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Rhinovirus infections in infants suggest that early detection can prevent unnecessary treatment

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ABSTRACT

Background: Human rhinoviruses (hRV) are small, RNA viruses of the *Picornaviridae* family, which are divided into three subtypes (A, B, C). hRVs are among the most common causes for acute respiratory illnesses (ARI) involving both the upper and lower respiratory tract.
Objectives: This study aimed to assess the magnitude and characteristics of hRV infections in hospitalized children, aged less than 5 years, hospitalized in Israel during 2011-2012.
Study design: The 2503 respiratory samples were subjected to real-time PCR, to detect hRV and other respiratory viruses. Rhinovirus-positive samples were further tested by sequencing to identify the infecting species.
Results: Of these 2503 respiratory samples, 422 tested positive for hRV, of them, 243 were from children under 5 years of age (58% of all rhinoviral-positive samples). We also found that among the ARI-associated hospital admissions, 16% were positive for rhinovirus. hRV type A was the most common species. Laboratory data showed monocytosis in 51%, hypercalcemia in 61% and lower respiratory tract involvement in 75% of patients.
Conclusions: We thus recommend including rhinovirus testing as part of the routine testing performed in young children presenting with ARI.

1. Background

Human rhinoviruses (hRV) are small, non-enveloped single-stranded, positive-sense RNA viruses [1]. They are a part of the *Picornaviridae* family, and are divided into three species (A, B, and C), with over 150 known serotypes [2,3]. hRVs are transmitted from person to person, either directly or through contaminated surfaces [1,4].

The clinical spectrum of hRV-related diseases ranges from mild flu-like illness to severe respiratory disease, at times necessitating intensive care unit (ICU) admission [5,6]. They are among the most common causes for acute respiratory illnesses (ARI), involving both the upper respiratory tract and lower respiratory tract (LRT) [7]. They are involved in diverse respiratory syndromes including common cold, acute otitis media, and rhino sinusitis [8], however, in recent years, LRT involvement is known to be higher than previously thought [1,3]. A well-established association exists between rhinoviral infections and childhood wheezing illnesses [1,3]; Children younger than 3 years of age with a wheezing illness positive for rhinovirus, have a substantially increased risk for asthma at the age of 6 years [9].

hRV infections affect all age groups, at a rate of 2–3 times per year in adults and at a higher rate of up to 12 illnesses a year in children [10]. Simultaneous rhinoviral epidemics, combined with relatively long shedding periods of these viruses and their high infectivity, may explain the high rate of hRV infections [11]. Treatment of rhinoviral infections consists of supportive care. To date, there is no specific anti-rhinoviral treatment.

Here, we report the central role of hRV in the hospitalization of young children under 5 years of age over a one-year study period. We further demonstrate the year wide and subtypes distribution, clinical characteristics, imaging and laboratory findings, together with the influence of a concomitant viral infection. To our knowledge, this is the first report of rhinovirus seasonal patterns, occurrence, and clinical

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characteristics in hospitalized patients in Israel.

2. Study design

2.1. Ethical approval

This study was performed on respiratory samples from hospitalized patients with clinical symptoms of ARI, which were analyzed for the presence of various viruses, as part of the routine tests performed in the Chaim Sheba Medical Center. The institutional review board of the Sheba Medical Center approved this research (Helsinki Number 9750-12-SMC).

2.2. Sample collection and human rhinovirus detection

This study is a retrospective analysis. Nasopharyngeal swabs or aspirates from patients with ARI who were hospitalized at Chaim Sheba Medical Center in Israel, were collected between July 1, 2011 and June 30, 2012. Sheba medical center, the largest medical centers in Israel, holding about 1500 beds, encompasses Safra Childrens' hospital, holding about 350 beds, receiving around 25,000 admissions in a year. This hospital is located in the center of Israel and provides services mostly to the population in this area. Viral genome was extracted with NucliSENS easyMAG (BioMerieux, France) and samples were tested for the presence of several respiratory viruses (adenovirus, human metapneumovirus (hMPV), respiratory syncytial virus (RSV), parainfluenza-3 and influenza viruses (A/H3N2, A/H1N1pdm, Influenza B) using real-time (RT)-PCR, as previously described [12].

Following the routine tests, all samples were tested for rhinovirus, using primers and probes that targeted the highly conserved hRV 5' noncoding region (5'NCR), as previously described [13].

2.3. Determination of hRV species and phylogenetic analysis

All hRV positive specimens were retested using different primers to amplify and sequence the VP4/VP2 coding region. RT-PCR products were sequenced using the ABI PRISM Dye Deoxy Terminator cycle sequencing kit (Applied Biosystems, Foster City, CA). Reaction mixtures were analyzed on Applied Biosystems [14].

For the phylogenetic analysis, 100 serotypes from hRV A, B and C species we randomly selected. The Sequencher® 5.0 program (Gencodes Corporation, Ann Arbor, MI) was used to compare the nucleotide sequences. A phylogenetic tree was constructed by MEGA6 software (Molecular Evolutionary Genetics Analysis Version 6.0).

2.4. Statistical analysis

The Pearson chi-square test and Fisher's exact test were applied to evaluate the differences between the compared groups. A p value < 0.05 was considered to be statistically significant. Parameters associated to ICU admission were analyzed using a univariate logistic regression model. A binomial 95% confidence interval (CI) was calculated for determination of hRV subtype distribution. All statistical analyses were performed using SPSS (version 21.0.0. SPSS Inc., Chicago, IL, USA), SAS (SAS 9.1, SAS Institute Inc, Cary, NC, USA) and Microsoft Excel 2010 software.

3. Results

3.1. Rhinovirus morbidity during 2011–2012

Overall, 2503 samples were tested for the presence of hRV and other respiratory viruses routinely tested in our lab. Of these, 422 (16.9%) tested positive for rhinovirus, almost half being hRV-positive (n = 243, 58%) were children under 5 years of age. Of all samples tested, 972 samples had been collected from children below the age of 5, of which

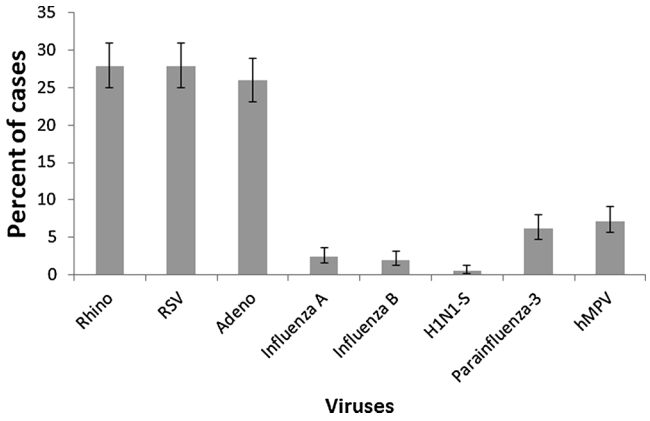

Fig. 1. Distribution of the respiratory viruses found in all samples of children aged less than 5 years.
Distribution of hRV and respiratory viral agents routinely examined (adenovirus, human metapneumovirus (hMPV), respiratory syncytial virus (RSV), parainfluenza-3 and influenza viruses (A/H3N2, A/H1N1pdm, Influenza B)) in samples of children aged less than 5 years hospitalized with acute respiratory illness. Error bars represent 95% confidence interval (CI).

874 were positive for at least one of the respiratory viruses tested, demonstrating high respiratory viral infection prevalence (89%) in children admitted with acute respiratory illness.

hRV, adenovirus and RSV were the most common viral infections in this age group (28%, 28% and 26% respectively), while influenza viruses, parainfluenza-3 and hMPV were the least common (< 10%) (Fig. 1). Both hRV and adenovirus were detected throughout the year (Fig. 2). Conversely, hMPV, RSV, parainfluenza-3 and influenza viruses demonstrated clear seasonal patterns.

Of the hRV-positive samples collected from children under 5 years (n = 243), 20 had a bacterial co-infection and 112 showed co-infection with viruses (72 with adenovirus and 18 with RSV). 111 children (45%) were positive exclusively for hRV (ehRV), of which, 58% were males. Analysis of patient medical records showed that 63% of all hRV-positive children had a certain chronic illness (pulmonary, cardiac, malignancy or prematurity). Table 1 shows the demographic, medical history and hRV subtypes. No significant correlation was noted between hRV subtypes and any of these parameters.

3.2. Distribution of human rhinovirus subtypes in children less than 5 years of age

Analysis of the rhinovirus subtype distribution for all 205-positive samples (samples with subtype affiliation) revealed that the three subtypes appear perennially, with subtype A being the most common (n = 131; 64%), followed by subtype C (n = 51; 25%), and then by subtype B (n = 23; 11%). No seasonal pattern of any of the subtypes was shown throughout the study period (Fig. 3A).

Analysis according to age groups (0–1, 1–2, 2–5 years) revealed that serotype A is the dominant serotype in all age groups (Fig. 3B).

3.3. Clinical presentation of hRV in children under 5 years of age

The most prevalent clinical symptoms presented by the ehRV patients at the time of sampling were cough (62.2%), rhinorrhea (57.7%), fever (55%), shortness of breath (44.1%) and a decrease in appetite (38.7%). Gastrointestinal involvement appeared in 39.6% of the ehRV patients, while restlessness appeared in 23 of the 86 patients 2 years of age or younger (26.7%) (Fig. 4). Clinical symptoms of the co-infected patients were similar compared with patients with ehRV.

Lower respiratory tract (LRT) involvement was determined by the presence of one or more of the following: shortness of breath, low oxygen saturation, oxygen supportive care acute necessity, pathological

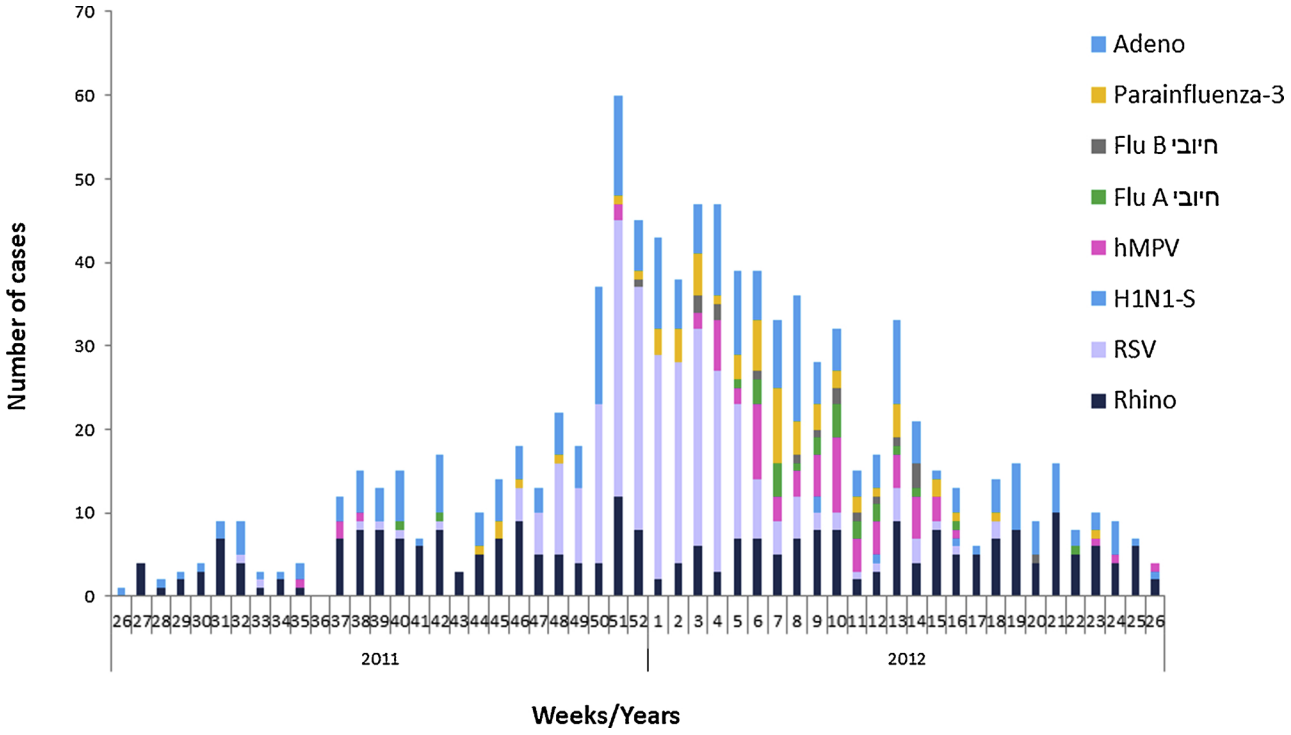

Fig. 2. Weekly distribution of all examined respiratory viral agents.
Weekly distribution of the number of all hRV-positive samples of children less than 5 years of age, tested during the study period 2011-2012.

breathing sounds on lung auscultation or pathological findings on chest x-ray. Evaluation of the LRT involvement revealed that 82 of the ehRV patients (73.8%) and 54 of the viral co-infection group (70%) met at least one of the examined criteria.

Furthermore, 10% (11 patients) of the ehRV patients had at least one documented episode of apnea, bradycardia, or cyanosis of which, 20% of whom were infants aged 0–6 months. Moreover, five of the 17 patients who were prematurely born and who were infected with hRV only, had such an episode (29.4%).

3.4. Phylogenic analysis of rhinovirus-infected patients

In order to determine the diversity of human rhinovirus serotypes, we performed phylogenetic analysis of approximately 100 randomly selected samples. A large variety of rhinovirus serotypes was obtained (Fig. 5). Both species A (hRV-A) and B (hRV-B) have a different single branch, while species C (hRV-C) split into two different branches. The phylogenic analysis also showed that the Israeli rhinovirus strains resemble the circulating strains in the world.

3.5. hRV as a risk factor for ICU admission

Of all ehRV patients, 18% were admitted to the ICU, whereas, 25% with a co-infection with adenovirus or RSV required ICU hospitalization ($p < 0.05$, increase ratio of 31.5%). Analysis of the risk factors for ICU admission together with hRV infection revealed prematurity as a significant risk factor (odds ratio (OR) = 4, $p < 0.02$). Moreover, we found that cyanosis was also a risk factor with marginal significance ($p = 0.06$) (Table 2).

3.6. Laboratory examinations, imaging tests and treatment

Complete blood counts test results revealed monocytosis in nearly half of the patients of the ehRV and co-infection groups (non-

Table 1
Demographic data of all patients is presented according to gender, age groups prematurity and co-morbidity and their distribution by hRV subtype (A, B or C).

			A		B		C		Total		P-value (2 sided)
			N	%	N	%	N	%	N	%	
Age group		**0-3m**	20	29.4%	2	22.2%	11	32.4%	33	29.73%	0.6900
		3-6m	12	17.6%	1	11.1%	4	11.8%	17	15.32%	
		6-12m	9	13.2%	2	22.2%	8	23.5%	19	17.12%	
		1-2Y	11	16.2%	3	33.3%	3	8.8%	17	15.32%	
		2-5Y	16	23.5%	1	11.1%	8	23.5%	25	22.52%	
		Total	68	100%	9	100%	34	100%	111	100%	
Gender		**M**	40	58.8%	7	77.8%	17	50%	64	57.66%	0.3605
		F	28	41.2%	2	22.2%	17	50%	47	42.34%	
		prematurity	10	14.7%	1	11.1%	6	17.6%	17	15.32%	0.9158
	Asthma/HRAD (Hyper-Reactive Airway Disease)		8	11.8%	2	22.2%	9	26.5%	19	17.12%	0.1280
Co-morbidity	**CLD (Chronic lung disease)**		7	10.3%	0	0	1	2.9%	8	7.21%	0.3397
	Heart disease		12	17.6%	2	22.2%	5	14.7%	19	17.12%	0.7295
	Malignancy		4	5.9%	0	0	2	5.9%	6	5.41%	1.0000
	Any co-morbidity		31	45.6%	5	55.6%	18	52.9%	54	48.65%	0.7277

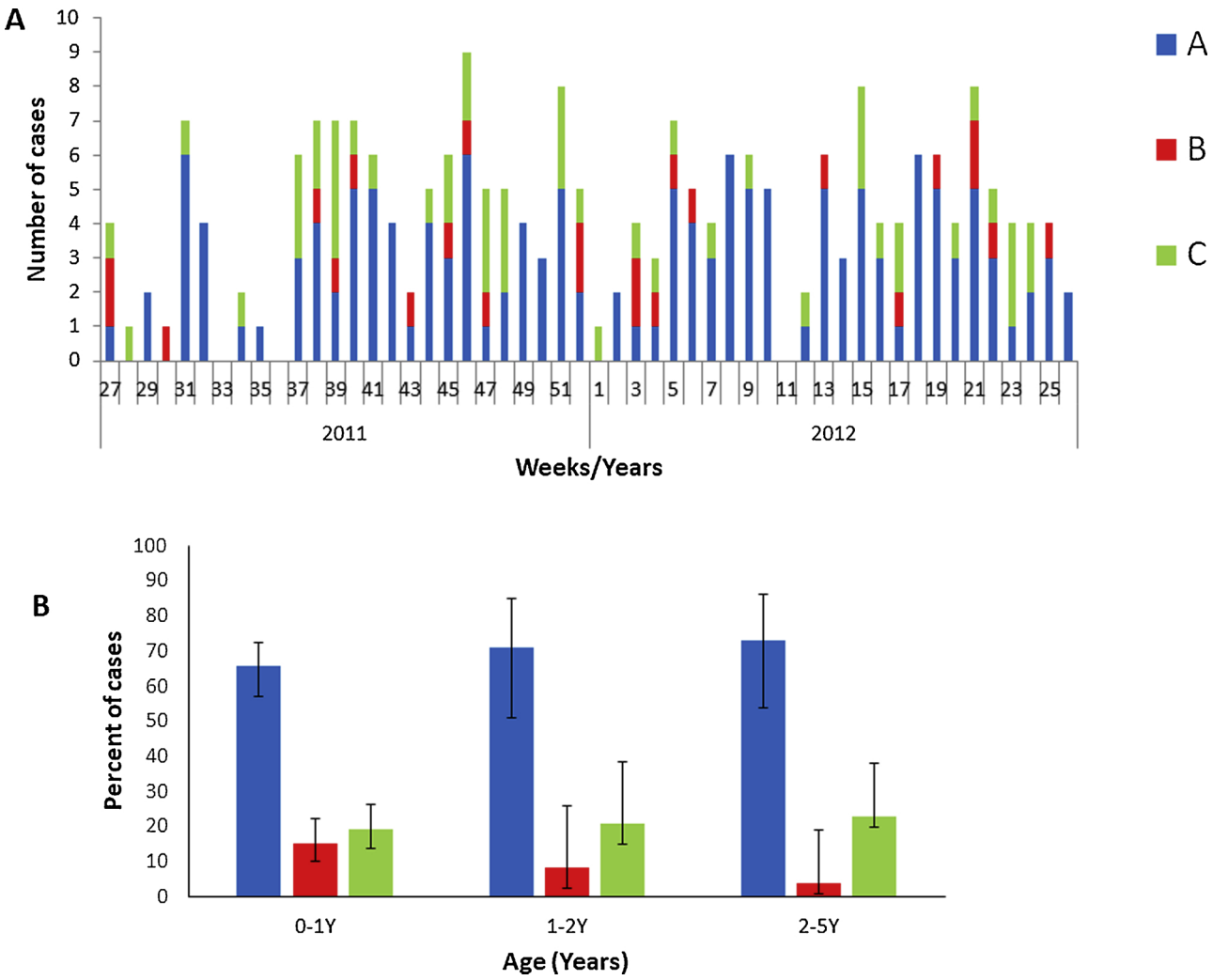

Fig. 3. Analysis of the rhinovirus subtype for all hRV-positive samples. (A) Weekly hRV subtype (A, B or C) distribution –the number of all ehRV-positive children below the age of 5 that occurred during the study period 2011-2012. (B) hRV subtype (A, B or C) distribution - all hRV-positive samples of children below the age of 5, divided by age groups. Error bars represent 95% confidence interval (CI).

significant, data not shown). Examination of additional laboratory parameters revealed hypercalcemia (≥10.5 mg/dL) in 52 cases of the ehRV patients (46.8%) and in 34 cases in the viral co-infection group (44.1%) (Non-significant). Surprisingly, examination of 24 randomly positive adenovirus only samples, of children under 5 years, revealed only one patient with hypercalcemia (4.2%), which is significantly lower compared to the rate in both exclusively and co-infected hRV infections ($p < 0.001$). No other significant differences in the laboratory parameters were found between the serotypes, including leucocyte count and differential, atypical lymphocytes, platelets count, inflammatory markers, blood gases and others.

Chest X-rays were performed in 70 patients (63.1%) with ehRV infection, among whom, 38 (54.3%) presented pathological finding, while 29 (61.7%) of the 47 patients with a viral co-infection showed pathological findings. Most of the patients (63%) received antibiotic treatment and 42% received systemic steroids. In addition, the majority of the patients (60%) received inhaled medications during their hospitalization (β-agonists, anticholinergic, steroidal, hypertonic saline, adrenaline). No difference was found in treatments administered between the different subtypes (data not shown).

4. Discussion

Rhinovirus, although mostly associated with mild disease, can also be a cause of severe illness [1,15]. In our study, of the 2503 samples collected from hospitalized ARI patients in a single center, 422-tested positive for rhinovirus (16.9%), emphasizing the magnitude of hRV burden on health care services. Of all samples collected, 972 were from children under the age of 5 years, of which 243 tested positive for hRV (25%). Due to its high prevalence in young hospitalized children, we decided to focus mainly in hRV morbidity, subtype distribution, clinical presentation and risk factors for ICU admission in children under 5 years of age, infected exclusively in hRV or together with other respiratory viral agent. While the literature contains many reports on hRV infections, very few refer to their prevalence among young children.

As in the general population, we noted a perennial pattern of human rhinovirus infections in children below the age of 5 years and the dominance of species A, as previously described [7,16]. No clinical differences in various parameters symptoms (physical findings, vital signs, laboratory data and imaging findings) were observed between the species. Conflicting reports exist regarding clinical severity and hRV subtype; while some publications showed that hRV C was associated with wheezing and more severe illness [17], others, similar to our findings, did not find any association between rhinovirus species and clinical severity [18].

Our phylogenic analysis demonstrated the large diversity of hRV strains in our patient population. Moreover, it showed correspondence between the Israeli strains and those circulating around the world. The

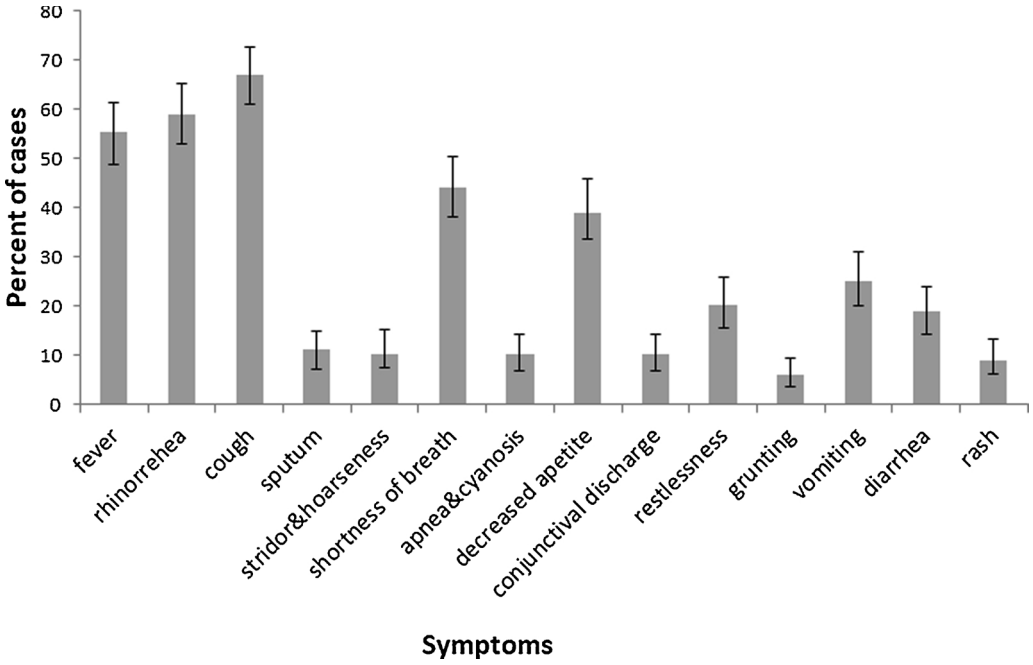

Fig. 4. Clinical symptoms presented by the patients infected exclusively by hRV.
The symptoms and signs of exclusively hRV-positive children under 5 years of age. Error bars represent 95% confidence interval (CI).

phylogenic analysis was similar to other previously described analyses, with two branches of the subtype hRV C [3].

Clinical symptoms of both co-infected and ehRV patients were similar to those previously reported fever, mostly cough, rhinorrhea, shortness of breath, decrease of appetite and gastrointestinal involvement [19]. There are several reports of the association between hRV and apnea [20] bradycardia [21] or cyanosis [22] in preterm neonates, suggesting hRV is one of the possible etiologies. These reports suggest that hRV play a significant role in these severe respiratory conditions, however, they did not directly correlate exclusively hRV and these symptoms. In our study, 10% of the ehRV patients had at least one documented episode of apnea, bradycardia, or cyanosis of which, 20% were infants aged 0–6 months. Episodes of apnea, bradycardia, or cyanosis are often seen in premature neonates in the first few weeks of life, as well as in term infants during infections, most commonly RSV or pertussis [23–25]. These data emphasize the need for close follow up of prematurely born infants during a hRV infection occurring in the first six months of life.

Although typically considered a minor risk factor for severe respiratory illness leading to ICU admittance, here we found, that 18% of the ehRV patients were admitted to the ICU, suggesting hRV as an important cause for severe respiratory morbidity. Previous studies demonstrating RSV as a major cause for ICU admittance among young children, also reported hRV as the second-most frequently identified virus, though, mainly in co-infections [26,27], but found that co-infection of RSV and hRV did not increase the percent of ICU admittance. In our study, we found that co-infection of hRV with adenovirus or RSV increased the risk for ICU admittance to 25%, compared to the exclusively hRV infections.

Prematurity is a well-known risk factor for ICU admission together with viral infections, mostly RSV [28]. Here we show that prematurity was a significant ICU admissions risk factor among hRV-positive infants (OR = 4). Taken together, this data indicates the clinical significance of hRV infections, should be considered when diagnosing young hospitalized children.

As hRV can also be a-symptomatic, we confirmed that all patients were diagnosed with hRV had severe "flu-like" symptoms and were negative to the common respiratory viruses. Therefore, it is most possible that the symptoms of the patients were caused by hRV, and a selection bias, if any, will be very low.

Laboratory examinations revealed monocytosis and hypercalcemia in nearly half of hRV-infected patients. While monocytosis is commonly found in patients with viral infections [29], a specific connection with hRV infection, has not been previously established in the literature. Similarly, hypercalcemia in hRV patients has not been previously reported. In our study, hypercalcemia was noted in almost half of the ehRV patients and the presence of a viral co-infection as well. These calcium levels results were significantly higher than those measured in samples randomly selected from hospitalized children less than 5 years, exclusively infected with adenovirus. Hypercalcemia in children whom age is up to 1 year may be partially due to the vitamin D additive, which is given to all Israeli infants in their first year of life, in accordance with the Israeli Ministry of Health recommendations [30], which can cause hypercalcemia. However, in this research, children age above 1 year were also found to have hypercalcemia together with hRV infection, hence the mechanism for the development of hypercalcemia with hRV is yet to be explained.

Chest X-ray was performed in most of the ehRV patients (63.1%); more than half showed pathological findings. These may relate to the high percentage of patients with LRT involvement or to the higher clinical severity in these patients. Moreover, 63% of the hRV-infected patients received treatment including antibiotic treatment, systemic glucocorticoids, and inhaled glucocorticoids or hypertonic saline. For some of these patients, preliminary hRV diagnosis could have prevented the unnecessary exposure of these young children to X-ray or unnecessary medications.

This study highlights the importance of hRV identification especially in young children with chronic illnesses, which are likely to demonstrate a more severe clinical course. Moreover, for young children who are otherwise healthy, in whom the clinical manifestation of hRV infections is mostly mild, identification of hRV as the infectious agent can prevent unnecessary imaging and medications. This data may suggest that due to the high prevalence and burden of hRV in these patients, in order to optimize supportive care and to avoid unnecessary treatment, adding hRV testing to the routine battery of respiratory viruses tested for in the setting of ARI in emergency care units and in

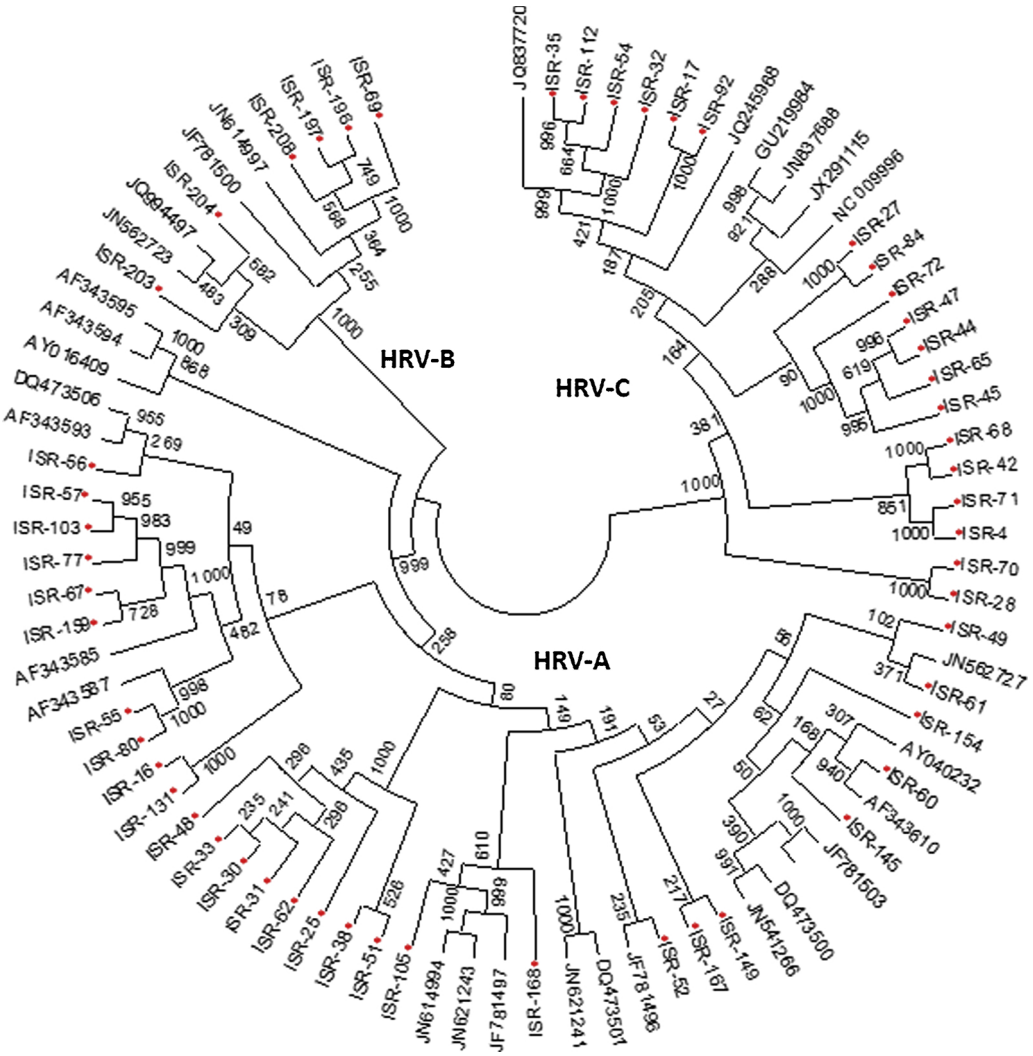

Fig. 5. Phylogenetic analysis of hRV patients.
Phylogenetic tree generated by comparing the VP4/VP2 coding region of 100 hRV-positive samples, divided by subtypes A, B or C. All Israeli strains (marked in a red dot) were compared with other hRV strains circulating in the world.

Table 2
Risk factors for ICU admission.The table presents analysis of the risk factors for ICU admission together with hRV infection. Data presented as odds ratio, A binomial 95% confidence interval (CI) and p value ($p < 0.05$ was considered significant).

Variable	Odds Ratio	Lower 95% CL	Upper 95% CL	P-value
Age (months)	1.005	0.97	1.04	0.7483
prematurity	4.000	1.30	12.26	0.0153
Asthma (HRAD)	0.200	0.03	1.59	0.1282
Dyspnea	1.868	0.65	5.35	0.2443
Cyanosis	3.648	0.94	14.22	0.0622
Restlessness	0.193	0.02	1.54	0.1207
Wheezing	0.400	0.08	1.90	0.2492
Maximal fever	0.978	0.95	1.01	0.1437
Low saturation	0.996	0.92	1.07	0.9269
Leukopenia	1.217	0.13	11.67	0.8650
Max CRP level	1.000	0.99	1.01	0.9962
Duration of fever	0.716	0.47	1.09	0.1203

HRAD -Hyperreactive airway disease.

hospitalized patients is advised.

Conflict of interest

The authors declare no competing interests or conflict of interest.

Ethical approval

The institutional review board (IRB) of the Sheba Medical Center approved this research (Helsinki Number 9750-12-SMC). Informed consents were not required for this study.

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