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Annual prevalence of HRV and its genotypes in Asia, review

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Abstract
Human rhinovirus is the major pathogen among all age groups causing common cold and can be associated with severe infections like asthma, pneumonia, wheezing which may lead to hospitalization. Phylogenetic analysis has led to the classification of human rhinovirus into three genotypes i-e HRV-A, HRV-B and HRV-C. These genotypes have different biological properties, clinical outcome and provide information for studying the epidemiology and pathogenesis. This review article characterizes the distribution of HRV and its genotypes for the first time in Asia. 94 published articles (2005-2015) related to HRV and its genotypes in Asia were searched. Children were more infected with HRV in Asia than in any other age group. HRV is the main agent causing acute respiratory infections in Asian countries, responsible for mild to severe respiratory infections in all age groups, particularly in children. Effective preventive measures are needed on urgent basis to control the disease burden.

Keywords: Human rhinoviruses, genotypes, ALRTs, epidemiology, prevalence, seasonality and transmission

Introduction
Respiratory infections are the most common in human beings all around the world and a root cause of death in children less than 5 years of age [1]. Due to the ease in transmission among hosts, viral ARTIs within childhood spark a wide-range connected with disease severeness; from common cold to severe life-threatening respiratory tract infections. Thus, they impose extensive load on healthcare systems and is a reason for a large amount of emergency visits to hospital and hospitalizations and due to which viral ARTIs are the main concernin the global health problems. Inspite of the progression within medication, the common cold is still a great burden on society regarding human sufferings, medical visits, school and work absenteeism and economic losses. Of the several viruses that cause the disease, the role of rhinoviruses is most prominent. Dr. Winston Price in 1956 first isolated human rhinoviruses at Johns Hopkins University. It is responsible for upper respiratory tract infection (URI), common cold, acute otitis media, sinusitis, chronic pulmonary disease, asthma, severe bronchiolitis in infants and children, pneumonia in elders and immunocompromised adults [2]. HRVs infections are restricted mostly to the upper airways due to the best replication of HRVs at a temperature of 33-34 °C [3]. Being acid labile it do not replicate in the gastrointestinal tract and this helps in distinguishing Rhinoviruses from other enteroviruses [4].
Rhinovirus infections occur in all seasons. In temperate climates it is most prevalent in the fall and spring. It is usually transmitted by respiratory- salivary route, directly from one individual to another or through aerosol [5]. HRVs show greater genetic diversity and three species have been recognized: HRV-A, HRV-B, and HRV-C [6].There are more than 100serotypes of human rhinoviruses, HRV-A with 74 serotypes, and HRV-B with 25 serotypes. HRVs are non enveloped single stranded RNA (ssRNA) containing viruses having a diameter of 24 to 30 nm and 7200 bp belongs to genus Enterovirus and family *Picornaviridae*. The viral capsid is made of 4 proteins designated VP1, VP2, VP3 and VP4, arranged in 60 repeating protomeric icosahedral units carrying the RNA genome while the nonstructural proteins are involved in replication and assembly. Proteins VP1, VP2 and VP3 have antigenic sites and are responsible for host immune response, VP4 holds the RNA core to the capsid. The 5′UTR is typically ~650 bases, the open reading frame ~6500 bases (~2100 encoded amino acids) and the 3′UTR consists of ~50 bases [2].
Recently in America, Australia, and Hong Kong a new variant of HRV was recognized in patients having acute RTIs that shares 53 to 57% homology at the amino acid level to HRV-A

and HRV-B. The main symptoms of patients infected with this new strain vary by location: patients from Australia and Hong Kong mainly have bronchiolitis, wheezing, and asthmatic exacerbation, while in contrast to America primarily present with flu-like symptoms [7]. The aim of the present review is to find the prevalence and clinical impact of HRV in Asia. Asia is the world largest continent, covering about 30% of the earth's land. There are 53 countries in Asia. As vaccination is currently inaccessible for human rhinoviruses, it is necessary to observe epidemic patterns, efficient identification of serotypes and their control to prevent future epidemics. This study will help to determine disease burden associated with human rhinovirus infection in Asia.

HRV prevalence

In this study, we report for the first time in Asia the prevalence of HRV in different age groups. Data related to HRV was found in 94 articles from different countries i.e Cambodia, Taiwan, Turkey, India, Israel, Japan, Iran, Jordan, Laos, Kuwait, Malaysia, Mongolia, Philippine, Thailand, Vietnam, Saudi Arabia, Singapore, Qatar, Korea, Cyprus, China and Bangladesh. 126,026 individuals were screened for HRV and 21,156 (16.8%) were infected.

Table 1: Prevalence of HRV infection determined by molecular methods, sampling, associated symptoms and seasonal distribution in several countries

Country	HRV+/Total %	Method of detection	Sample	Symptoms	Seasonality	Ref
Bangladesh	52/177 (29.3%)	Realtime RT-PCR	Nasopharyngeal aspirate	Sneezing, nose picking	Jan, Feb, June, July, Nov, Dec	[8]
Cambodia	1229/20507 (6%)	Multiplex RT-PCR, Mass Tag PCR	Blood culture, nose & throat swab	Pneumonia, cough, bronchiolitis, fever ≥38 °C.	-	[9-12]
Cyprus	116/325 (35.7%)	Multiplex RT-PCR	Nasopharyngeal swab	-	Winter	[13, 14]
Taiwan	53/216 (24.53%)	RVP assay, cell culture	-	Febrile ARTI	-	[15]
Turkey	49/182 (27%)	Multiplex RT-PCR	Nasopharyngeal aspirate, middle ear fluid	Bronchiolitis, cough, runny nose, acute otitis media	-	[16, 17]
India	6/2737 (0.2%)	Conventional RT-PCR	Nasal & throat swab	-	-	[18]
Israel	346/465 (74.4%)			Acute bronchiolitis	Winter	[19]
Iran	166/1107 (15%)	Real time PCR, Reverse transcriptase PCR	Nasal wash, nasopharyngeal swab	Cough, sore throat, wheezing, asthma, sneezing, rhinorrhea	Autumn, winter	[20-25]
Japan	143/946 (15.1%)	Multiplex real time PCR, Viral culture, RT-PCR	Nasal mucus, nasopharyngeal aspirate and swab	Pharyngitis, bronchitis, asthma, wheezing, fever ≥38 °C	Sep, dec, march, april, june	[26-28]
Jordan	276/1053 (26.2%)	Real time RT-PCR	Nasopharyngeal aspirate	Fever respiratory symptoms	-	[29, 30]
Korea	4395/19522 (22.5%)	Multiplex RT-PCR, real time PCR	Nasopharyngeal aspirate, oropharyngeal swab, throat swab	Bronchiolitis, pneumonia, croup, asthma, acute respiratory infection	-	[31-44]
Kuwait	188/2252 (8.3%)	Real time PCR,RT-PCR, Conventional PCR	-	Pneumonia, bronchiolitis, recurrent chest infection, croup	Autumn& winter (oct to march)	[45-47]
Laos	102/292 (35%)	Multiplex RT-PCR	Nasopharyngeal & throat swab	Cough, fever, polypnea	All seasons	[48]
Malaysia	69/268 (26%)	Reverse transcriptase PCR	Nasopharyngeal aspirate & throat swab	Rhonchi, vomiting, asthma, bronchiolitis, wheezing	-	[49, 50]
Mongolia	552/4907 (11.2%)	Multiplex real time PCR	Nasopharyngeal swab	Acute RTI	All seasons peak in fall	[51, 52]
Philippine	787/3666 (21.46%)	RT-PCR, Taq man & multiplex real time PCR	Nasopharyngeal & throat swab, serum, blood culture	Pneumonia, fever≥ 38 °C, cough, wheezing, runny nose	-	[53-55]
Qatar	102/1038 (10%)	Real time PCR,DFA	Nasal swab	Asthma, COPD, acute bronchiolitis	winter	[56, 57]
Thailand	5741/30870 (18.6%)	RT-PCR	Nasopharyngeal swab	Pneumonia, abnormal WBC count, abnormal breath sound	-	[58-61]
Singapore	64/500 (13%)	Hemi nested PCR	Nasopharyngeal swab	-	-	[62]
Vietnam	1161/4825 (24%)	Multiplex RT-PCR	Nasopharyngeal aspirate, nose & throat swab, blood	Cough, breathing difficulty, pneumonia, bronchiolitis, hypoxia, SARI	-	[63-67]
Saudi Arabia	1307/3433 (38%)	RT-PCR, multiplex PCR	Sputum, nasopharyngeal swab	Pneumonia, earache, wheezy chest, runny nose, sore throat	-	[68-71]
China	4252/26738 (16%)	RT-PCR, conventional PCR, multiplex RT-PCRVRDAL multiplex PCR, viral isolation	Nasal & throat swab, nasopharyngeal aspirate	Sore throat, cough, wheezing, nasal congestion, laryngitis, asthma, bronchitis, headache	Winter, spring, autumn at peak	[72-101]
Total	21156/126026 (16.8%)					

HRV associated hospitalizations and non hospitalizations

Nasopharyngeal aspirates or throat swabs were collected from both hospitalized and non hospitalized patients. 54 articles were related to it. Total hospitalization due to respiratory infections were 75,726. Among them due to HRV were 16,353(21.6%) and non hospitalization were 1573(2.07%). Bronchitis, bronchiolitis, asthma and pneumonia accounted for the majority of the hospitalizations for ALRI.

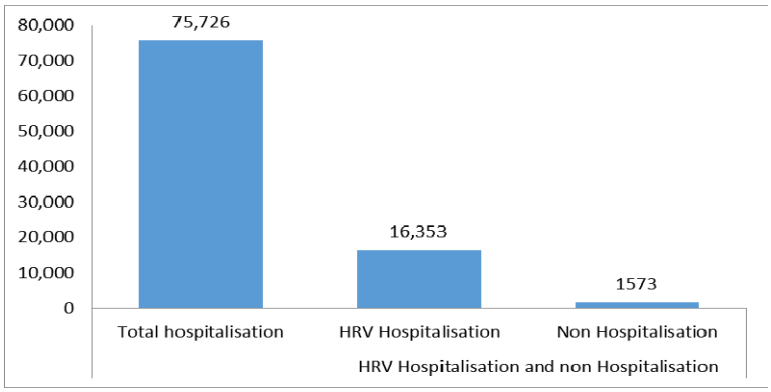

Fig 1

Age wise incidence of HRV

Age wise incidence of HRV was found in 78 articles comprising 17,762 patients. The data were divided into four age groups, i.e infants, children, adults and elders. Infants were ≤ 2 years old with 6135 (34.5%) patients, followed by 3-18 years age group of children with 9042 (51%) patients, 19-40 years age group was considered as adults with 1353 (7.6%) patients and above 40 years were elders with 1232 (7%) patients. Total analyzing results showed that most of the Human rhinovirus was detected in samples from infants and children. The adults and the elder age group were smaller compared to the first two groups. The high detection of HRV in children is consistent with those of the literature.

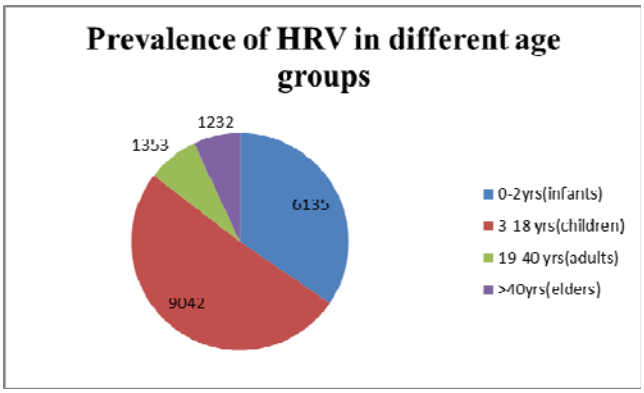

Fig 2

Frequency of HRV in different genders

Studies based on sex wise prevalence of HRV were found in 26 articles. Out of which 10,142 (55.28%) male were HRV positive and 8,202 (45%) female were HRV positive. In these articles HRV infection is more frequent in male individuals.

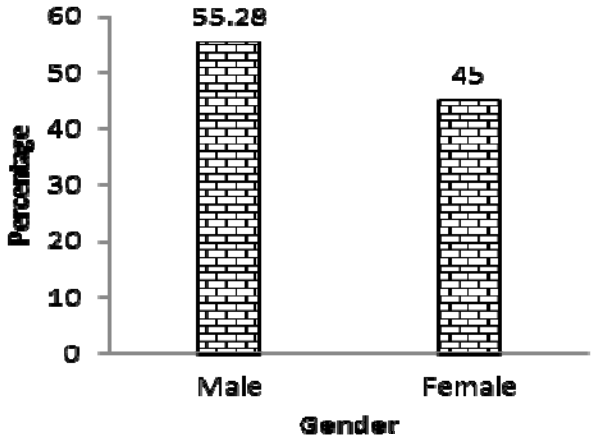

Fig 3

Genotypic distribution of HRV in different Asian countries

Of the total articles included in this study, 21 studies were based on genotypic variation showing the predominance of HRV-A and total of 21,156 individuals were reported with HRV. Of these 1014/2034(50%) individuals were infected with HRV-A genotypes and 164/1888(8.7%) were infected with HRV-B genotypes while 705/1982(35.6%) individuals infected with HRV-C genotypes. HRV-A is dominant in some countries like Japan, Cyprus, Jordan, Malaysia, Mongolia, South korea, Singapore and China while HRV-C is dominant in Thailand. HRV-B has less prevalence in almost all Asian countries.

Table 3: Distribution of HRV genotypes in different asian countries

S. No	Country	HRV+	HRV-A	HRV-B	HRV-C	Ref
1.	Cambodia	85	5/17	5/17	7/17	[12]
2.	Cyprus	68	36	5	27	[13]
3.	Japan	120	71	2	47	[26,27]
4.	Jordan	240	131	7	62	[29]
5.	Malaysia	54	22/36	-	14/36	[49]
6.	Mongolia	552	102/204	17/204	85/204	[51,52]
7.	Philippine	432	107/324	17/214	95/272	[53,55]
8.	Singapore	64	47	9	2	[62]
9.	Thailand	87	29	8	50	[61]
10.	South Korea	148	33/54	4/54	17/54	[41]
11.	China	821	431/820	90/820	299/820	[76,77,78,86,87,88,93,94]
	Total	21,156	1014/2034	164/1888	705/1982	
	Percentage		(50%)	(8.7%)	(35.6%)	

Annual prevalence of HRV and its genotypes from year 2005 to 2015

The annual prevalence of HRV shown in table reflects gradual increase from 2008 to 2015. Highest prevalence was found in 2014. Least prevalence was found in 2005 to 2007 as few articles regarding the HRV epidemiology was found in that year. HRV-A was more prevalent as compared to HRV-B and HRV-C in Asia annually.

Table 4: Annual prevalence of HRV and its genotypes from year 2005 to 2015 in Asia

S. No	Year	Total sample	No of HRV+	HRV-A	HRV-B	HRV-C
1.	2005	3000	1260			
2.	2006	1286	178			
3.	2007	4220	712			
4.	2008	5734	1491	34	12	14
5.	2009	4839	1196	262	40	150
6.	2010	3553	732	51	10	38
7.	2011	8694	1839	75	2	73
8.	2012	5532	1045	103	17	69
9.	2013	23,100	3932	145	26	82
10.	2014	61,406	7807	308	52	252
11.	2015	4662	964	36	5	27
Total		126,026	21,156	1014	164	705
Percentage			16.8%	4.8%	1%	3.3%

Discussion

Respiratory infection is a primary cause of morbidity, fatality, hospitalization and death in pediatric patients. Approximately 80% of upper RTIs have viral etiology and can lead to asthma exacerbation and acute otitis media. Additionally, lower RTIs are manifested as bronchitis, bronchiolitis, and pneumonia, wheezing [91]. Human rhinoviruses causes respiratory infections in all geographical areas of the world and among all age groups. HRV frequency in present study was 21,156 (16.8%). The largest infected group was of children (51%). Adults (7.6%) and elders (7%) might have lesser amount of respiratory secretions and lower viral load in comparison to the children. In China most of the children having HRVs infection were younger than 5 years (94.4%) and these patients have bronchiolitis (23.1%), asthma (20.0%), pneumonia (1.0%), bronchitis (4.4%) and upper respiratory tract infections (4. 1%) [92] were the first to recognize that HRV was also associated with early wheezing as a risk factor for asthma. The epidemics and seasonal patterns of HRV varies geographically in different countries or regions. In Japan HRV-C infections are comparatively more severe than HRV-A or HRV-B and is more prevalent during autumn and early spring while HRV-A detected during spring and summer [93].

In Thailand HRV-C represents the dominant genotype causes wheezing and asthma exacerbation in infants and young children [94]. In America HRV-C was predominant during October [95]. In Hong Kong it shows high prevalence in fall and winter while in Gansu China it is in December and April [96-99]. In Spain it represents a high prevalence between September and December [96]. HRV-C strains were also detected in Beijing among hospitalized children and they reported that it is spreading globally and should be taken a serious public health concern [100]. In our study in 20 articles seasonality was mentioned, though rhinovirus was found throughout the year yet it represents the high prevalence of HRV during spring, fall and winter. It may be related to the variables such as temperature, humidity and precipitation [101-103]. In our study 21 articles were related to the genotypes. Among 21,156 individuals, 50% belongs to HRV-A, 8.7% to HRV-B and 35.6% to HRV-C. From 2008 onwards enough data were found related to HRV epidemiology. Gender was mentioned in 26 papers and according to it out of 18,344 cases, 10,142were male (55.28%) and 8,202 were female (44.7%). In Pakistan no data are available regarding HRV and its genotypes.

There is no vaccination for HRV genotypes that's why developing countries face more HRV outbreaks. There could be several risk factors responsible for the transmission of HRV like residential crowding, indoor smoke pollution, direct or indirect contact with NPS or droplets, social-economic status, aerosols and seasonal variations. Various laboratory techniques like PCR (multiplex PCR, Semi nested PCR, reverse transcriptase PCR, Real time PCR, Hemi nested PCR), virus culture is used for detection of HRV. Molecular methods are most sensitive for detecting Human rhinovirus in clinical specimens. This study demonstrates the usefulness of real time and multiplex PCR/RT-PCR to detect

HRV infections and to expand our knowledge of respiratory infections in such country where the data are still sparse. The frequency of HRV infection should be taken into account by pediatricians to avoid unnecessary use of antibiotics.

Conclusion

HRVs are related to hospitalizations among children having severe acute respiratory infections. The disease places a burden on the health services in term of admission to hospitals. Public awareness is needed to improve personal hygiene, use of handkerchief during coughing or sneezing and also proper hand washing before eating or touching any object. As there is no vaccination so far to prevent infections, HRV genotypes needs to be further studied in order to identify risk factors of susceptibility/severity, and new treatment targets for these agents.

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