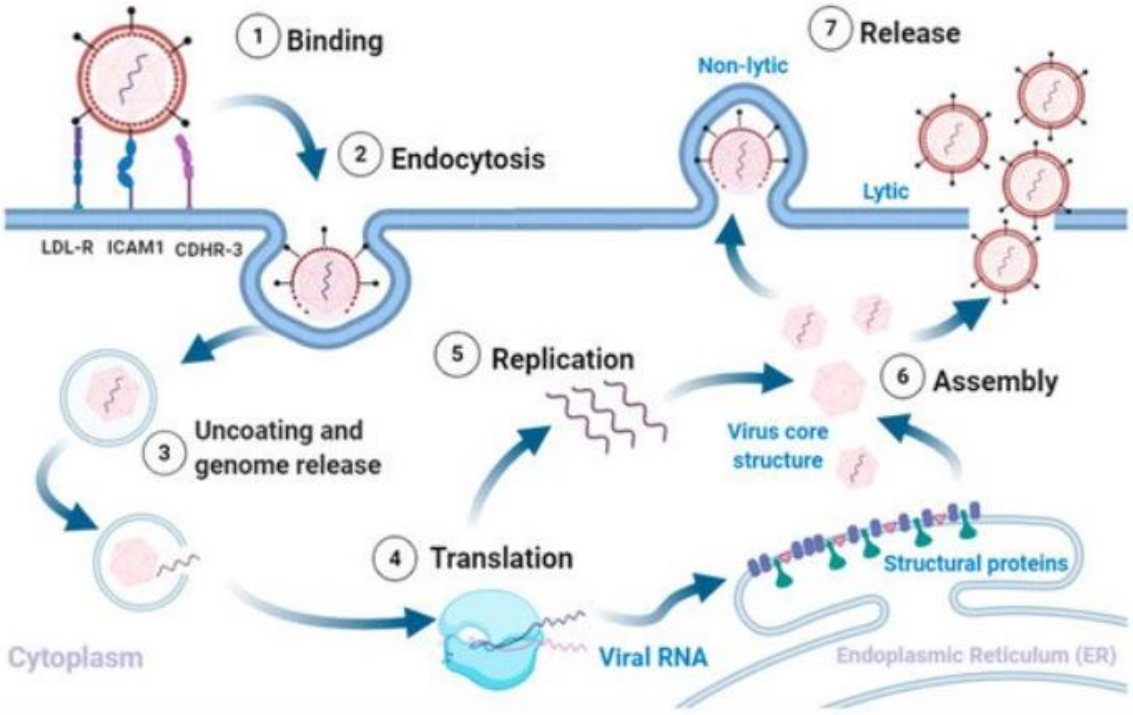

Figure 3. HRV Replication Process. (1) Binding of virions to host cell receptors (2) absorption of virions into cells through the process of endocytosis (3) the virus undergoes conformational changes and causes the genome to be released in the cytoplasm. (4) Translation of the RNA genome into a single polyprotein form (5) Replication of the single RNA genome to form a double RNA used as a mold (6) Assembly of new infectious virions (7) New infectious virions are released out of the cell through breaking down of cell lysis [24].

3.5 Epidemiology

HRV is the most frequently detected respiratory virus throughout the year. It can infect infants six to eight times per year and adults two to four times per year. Despite its high prevalence, molecular epidemiologic studies of the virus are rare due to its high genotypic diversity [25]. Younger age groups are more likely to experience recurrent HRV infection, but no individual is reinfected with the same genotype, as specific immunity to an HRV serotype can last more than one year [26].

HRV can infect throughout the year, but increase sharply when temperatures tend to be low such as winter, spring and fall in most temperate (subtropical) countries such as Amerika, Europe and Australia. While in tropical countries such as Indonesia, India and Africa, the virus will infect mostly during the rainy season with high intensity (Figure 4) [4][22].

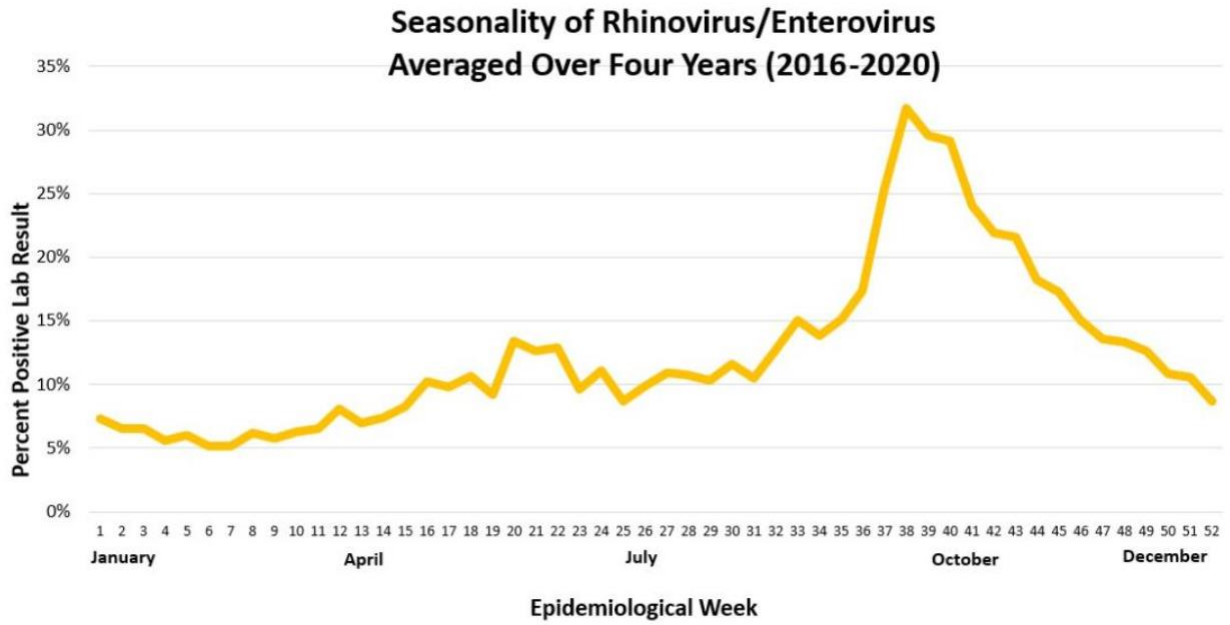

Figure 4. Epidemiological graph of HRV in Wincosin State (USA) during 2016-2020. There is an increase in HRV cases during the fall and winter months from September to December with a peak of 33% in October [27].

In winter, there are can be an increased prevalence of viral infections. This occurs because at low temperatures and humidity there is inhibition of respiratory defence mechanisms by cold air. In addition, temperatures that tend to be cold also may favor the survival of HRV so that it is more contagious and has the potential for cross-infection [28].

There are three factors that can cause seasonal respiratory virus infections, including environmental factors, human behavioral factors and viral factors. Environmental factors such as temperature, humidity, sunlight and vitamin D status can affect host susceptibility because they can modulate host airway immune response systems and influnce the sustainability and spread of respiratory viruses. Meanwhile, behavioral factors can influence the level of connection between contaminated and susceptive individuals. (Figure 5) [29].

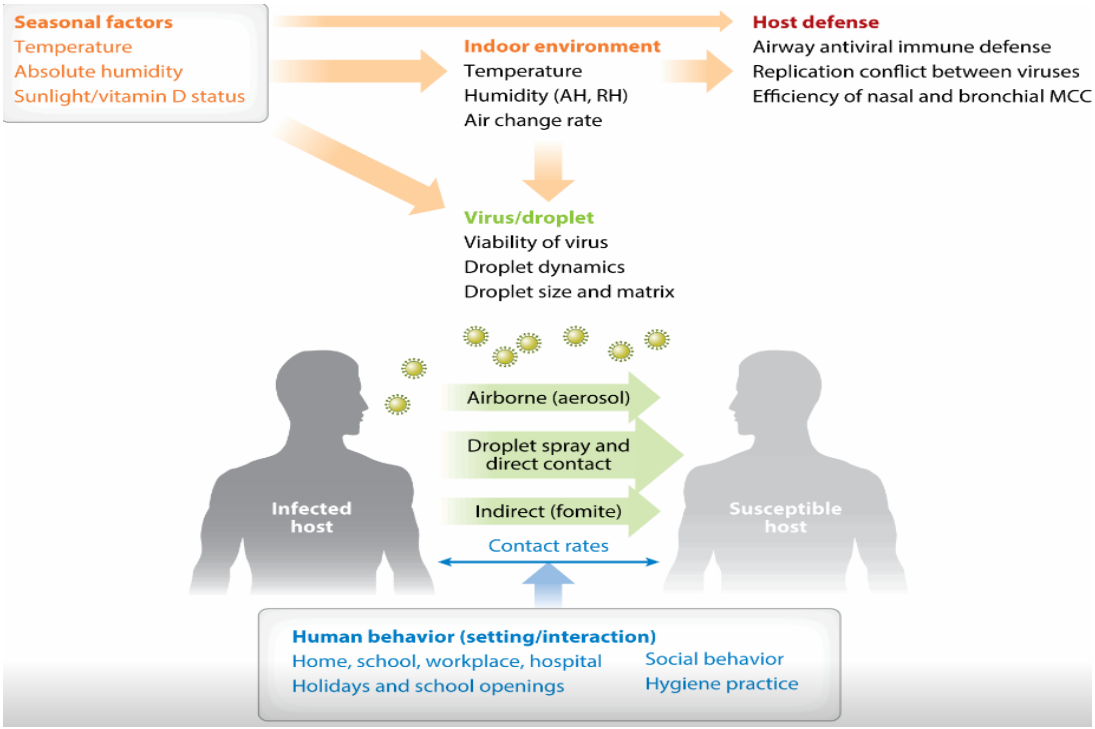

Figure 5. Factors affecting the spread of respiratory viruses. Consists of environmental factors, human behavioral factors and viral factors. Environmental factors can modulate the response and affect the host's respiratory immunity, including the survival and mode of transmission of respiratory viruses. Meanwhile, human behavior influence the level of connection between contaminated and susceptive individuals [29].

3.6 Immune Response to HRV

Airway epithelial cells are the main sites that can be infected by HRV. Unlike other respiratory viruses such as syncytial virus and influenza virus, HRV itself does not cause lineal damage to respiratory epithelial cells and has no definite cytopathic effect. The virus initially infects epithelial cells that constitute the physiological mucosal barrier through receptors. After the virus enters, the HRV RNA genome shall cross the endosomal membrane to enter the cytosol. In endosomes, the viral RNA is recognized by Toll Like Receptor (TLR) 3, 7 and 8 and induced by Retinoic Acid Inducible Gene-1 (RIG-1) and Melanoma Differentiation Asscociated Gene-1 (MDA-1). TLR, RIG-1 and MDA-5 stimulate interferon-β (IFN-β) and IFN-λ responses, as well as the production of proinflammatory cytokines and their gene expression, including C-X-C Motif Chemokine Ligand-10 (CXCL10), interleukin-6 (IL-6) and interleukin-8 (IL-8) [30].

Other studies have shown that the capsid and RNA sensors of the virus are also able to trigger the antiviral innate immune response and activate the chemokines release and growth factors that can attract and stimulate leucocytes, especially the IFN response, which can lead to higher disease severity in infants. The infection can also cause an intensify in airway neutrophils and mononuclear cells through the critical phase, but during convalescence there will be a decrease in eosinophil counts [20]. Moreover, HRV can also cause provocative and protective reactions in the innate immune system that act as antivirals so that the infection can be cleared effectively. This is characterized by the endoplasmic reticulum being under stress, which triggers autophagy and the activation of many antiviral processes, such as IFN expression and the open protein reaction. In individuals with chronic

lung disease, these reactions can lead to overreaction, making infection clearance more difficult and causing exacerbations [31].

3.7 Mechanisms of Antibody-Mediated Neutralization of HRV

HRV can be neutralized by neutralizing antibodies (nAb) through several mechanisms depending on the place and valence of interaction with the capsid. nAb plays a role in preventing viral infection by attaching to the capsid virus directly so that it can disrupt with the binding and entrance of the virus into the host cell.

There are several mechanisms of neutralization by nAb, including: Inhibition of virus binding to host cell receptors due to stabilization of the viral capsid or physical interference by nAb. nAb binding to VP1 bivalently can cross the 2-fold symmetry axis so as to harden or stabilize the capsid structure that interferes with attachment, induction of viral genome release before the process of virus attachment to host cells due to changes in capsid structure. The genome is supposed to be released after the endocytosis process into endosomes, but the neutralizing mechanism by nAb causes a change in capsid conformation, leading to premature release of RNA, prevention of virus uncoating due to Fab attack, aggregation of virions with antibodies. This aggregation contributes to the loss of infectious power in HRV. This is influenced by 3 (three) things, namely the physicochemical environment, 10x higher nAb concentration and nAb preference for singlevalent bonding and antigen admission, neutralization by tripartite motif containing-21 (TRIM21) in host cells. TRIM21 is a elevated-affinity immunoglobulin receptor that is able to attach to IgG, IgA and IgM in the cytosol through the interaction of FC antibody with TRIM21 PRYSPY domain and then targeted for decomposition. This systems is well known as Antibody-Dependent Intracellular Neutralization (ADIN), Antibody-Dependent Cellular Phagocytosis (ADCP). These antibodies contribute to the removal of virus-contaminated cells and antigen presentation, stimulating the immune response to HRV infection. (Figure 6).[32]

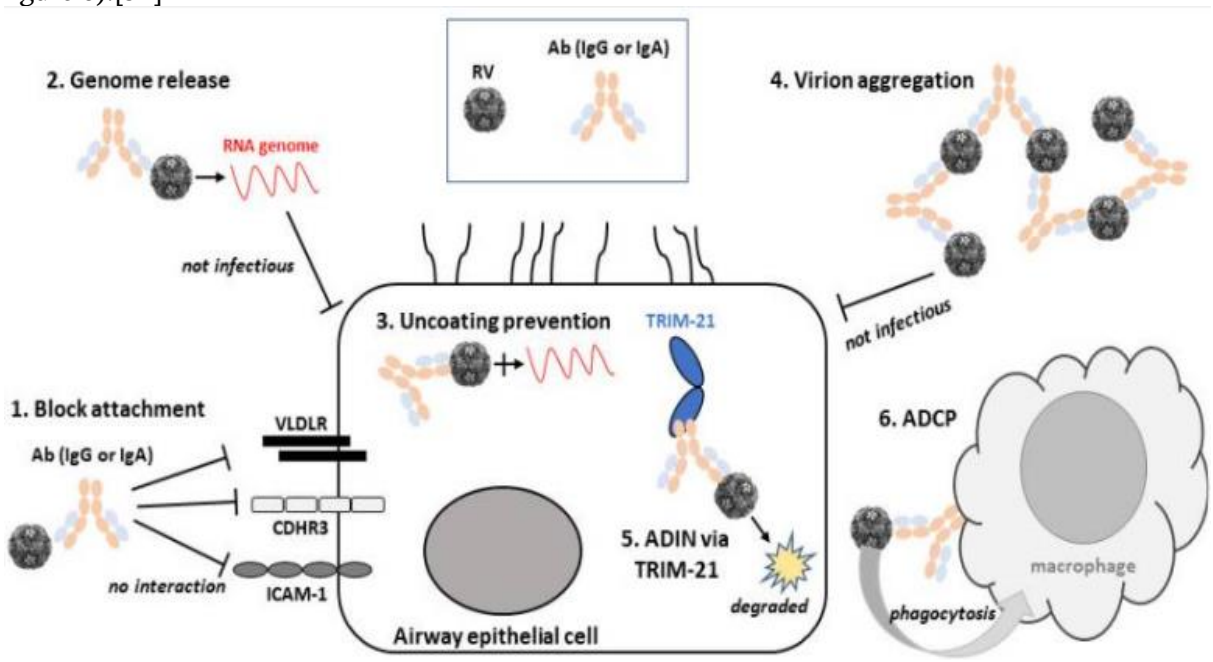

Figure 6. Mechanisms of HRV Neuralization by Antibodies. 1) Inhibition of virus binding to host cell receptors 2) Induction of viral genome release 3) Prevention of viral uncoating. 4) Viral aggregation 5) Antibody-dependent intracellular neutralization (ADIN) 6) ADCPs [32].

3.8 Detection

To choose the optimal treatment, it is crucial to identify the viral pathogen causing the respiratory infection. If this is done, it can avoid unnecessary use of antibiotics, save individual lives and stop epidemics. The traditional method of diagnosing the virus is through virus culture isolation combined with an acid stabilisation test. These methods aim to detect viral antibodies using immunological techniques such as Complement Fixation Test (CFT), Hemagglutination Inhibition (HI), Immunoflourecent (IF) and ELISA tests [33]. Current research indicates that PCR is more effective than conventional antigen tests and virus cultures in identifying respiratory pathogens. Because PCR can practically detect respiratory viruses more widely and faster, it is assumed PCR as the gold benchmark for diagnosing respiratory viruses [34].

With the development of modern technology, various new PCR-based diagnostic techniques for detecting HRV have emerged, one of which is RT-qPCR (Real Time-quantitative Polymerase Chain Reaction). This technique has high sensitivity and specificity but must be implemented by trained personnel and uses expensive and complicated instruments [35]. In addition, there is also RT-ddPCR (Reverse Transcription droplet digital Polymerase Chain Reaction) which has higher measurement accuracy and can be used for standard analysis, and helps improve measurement compatibility. In this method, RM (Reference Material) is needed to improve the reliability of molecular tests because RM can provide precise reference values for the absolute number of viral target gene copies, and can be used as a reference for various studies [36].

3.9 Theraphy and Prevention of HRV

HRV can infect individuals at any time of year so mitigation efforts are needed in the form of disseminating information about the sources of contagion of the virus and precautionary action to avoid infection, both in the work environment, as well as in health care facilities and the community [21]. So far, there is no vaccine, treatment or medicine that can be used to prevent or cure rhinovirus infection, so all that can be done is to reduce the risk of infection and reduce the risk of the spreading the virus [37].

Numerous in vitro and in vivo studies have been conducted to understand the immunological basis of this viral infection, but have yet to produce effective antiviral therapies, one of which is Ribavirin. In vitro, Ribavirin has long been used as an oral antiviral that can be used to treat several strains of HRV. It has broad spectrum activity and is commonly used for the treatment of RSV (Respiratory Syncytial Virus), influenza and hepatitis C (given with pegylated IFN-α2α). In vivo, this drug has been shown to clear HRV RNA in HRV patients with hypogammaglobulinaemia, but in the following months patients can still experience recurrent HRV infections [14].

In another journal, it was explained that Direct-Acting Antivirals (DAAs), such as capsid binders and inhibitors of viral enzymes have been created as treatments for HRV infection. Capsid binders can prevent exfoliation of the antiviral coating and genome discharge by binding to the canyon in the external structure of VP1 with Plenonacril as an example of a drug that has a good oral pharmacokinetic profile. These antivirals work by disrupting interaction between the virus and host celluler receptors, thus inhibiting viral replication. Protease inhibitors such as Rupintrivir and polymerase inhibitors such as Gemcitabine are examples of viral enzyme inhibitors that have shown potential as antiviral drugs [15][38].

Regarding vaccine development, so far no approved vaccine product has been found that can protect individuals completely. This is largely due to the fact that a general consensus has not yet been formed that can combine several types of viral strains due to the high antigenic variability of these viruses so that a vero cell-based viral vaccine platform can be considered for the development of HRV vaccines. However, most HRV strains cannot replicate on vero cells due to the lack of the main receptor on HRV-A and HRV-B, namely ICAM-1, also known as CD54. Therefore, before a vaccine

is produced, the ICAM-1 gene must first be transfected in vero cells, then select clones that can overexpress ICAM-1 on the surface of vero cells [39].

4. Conclusion

HRV is a part of the Picornaviridae family and is primary lead of acute respiratory infections (ARI). Additionally, this virus also associated with recurrent wheezing, fatal pneumonia, asthma and chronic obstructive pulmonary disease in childern and adults and elders with immunocomromised condition. This virus is classified into three species based on nucleotide variations in the VP4/VP2 and VP1 regions: HRV-A, HRV-B and HRV-C. Among these, HRV-C is the most frequently associated with severe infections in affected individuals. PCR is the recommended technique for diagnosing respiratory viruses due to its high sensitivity and specificity, particularly RT-qPCR and RT-ddPCR. A consensus sequence created by merging multiple virus strains is necessary to create a vaccination that protects against all virus types.

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