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# Rhinovirus Frequently Detected in Elderly Adults Attending an Emergency Department

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The general aim was to investigate the burden of respiratory virus illness in a hospital emergency department, during two different epidemic seasons. Consecutive patients attending an emergency department during two study periods (February/March 2009 and 2010) were enrolled using broad inclusion criteria (fever/preceding fever and one of a set of ICD-9 codes suggestive of respiratory illness); nasopharyngeal washes were tested for the most common respiratory viruses using PCR-based methods. Influenza A virus was detected in 24% of samples collected in February/March 2009, whereas no samples tested positive for influenza during February/March 2010 (pandemic H1N1 Influenza A having circulated earlier in October–December 2009). Rhinovirus (HRV) was detected in 16% and 8% of patients recruited over the two study periods, respectively. Other respiratory viruses were detected rarely. Patient data were then analyzed with specific PCR results, comparing the HRV-positive group with virus-positive and no virus-detected groups. Individuals over 65 years old with HRV presented with signs, symptoms and underlying conditions and were admitted to hospital as often as the other enrolled patients, mainly for dyspnoea and chronic obstructive pulmonary disease acute exacerbation. Conversely, younger individuals with HRV, although presenting with respiratory signs and symptoms, were generally diagnosed with non-respiratory conditions. HRV was detected frequently in elderly patients attending the emergency department for respiratory distress without distinguishing clinical features. Molecular diagnosis of lower respiratory tract infections and surveillance of infectious diseases should include tests for HRV, as this virus is associated frequently with hospitalization of the elderly. ***J. Med. Virol. 83:2043–2047, 2011.*** © 2011 Wiley-Liss, Inc.



**KEY WORDS:** respiratory viruses; molecular diagnosis; influenza-like illness; respiratory distress

## INTRODUCTION

During the winter months, various viruses that may cause respiratory illnesses circulate widely in the adult population, leading to a disease burden in public health that is of considerable concern. Diagnosis of respiratory infection is usually based on clinical and epidemiological criteria, with only severe cases being confirmed by pathogen detection; hence, data for patients admitted to hospital remain limited, the one partial exception being the influenza virus [Mangtani et al., 2006; Elliot et al., 2008; Schanzer et al., 2008; van den Dool et al., 2008; Ison, 2009]. In order to evaluate the costs and benefits of molecular diagnosis, there is a need for better definition of the prevalence of common respiratory viruses [Gilca et al., 2009].

In recent years, with the use of molecular techniques, the human rhinovirus (HRV) has been recognized as a common cause of hospital admission, both as an agent of bronchopneumonia and through exacerbation of chronic pulmonary conditions in the elderly

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[Puro et al., 2005; McManus et al., 2008]. However, few studies have been conducted in adult patients attending emergency departments to estimate the burden of respiratory infections from HRV compared with other respiratory viruses. In our previous study [Pierangeli et al., 2010], we showed that triage criteria based on case definitions of influenza-like illness did not lead to the identification of all patients infected with the influenza virus and also included patients who were HRV-positive.

Lack of laboratory-confirmed diagnoses of respiratory infections on presentation at an emergency department could impede the prevention of virus spread and appropriate case management.

Within the framework of a respiratory infection surveillance project in the emergency department of the Policlinico Umberto I hospital, "Sapienza" University of Rome, the results of a study during February and March 2009 and February and March 2010 are presented in which PCR-based tests for the major respiratory viruses, including HRV, were undertaken on patients presenting with fever/preceding fever and respiratory symptoms. The results of this virological and clinical characterization of respiratory illnesses in an emergency department has led to new insights into the characterization of HRV-related clinical manifestations compared with other respiratory conditions.

## MATERIALS AND METHODS

### Patients

Consecutive patients who met the inclusion criteria were enrolled in the study in February and March 2009, and in February and March 2010, from those attending the Policlinico Umberto I hospital emergency department, one of the largest emergency departments in Rome (approximately 2,500 consultations per month for non-traumatic conditions). Inclusion criteria were: presenting with fever at admission or in the preceding 5 days, and one of the following diagnoses at triage according to the International Classification of Diseases, 9th revision (ICD-9 codes): pharyngitis acute (462), bronchitis, acute (466.0), bronchopneumonia, organism not otherwise specified (485), pneumonia (codes 480–486), dyspnea and respiratory distress (786.0), cough (786.2), thoracic pain (786.5), abnormal findings on diagnostic imaging of lung (793.1), influenza (487), influenza with pneumonia (487.0), influenza with other respiratory manifestations (487.1).

Informed consent and clinical data were obtained from a total of 238 patients: 103 patients in February/March 2009 (57 men and 46 women; median age, 74 years, age range, 22–98 years), and 135 in February/March 2010 (63 men and 72 women; median age, 68 years, age range, 18–95 years). The study was approved by the hospital's Ethics Committee and informed consent was sought from the participating patients. After medical examination, patients were either referred to their general practitioners or admitted to different departments of the hospital, that is, the Emergency Medicine, Infectious Disease and Internal Medicine departments.

### Detection of Respiratory Viruses

Nasopharyngeal washes were collected from all patients within 4 hr of first contact and then delivered on ice to the virology laboratory within 1–5 hr of collection; RNA extraction was undertaken using QIAamp Viral RNA Mini Kit (Qiagen Spa, Milan, Italy), the remainder being frozen at $-80^{\circ}$C. Extracted RNA was then subjected to reverse transcriptions with random hexamers and then 5 $\mu$l cDNA were added to polymerase chain reactions (PCRs), to detect the main respiratory viruses. In particular, a PCR amplified the untranslated 5′-region of HRVs [Deffernez et al., 2004], a multiplex PCR targeted the genomic segment 8 of influenza A and B [Grondahl et al., 1999], a PCR amplified the conserved F1 subunit of respiratory syncytial virus (RSV) A and B [Grondahl et al., 1999], a PCR targeted the L gene of human metapneumovirus (hMPV) [van den Hoogen et al., 2003], and specific or nested PCR was undertaken as described previously for parainfluenzaviruses 1–3 [Pierangeli et al., 2007]. Amplification products were run on agarose gel with molecular weight markers for identification; positive samples were confirmed by testing a second aliquot.

### Statistical Methods

A Chi-squared test was used to compare patient data according to virus results, with significance being fixed at the 5% level. The analysis was performed using SPSS v.13.0 for Windows$^{TM}$.

## RESULTS

### Prevalence of Respiratory Viruses

A total of 238 nasopharyngeal washes were collected prospectively from enrolled patients: during February/March 2009, 41% of samples (42/103) were virus positive, whereas during February/March 2010 the virus positive rate (16/135 = 12%) was significantly lower ($P < 0.05$, calculated using Chi-squared test).

Rhinoviruses were detected in 17/103 (16%) samples in 2009 (one of these was also positive for influenza A and is therefore included in the "other virus" group in Tables I and II) and in 11/135 (8%) in 2010.

PCR results positive for influenza A were obtained in 25/103 (24%) samples from patients enrolled during the first study period, all positive results occurring in samples collected in February 2009; influenza B was not detected in any sample. Other nasopharyngeal washes that tested positive for viruses included one sample positive for RSV in 2009 and three in 2010, and two samples positive for hMPV in 2010.

TABLE I. Patient Presentation at the Emergency Department, Distributed by Respiratory Virus Results

| Patient data at presentation | HRV[a], n = 27 | Other virus[b], n = 31 | No virus[c], n = 180 |
|---|---|---|---|
| Mean age ± SD | 70.9 ± 19.6[d] | 70.5 ± 18.4[d] | 62.6 ± 20.9[d] |
| Fever[e] | 12 (44%) | 8 (26%)[f] | 106 (59%)[f] |
| Preceding fever[g] | 2 (7%) | 9 (29%)[h] | 3 (2%)[h] |
| Cough | 15 (56%) | 24 (77%) | 78 (43%) |
| Influenza symptoms[i] | 7 (26%) | 8 (26%) | 78 (43%) |
| Dyspnea | 15 (56%) | 23 (74%)[j] | 90 (50%)[j] |
| Thoracic pain | 7 (26%) | 5 (16%) | 32 (18%) |

[a]Only human rhinovirus (HRV) single infections were considered.
[b]Other virus-positive cases include: influenza virus (IV) A n = 24, IVA + HRV n = 1; respiratory syncytial virus (RSV) n = 4, human metapneumovirus (hMPV) n = 2.
[c]Samples negative for IV A and B, RSV, HRV, hMPV, and parainfluenzaviruses 1–3.
[d]No virus- mean age younger than HRV- and other virus-group: $P < 0.05$, calculated using Chi-squared test.
[e]Fever: temperature ≥38°C.
[f]Patients with fever in other virus- versus no virus-group: $P < 0.05$, calculated using Chi-squared test.
[g]Preceding fever: reported fever in the 5 days before enrolment, with no fever at Emergency Department triage.
[h]Patients with preceding fever in other virus- versus no virus group: $P < 0.05$, calculated using Chi-squared test.
[i]Typical influenza symptoms: headache, asthenia, arthralgia, myalgia, thoracic pain.
[j]Patients with dyspnea in other virus group versus negative: $P < 0.05$, calculated using Chi-squared test.

TABLE II. Patient Clinical Data, Hospitalization, Diagnosis by Age Group and Respiratory Virus Infection

| | Patients: n (%) | | | | | |
|---|---|---|---|---|---|---|
| | 18–65 years: n = 95 | | | >65 years: n = 143 | | |
| Clinical data | HRV[a] n = 6 (6%) | Other virus[b] n = 9 (9%) | No virus[c] n = 80 (84%)[d] | HRV[a] n = 21 (15%) | Other virus[b] n = 22 (15%) | No virus[c] n = 100 (70%)[d] |
| WBC > 11,000/mm$^3$ | 2 (33%) | 3 (33%) | 23 (29%) | 8 (38%) | 7 (32%) | 33 (33%) |
| Abnormal chest X-ray with consolidation | 2 (33%) | 6 (66%) | 21 (26%) | 5 (23%)[e] | 9 (40%) | 57 (57%)[e] |
| Underlying conditions[f] | | | | | | |
| None | 5 (83%) | 5 (56%) | 48 (60%) | 1 (5%) | 1 (4%) | 3 (3%) |
| Respiratory | 0 | 1 (11%) | 10 (12%) | 1 (5%) | 3 (14%) | 11 (11%) |
| Respiratory + others | 1 (17%) | 0 | 14 (17%) | 12 (57%) | 14 (64%) | 62 (62%) |
| Others | 0 | 3 (33%) | 8 (10%) | 7 (33%) | 4 (18%) | 24 (24%) |
| Diagnosis[g] | | | | | | |
| Fever/ILI | 1 (17%) | 3 (33%) | 25 (31%) | 2 (10%) | 1 (4%) | 10 (10%) |
| URTI | 2 (33%) | 0 | 10 (12%) | 0 | 2 (9%) | 2 (2%) |
| LRTI | 0 | 5 (56%) | 24 (30%) | 5 (24%) | 8 (36%) | 52 (52%) |
| Dyspnoea/COPD exac | 0 | 1 (11%) | 5 (6%) | 9 (43%)[h] | 10 (45%)[h] | 20 (20%)[h] |
| Non-respiratory | 3 (50%)[i] | 0[i] | 16 (20%) | 5 (24%) | 1 (4%) | 16 (16%) |
| Hospitalization[j] | | | | | | |
| No | 5 (83%) | 3 (33%) | 39 (49%) | 2 (10%) | 2 (9%) | 3 (3%) |
| Emergency medicine | 1 (17%) | 4 (44%) | 10 (12%) | 7 (33%) | 15 (7%) | 32 (32%) |
| Infectious disease | 0 | 2 (22%) | 13 (16%) | 7 (33%) | 1 (4%) | 15 (15%) |
| Internal medicine | 0 | 0 | 10 (12%) | 2 (10%) | 2 (9%) | 36 (36%) |
| Other departments | 0 | 0 | 8 (10%) | 3 (14%) | 2 (9%) | 10 (10%) |

HRV, human rhinovirus; WBC, white blood cells; ILI, influenza-like illness; URTI, upper respiratory tract infection; LRTI, lower respiratory tract infection; COPD, chronic obstructive pulmonary disease.
[a]Only HRV single infections were considered.
[b]Other viruses detected in patients 18–65 years are: influenza virus (IV) A n = 8, IVA + HRV n = 1; in patients >65 years: IV A n = 16, Respiratory Syncytial Virus (RSV) n = 4, human metapneumovirus (hMPV) n = 2.
[c]Samples negative for IV A and B, RSV, HRV, hMPV, and parainfluenzaviruses 1–3.
[d]No virus detected in patients 18–65 years versus >65 years: $P < 0.05$, calculated using Chi-squared test.
[e]Abnormal chest X-ray with consolidation in patients > 65 years more frequent in no virus- versus HRV-group: $P < 0.05$, calculated using Chi-squared test.
[f]No underlying conditions in patients 18–65 years versus >65 years: $P < 0.001$, calculated using Chi-squared test.
[g]Clinical diagnosis given at discharge from the emergency department or after medical observation for patients not admitted to the hospital.
[h]Diagnosis of Dyspnea/COPD exacerbation in patients > 65 years more frequent in HRV- and other virus- versus no virus-group: $P < 0.05$, calculated using Chi-squared test.
[i]Non-respiratory diagnosis in patients 18–65 years more frequent in HRV- versus other virus-group: $P < 0.001$, calculated using Fisher's exact test.
[j]No hospitalization of patients 18–65 years versus >65 years: $P < 0.01$, calculated using Chi-squared test.

### Patient Presentation at Emergency Department

Patient age and signs and symptoms at emergency department presentation, stratified by virus results, are shown in Table I. Virus-negative patients were significantly younger than those who were HRV- and other virus-positive. Other significant differences were found in patients' signs and symptoms at presentation: patients infected with viruses other than HRV presented less frequently with fever but more frequently with preceding fever and dyspnoea at triage, compared with patients in whom no virus was detected (Table I).

### Clinical Features

Patients' white blood cell (WBC) counts, abnormal chest X-ray results (presence of lung consolidation, indicative of pneumonia), previous chronic conditions, diagnosis after emergency department medical examination and subsequent hospitalization are shown in Table II, distributed between two age groups—18–65 years and older than 65 years—and then by virus (HRV, other virus, no virus detected).

No significant differences were found between age and infection groups (Table II) in the numbers of patients who presented with leucocytosis [defined as WBC $> 11{,}000/mm^3$]. Abnormal chest X-rays with consolidation were observed significantly more often in elderly patients in the "no virus detected" group than in those who were HRV-positive. As expected, pre-existing health conditions were more frequent in patients over 65 years old but no significant differences were observed between HRV-positive patients and other virus-positive or virus-negative groups (Table II). Diagnoses of fever/influenza-like illness, upper respiratory tract infection, lower respiratory tract infection, dyspnoea/chronic obstructive pulmonary disease, and other non-respiratory diagnoses were as frequent in HRV-positive patients as in the other groups (Table II) in patients over 65 years, whereas younger patients who were HRV-positive had received more frequently a diagnosis of non-respiratory illness. Patients over 65 years were admitted to hospital at a significantly higher rate than younger ones but no significant differences were observed between virus groups in terms of subsequent hospitalization (Table II).

## DISCUSSION

Over the last two winters, during February and March, consecutive patients seeking care for respiratory symptoms at a large emergency department in Rome were examined, and molecular tests for the most common respiratory viruses undertaken. Virus-positive rates in the 2009 and 2010 study periods (41% and 12%, respectively) differed significantly because there were no influenza A-positive samples in February/March 2010, due to the pandemic Influenza A H1N1 2009 virus circulation occurring earlier than usual (October/November 2009) for an epidemic influenza. However, there were no statistical differences in the incidence of HRV-positive cases for 2009 and 2010 (16% and 8% of total nasopharyngeal washes collected and 40% and 69% of virus-positive cases, respectively); these HRV noticeable rates are consistent with the rates of infection reported previously by several authors [Monto et al., 2001; Minosse et al., 2008; Lieberman et al., 2010].

As for other respiratory viruses, RSV and hMPV were detected in a few cases; influenza B and parainfluenzaviruses 1–3 were not found. Adenoviruses, coronaviruses and bocavirus were not tested for; however, given the very low multiple-infection rate found, we considered the HRV-positive samples to be a single virus infection.

At triage, patients with HRV presented as frequently as other patients with cough and other symptoms of an influenza-like illness, and had a tendency to present with more fever and fewer preceding fever symptoms than patients with other respiratory viruses. In patients aged 18–65 years, HRV did not appear to be the primary cause of illness: indeed, their diagnoses were either of a mild respiratory illness resulting in the lowest rate of hospitalization, or they were admitted to hospital for non-respiratory conditions. Conversely, most patients over 65 years with HRV were diagnosed with severe respiratory conditions that led to high rates of hospitalization similar to those from other respiratory virus infections. Patients over 65 years who were HRV-positive presented with abnormal chest X-rays with consolidation statistically less frequently than elderly patients who were virus-negative, most of whom suffered from bacterial pneumonia; however, abnormal chest X-ray results in patients who were HRV-positive did not differ significantly from those of other virus-positive patients. Overall, in patients aged over 65 years of age, HRV and the other respiratory virus infections contributed to about half of the diagnoses of dyspnoea and chronic obstructive pulmonary disease acute exacerbation; notably, HRV was the most frequent single agent detected in these diagnoses, as reported in previous papers [McManus et al., 2008; Kherad et al., 2010].

It has been recommended that HRV should be included in the virological diagnosis of severe respiratory infections [Gambarino et al., 2009; Lieberman et al., 2010], and recently developed commercial multiplex PCR panels for respiratory viruses include HRV. The inclusion of HRV in the virological diagnostic work-up of respiratory specimens may greatly increase virus detection frequency in acute and chronic respiratory tract diseases, without real clinical significance. Indeed, a positive PCR for HRV does not necessarily indicate an association with the overt disease, especially in younger adults, as evident in our group of 18–65 year-olds. However, the potential for HRV diffusion to frail patients should be considered, as emergency departments are important sites

of pathogen transmission. Virological diagnosis could be effective in preventing transmission of respiratory agents among at-risk patients and in appropriate case management.

An emergency department is often the first point of call for people seeking medical care, and syndromic surveillance has been implemented in Italy as in many other countries to report, in real time, admission peaks that could lead to early detection of infectious disease outbreaks [Marsden-Haug et al., 2007; Ansaldi et al., 2008; May et al., 2010]; conversely, a complete virological diagnosis to monitor those outbreaks would imply a time delay. As reported in this and other studies, HRV infection may resemble clinically an influenza-like illness [Monto et al., 2001; Pierangeli et al., 2010] and HRV cases might well confound syndromic surveillance. HRV was the most common virus detected in samples collected during the recent pandemic H1N1 2009 virus testing [Follin et al., 2009]. In addition, national surveillance of influenza in Sweden and France resulted in an alert for pandemic H1N1 influenza A circulation during the early weeks of September 2009 due to an increased incidence of influenza-like illnesses, the increase actually due to HRV infection [Linde et al., 2009; Casalegno et al., 2010]. Thus, virological diagnosis in emergency departments may be a price worth paying for additional information on the infecting agent during monitoring of infectious disease outbreaks.

Overall, results from this study showed that HRV is a major viral infection in adults seeking medical care for respiratory conditions in emergency departments, presenting with no obvious distinguishing clinical features and causing respiratory distress and lower respiratory tract illnesses in older patients. Virological diagnosis of respiratory infections should, whenever needed, include molecular tests for HRV, as this virus has a significant healthcare impact, being associated frequently with admission to hospital of the elderly.

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