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Review Article

Human Rhinoviruses: the Forgotten but Still Important Viruses

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Human rhinoviruses (HRVs) are responsible for many of the characteristic symptoms of the common cold, such as a sore throat, runny nose, nasal congestion, sneezing, and coughing. However, despite the high detection rate in children, most HRV infections are asymptomatic. As a result, these viruses are generally ignored, even though a close association between HRV infections in early life and the subsequent induction of asthma has been reported. Therefore, it is necessary to conduct further research into HRV diagnostics, treatments, epidemiology, and vaccines. This review describes recent studies of HRVs, including their genomic diversity, surveillance systems, taxonomy, and immune responses, as well as vaccines.

Key Words: Human rhinoviruses, Diagnostics, Treatments, Epidemiology, Vaccine

I. INTRODUCTION

Human rhinoviruses (HRVs), which were first identified in 1956, belong to the family *Picornaviridae*, genus *Enterovirus*. The "rhino" part of rhinovirus means "nose" in Latin. HRVs have a positive sense RNA genome comprising approximately 7.2 Kb (1, 2). HRVs measure about 27~30 nmin diameter. HRVs can be classified into three species based on their VP genes (VP4, VP2, and VP1): HRV-A, HRV-B, and HRV-C. In addition, HRVs comprise over 150 proposed types (3~7).

The HRV genome encodes 11 proteins comprising four structural proteins (VP1, VP2, VP3, and VP4) and seven non-structural proteins (2A, 2B, 2C, 3A, 3B, 3Cpro, and 3Dpol) (5, 8). The 5' end of the HRV genome is covalently linked to the 3B protein (VPg), and the 5' non-coding region (NCR) follows VPg (9). The 5' NCR has an internal ribosome entry site (IRES) that plays a critical role in viral replication and translation initiation (10~13).

HRVs are major pathogens that cause the common cold, which may be accompanied by a headache, sore throat, cough, and runny nose. Occasionally, they also cause severe lower respiratory tract infections in infants and the elderly (14, 15). It has been reported that most cases (50~85%) of asthma exacerbation are associated with HRVs (5, 16~18). Thus, HRV-induced diseases are important; however, they are not considered serious problems in virology and public health. Indeed, HRVs seem to be neglected viruses. Therefore, the epidemiological data regarding HRVs mostly comprise

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reports of infectious respiratory viruses obtained in local hospitals and research institutes, and national surveillance systems for HRVs are inadequate compared with those for influenza and respiratory syncytial virus (RSV). In addition, no studies regarding global trends in HRVs have been conducted.

In this review, we consider the sources of genetic diversity in HRVs, trends in global HRV outbreaks, and the immune responses induced by HRV infections.

II. Diversity and Evolution of HRV Genomes

The diversity of viral genomes is attributable to various factors such as mutations, re-assortment, and recombination (19~21). Re-assortment is particularly important as a source of diversity for segmented viruses such as hantaviruses and influenza viruses. Moreover, viral-host transitions and virus-induced pandemic diseases result from dynamic evolution via re-assortment, but not in viruses with single strand genomes (22~27).

Mutation is the major factor responsible for viral diversity and evolution (28~30). In particular, the mutation rate is very high in RNA viruses, i.e., 10^{-6} to 10^{-4} substitutions/nucleotide/cell infection (s/n/c), compared with DNA viruses (10^{-8} to 10^{-6} s/n/c), which is explained by the poor proof-reading efficiency of RNA-dependent RNA polymerase (28, 29). The average mutation rate is high in HRVs, i.e., 6.9×10^{-5} s/n/c, and similar to that in other RNA viruses (28). Thus, these nucleotide mutations increase the diversity of HRV, and the average shared identity of HRV genomes is

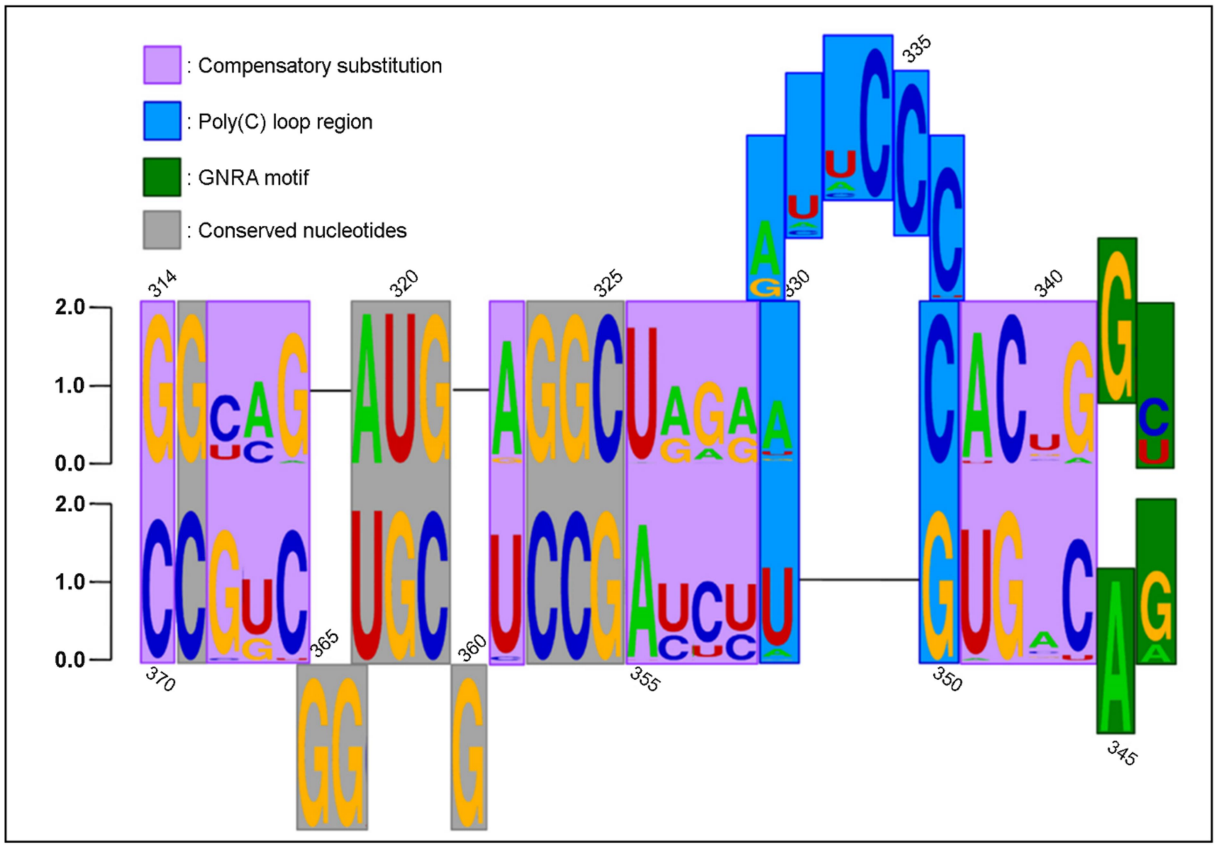

Figure 1. Compensatory substitution and conservation of the two-dimensional structure of SL-IVc in the human rhinovirus 5' internal ribosome entry site. This figure has been reproduced from a published study (32).

only 65.87% (31). The IRES sequences of each HRV strain are different, but the predicted secondary structures are remarkably similar because compensatory substitution events occur in the sub-domain stem-loop-IVc (SL-IVc) in IRES, as shown in Fig. 1 (32). Therefore, these compensatory substitutions conserve the secondary structure.

Recombination of the viral genome also contributes to diversity and evolution, and recombination events occur often in RNA viruses (19). Recombination events of enteroviruses and polioviruses, which belong to the family *Picornaviridae*, have contributed to their genetic evolution and diversity (33~35). Recently, recombination events have been detected in references and field-isolated HRVs. The breakpoints for recombination events in HRVs occur near 5'NCR-P1, P1-P2 and P2-P3 (5, 8, 31, 36, 37). In addition, intra- and inter-species recombination events have been identified (36). Therefore, HRVs exhibit frequent changes in diversity and evolution, which may contribute to their severity as well as dynamic pandemics.

III. HRV Detection by Surveillance System throughout the World

HRV symptoms are mild and their severity is usually lower than that of other respiratory virus infections such as influenza virus and RSV, so HRV surveillance or sentinel systems are generally not included in national respiratory illness surveillance systems. For example, the Center for Disease Control and Prevention (CDC) in the U.S. operates a National Respiratory and Enteric Virus Surveillance System (NREVSS) for monitoring the frequencies of RSV, adenovirus, enterovirus, metapneumovirus, parainfluenza virus, and rotavirus infections, but not that of HRV [*https://www.cdc.gov/surveillance/nrevss/index.html*]. Therefore, the main surveillance data regarding HRVs have been collected by community hospitals or short-term national surveillance studies (38~47).

However, some national sentinel systems include HRV surveillance, such as those implemented in the U.K., Canada, the Republic of Korea, and New Zealand. These surveillance data demonstrate that HRVs are among the major pathogens associated with acute and upper respiratory tract infections.

In the U.K., surveillance data for influenza and other respiratory viruses are collected by the Health Protection Agency (HPA), Health Protection Scotland (HPS), Public Health Agency (PHA) Northern Ireland, and Public Health Wales. Excluding influenza viruses, HRVs (29.5% of positive samples) were the most frequently detected pathogen, followed by RSV (28.3% of positive samples) and adenoviruses (16.4% of positive samples) during the winter season in 2014~2015. The highest activity levels for HRVs occurred at the beginning and the end of the influenza season. However, the activity levels of HRVs were low when influenza was circulating (48).

In the Canadian respiratory surveillance system, weekly data are collected by the Centre for Immunization and Respiratory Infectious Diseases (CIRID) of the Public Health Agency of Canada, and HRVs had the highest detection rate (13.6%) among non-influenza respiratory pathogens circulating during 2014 to 2015 (49).

The Institute of Environmental Science and Research (ESR) contributes to the national public health surveillance effort in New Zealand, and the annual virology report for 2014 produced by the ESR showed that HRVs were the second most common non-influenza respiratory pathogens (12.1% of positive samples) following RSV (14.0% of positive samples) (50).

The Korea Influenza and Respiratory Surveillance System (KINRESS) was a sentinel system operated by the Korea Center for Disease Control (KCDC) in the Republic of Korea. For one year, weekly surveillance samples comprising throat or nasal swabs were collected from enrolled outpatients with acute respiratory infections, including influenza-like illnesses, in over 100 hospitals in the 17 provinces. During 2014, HRVs had the highest detection rate (13.8%) among non-influenza respiratory pathogens. In addition, HRVs were detected throughout the year with a peak occurring during the late summer and fall. The activity levels of HRVs were low in the season when influenza was prevalent, similar to the findings in the U.K. (51).

IV. Classification and Distribution of HRV Species throughout World

HRVs were first discovered in 1953 and initially classified into two species (HRV-A and HRV-B) based on antigenically diverse neutralization assays (1, 2). More recently, a third species (HRV-C) was classified based on genomic sequence analysis. HRV-C species are difficult to isolate by *in vitro* culture and they are not detectable using conventional methods. Therefore, at present, over 150 genotypes of the HRV-A, HRV-B, and HRV-C species are classified by nucleotide analysis according to their VP1 or VP4/VP2 proteins (3~7). Gene sequence analysis has shown that HRV-C species have more heterogeneous genomes than HRV-A and HRV-B species. In addition, P1 in 5' NCR and the external capsid regions of HRV-C species are more diverse than those in HRV-A and HRV-B (52).

The infection rates with HRV-B are lower than those with HRV-A and HRV-C species based on global epidemiological

Table 1. Distributions of human rhinovirus (HRV) species throughout the world. Frequencies were compared using the chi-square test in SPSS v. 23.0 (IBM Corp., Armonk, NY, USA)

N (%)

Area	Country (reference)	Years	Sample	HRV type (%)			χ^2
				A	B	C	
Northeast Asia	Korea (36)	2008~2009	ARTIs and SLRTIs	52 (49.04)	5 (4.81)	48 (46.15)	44.121**
	China (Beijing) (39)	2007~2008	Pediatric patients with community-acquired pneumonia	51 (51.52)	10 (10.10)	38 (38.38)	
	Mongolia (45)	2008~2013	ARTIs	52 (44.44)	12 (10.26)	53 (45.30)	
Southeast Asia	China (Hong Kong) (38)	2004~2005	ARTIs	111 (50.45)	18 (8.18)	91 (41.36)	
	Thailand (40)	2006~2007	LRTIs	**29 (33.33)****	8 (9.19)	**50 (57.47)****	
Africa	Kenya (Kilifi) (41)	2007~2009	ILI symptoms	14 (53.84)	3 (11.53)	9 (34.61)	
	Tanzania (42)	2008	ARTIs	126 (51.63)	**42 (17.21)*****	**76 (31.14)****	
Europe	Cyprus (46)	2010~2013	ARTIs	36 (52.94)	5 (7.35)	27 (39.70)	
	France (43)	2009~2010	ILI symptoms (non-IFV and RSV infection)	33 (52.38)	4 (6.35)	24 (38.09)	
North America	Mexico (44)	LRTIs: 2010~2011 URTIs: 2011~2012	LRTIs and URTIs	67 (57.76)	**4 (3.45)***	45 (38.79)	
South America	Peru (47)	2009~2011	ARTIs	104 (50.24)	20 (9.66)	83 (40.10)	
Total				708 (52.44)	135 (10.00)	561 (41.56)	

*$p < 0.5$, **$p < 0.01$, ***$p < 0.001$
ARTIs: Acute respiratory tract infections / SLRTIs: Severe lower respiratory tract infections / LRTIs: Lower respiratory tract infections / URTIs: Upper respiratory tract infections / ILI: Influenza-like illness

and surveillance data. The distributions of HRV species have been determined in many studies based on molecular epidemiology research throughout the world. Previous HRV epidemiology studies considered the ages of subjects, countries, and patient populations (Table 1 and Fig. 2). The observed frequencies of HRV species in Southeast Asia were 50.45% for HRV-A, 8.18% for HRV-B, and 41.36% for HRV-C in China-Hong Kong (2004~2005), and 33.33% for HRV-A, 9.19% for HRV-B, and 57.47% for HRV-C in Thailand (2006~2007) (38, 40). The average detection rates for HRV species in China-Beijing (2007~2008), Mongolia (2008~2013), and Korea (2008~2009) in Northeast Asia were 48.29% for HRV-A, 8.41% for HRV-B, and 43.30% for HRV-C (36, 39, 45). The Mongolian study typed species using two regions comprising VP4/VP2 and the 5'-untranslated region (UTR). However, the distribution of HRV species can be classified better based on the VP4/VP2 or VP1 region because of recombination in the 5'-UTR. In Europe, the frequencies in Cyprus (2010~2013) and France (2009~2010) were 52.94% and 52.38% for HRV-A, 7.35% and 6.35% for HRV-B, and 39.70% and 38.09% for HRV-C, respectively (43, 46). The proportions of HRV species in Mexico (2010~2012, North America) comprised 57.76% for HRV-A, 3.45% for HRV-B, and 38.79% for HRV-C (44). The frequencies of HRV species in Peru (2009~2011, South America) were 50.24% for HRV-A, 9.66% for HRV-B, and 40.10% for HRV-C (47). In Africa, molecular epidemiology studies of HRV were conducted in Tanzania (2008) and

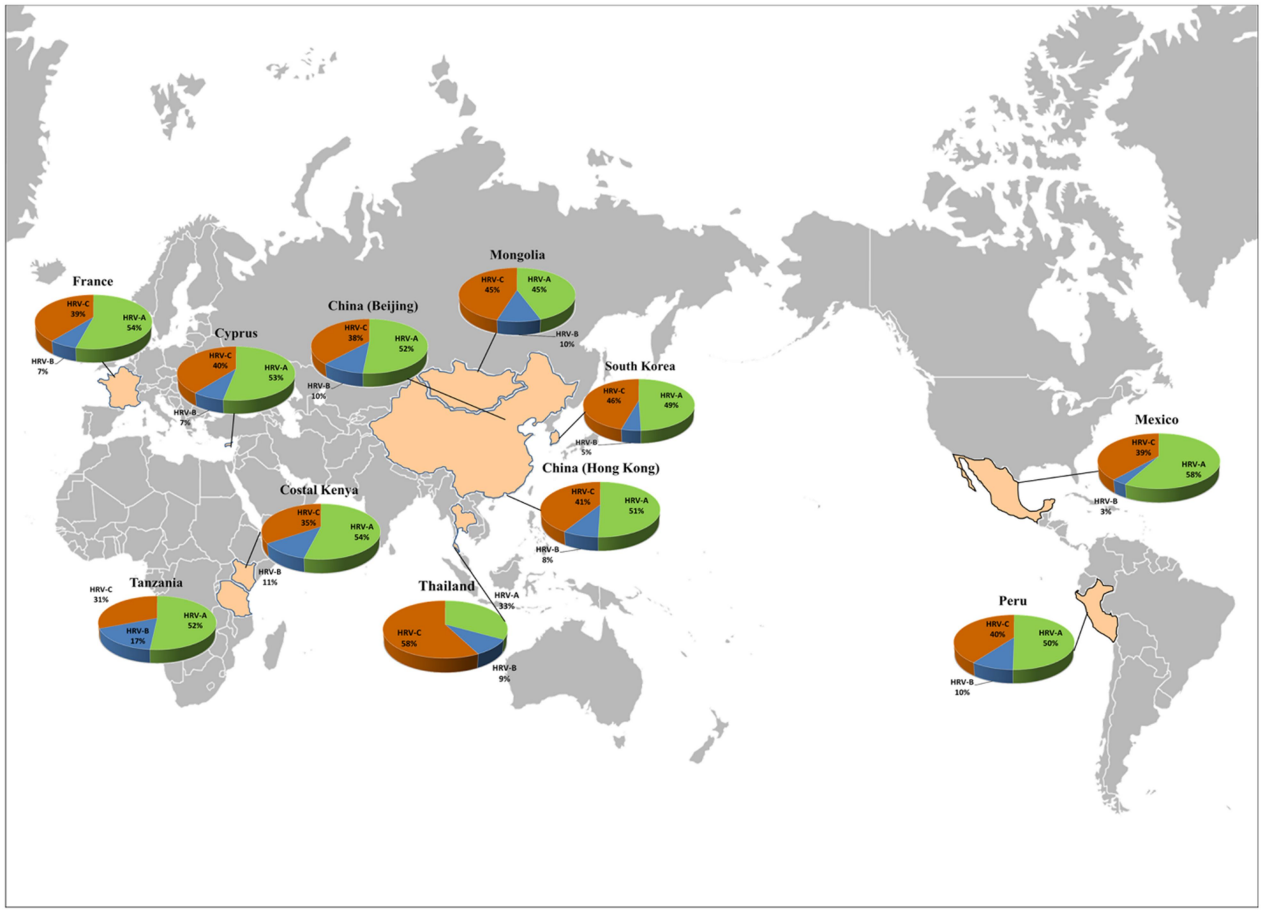

Figure 2. Worldwide distributions of infections by each human rhinovirus species.

Kenya (2007~2009) during 2015 and 2012, respectively (41, 42).

Therefore, according to most of the previous reports of the molecular epidemiology and classification of HRVs, HRV-A and HRV-C were the main circulating HRV species, with average HRV-A and HRV-C proportions of 52.44% and 41.56%, respectively, whereas the average detection rate for HRV-B species was only 10.00% (Table 1). The proportions of HRV species are similar in most previous studies, but some interesting results have been reported, where the ratio of HRV-C relative to HRV-A in Thailand, the ratio of HRV-B relative to HRV-C in Tanzania, and the frequency of HRV-B in Mexico were significantly different compared with the means according to the chi-square test. In particular, the frequency of HRV-B in Tanzania (2008) was higher than that in other areas ($p < 0.001$, chi-square test) according to Table 1. All of the data were analyzed using the chi-square test in SPSS v. 23.0 (IBM Corp., Armonk, NY, U.S.A.).

V. Immune Response to HRV Infection

No clear experimental evidence explains why the detection rates are lower for HRV-B than the other HRV species according to surveillance and epidemiological data. However, several previous studies that considered cytokine/chemokine levels, replication, and cytotoxicity suggest that HRV-B induces different immune response patterns compared with the other HRVs, which may contribute to the low detection rates.

Previous studies identified the cytokines/chemokines secreted when three types of HRV-A (A21, A31, and A36) and three types of HRV-B (B4, B35, and B48) infected Calu-3 cells (lung adenocarcinoma cell line), as well as after treating peripheral blood mononuclear cells (PBMCs) and cord blood mononuclear cells (CBMCs) by co-culture with the infected Calu-3 cells. When co-cultured with PBMCs, the levels of chemokine (C-C motif) ligand 3 (CCL3)/macrophage inflammatory protein (MIP)-1α, CCL4/MIP-1β, and CCL2/monocyte chemotactic protein (MCP)-1 were significantly higher with HRV-B infection, whereas infection with HRV-A caused no differences compared with the non-infected cells. In addition, C-X-C motif chemokine 5 (CXCL5 or ENA78) was expressed at high levels in cells infected with HRV-B but without PBMCs. By contrast, the expression level of CXCL5 was reduced in the presence of PBMCs. HRV-B significantly increased the cytokine/chemokine levels, especially that of interferon (IFN)-γ, which was induced by T cells, compared with HRV-A. In addition, when the Calu-3 cells infected by HRV-B were co-cultured with CBMCs, little or no increases were observed in the expression levels of MIP-1α, MIP-1β, and MCP-1 compared with those in the presence of PBMCs (53). These results suggest that HRV-B infections lead to an immunological memory response.

It was also demonstrated that HRV-B exhibited slower replication and lower cytotoxicity than HRV-A and HRV-B, where pro-inflammatory cytokines such as CCL5/RANTES, CXCL8/interleukin 8, CXCL10/interferon gamma-induced protein 10 (IP-10), CXCL11, and IFN-γ were induced at low levels when HRV-A, -B, and -C (A7, A16, A36, B6, B52, B72, C2, C15, and C41) were each used to infect human sinus epithelial cells (54). In addition, it has been shown that CXCL10 was increased in virus-induced asthma exacerbation compared with mild illness (55~58).

These findings suggest that HRV-B induces pro-inflammatory cytokines and anti-viral factors, which lead to a milder illness after infection compared with HRV-A and HRV-C. In addition, the immunological memory response after infection is highly induced by HRV-B compared with HRV-A. Therefore, repeated infection with HRV-B will be cleared by the host immune response before the onset of symptoms, so the probability of infectious disease owing to repeated infections with HRV-B may be reduced (Fig. 3). This HRV-B-induced immune response may explain the low level of HRV-B isolates obtained from patients in global surveillance studies.

VI. VACCINE

Some HRV-A types use the low-density lipoprotein receptor (LDLR) family to enter host cells, but most HRV-A and HRV-B types use intracellular adhesion molecule-1 as the host entry receptor as well as LDLR (59, 60), whereas HRV-C may use cadherin-related family member 3 (CDHR3)

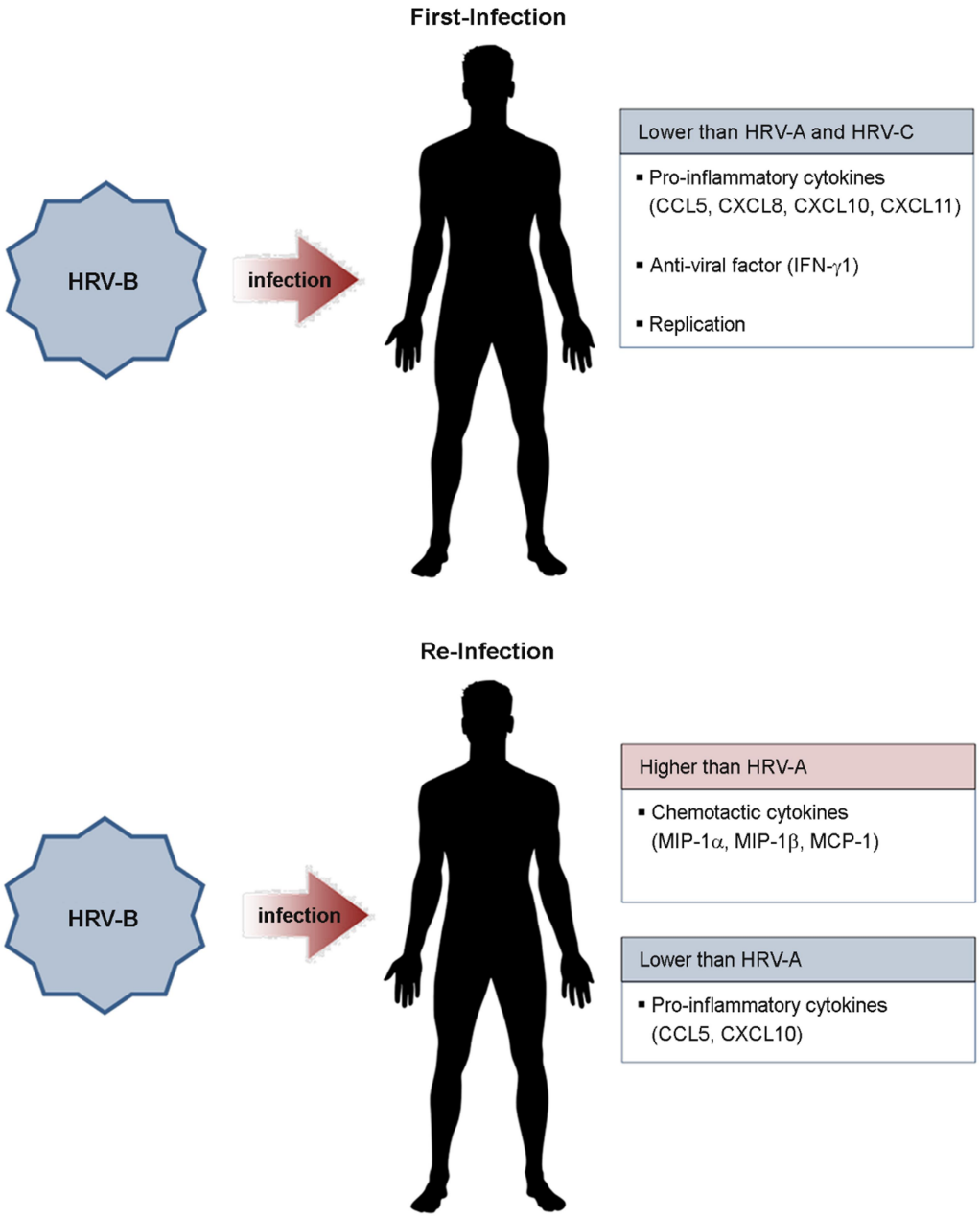

Figure 3. Immune response to initial infection and re-infection by human rhinovirus B (HRV-B).

as its receptor (61). Therefore, a vaccine for HRVs needs to induce a neutralizing antibody to prevent binding between HRV VP0 and its host receptor. Currently, no HRV vaccines are clinically available, but two types of HRV vaccines have been reported: a polyvalent inactivated HRV vaccine including 50 HRV serotypes and an HRV VP0 protein formulation with incomplete Freund's and CpG adjuvants (62, 63). Both of these vaccines induce neutralizing antibodies against HRVs. However, more research is required to develop clinical vaccines for HRVs.

VII. CONCLUSION

Previous studies have shown that the diversity of HRVs is attributable to mutations caused by the poor proofreading efficiency of RNA-dependent RNA polymerase and recombination events. In particular, intra- and inter-species recombination events occur, thereby suggesting the potential for a dynamic pandemic.

HRVs cause the common cold, but are also associated with severe respiratory illnesses and the exacerbation of asthma. Therefore, HRV monitoring should be included in national surveillance systems. Many countries have national surveillance systems for respiratory tract viral infections, and the U.K., Canada, the Republic of Korea, and New Zealand manage and track surveillance data regarding HRVs. National and regional data show that HRV-A and HRV-C are globally prevalent, whereas the infection rate with HRV-B is less than 10%.

Analyses based on cytokines and chemokines have shown that the induced immune responses differ among HRV species, which may be related to differences in the worldwide infection rates for HRV-A, -B, and -C.

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