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Prospective evaluation of rhinovirus infection in healthy young children

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ABSTRACT

Background: Although the incidence of human rhinovirus (HRV) infection is highest in young, no study has yet been published concerning the types of HRV circulating in this population, the incidence of symptomatic infections due to the different types, or duration of shedding

Objectives: This prospective study evaluated the circulation of HRV species and types, and established the incidence of asymptomatic and symptomatic infections in young children.

Study design: The study enrolled 93 healthy children aged <2 years, 88 of whom completed the follow-up of weekly household visits from November 2013 to February 2014. At each visit, a record was made of any signs and symptoms of acute infection, and a nasopharyngeal (NP) swab was taken in order to identify the HRVs by means of RT-polymerase chain reaction and to construct the phylogenetic tree of the HRV-positive cases.

Results: A total of 1408 NP samples were obtained and 326HRV infections were diagnosed (23.1%), leading to a mean number of 3.7 ± 2.3 infections per child: HRV-A in 72 cases (22.1%), HRV-B in 29 (8.9%), HRV-C in 122 (37.4%), and non-typeable HRV in 103 (31.6%). Shedding was significantly longer for HRV-A (14 days) and HRV-B (14 days) than HRV-C (7 days; $p = 0.002$ and $p = 0.012$). Most of the HRV infections (209/326, 64.1%) remained asymptomatic and, when symptomatic, were of marginal clinical relevance.

Conclusions: In healthy young children, HRV infection is extremely frequent, generally asymptomatic or with a mild clinical presentation, and viral shedding is limited in time.

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1. Background

Modern molecular methods of viral screening have shown that human rhinoviruses (HRVs) are members of the family *Picornaviridae*, genus *Enterovirus*, and can be divided into three species (HRV-A, HRV-B, and HRV-C) including many different viral types on the basis of their genetic characteristics [1]. They are all considered to be capable of causing respiratory disease as suggested by the frequent identification of the different HRV strains, alone or in association with other respiratory viruses [2], in the respiratory secretions of subjects with upper (URTI) or lower respiratory tract infection (LRTI) [3,4]. Moreover, HRVs are recognised as major triggers of asthma and chronic obstructive pulmonary disease exacerbations [5] and possible contributors to acute graft rejection in transplant recipients [6,7].

However, various epidemiological studies have shown that, in addition to being associated with respiratory problems, HRVs can be identified in 10–35% of apparently healthy subjects [8–11], thus raising doubts about their real clinical relevance and etiological role in respiratory diseases, particularly when found together with other infectious agents in respiratory secretions. This indicated that their presence in patients with respiratory disease did not necessarily mean that they were the causative agents because the disease may be due to a coincidental upper airways infection, carrier status, or the prolonged shedding of an HRV that caused a previous infection.

Furthermore, the duration of HRV shedding after symptomatic and asymptomatic infection has not been precisely defined. Recent studies suggest that HRVs can be found in respiratory secretions for 1–2 weeks in healthy subjects and for longer periods in primary immunocompromised patients or organ transplant recipients [12].

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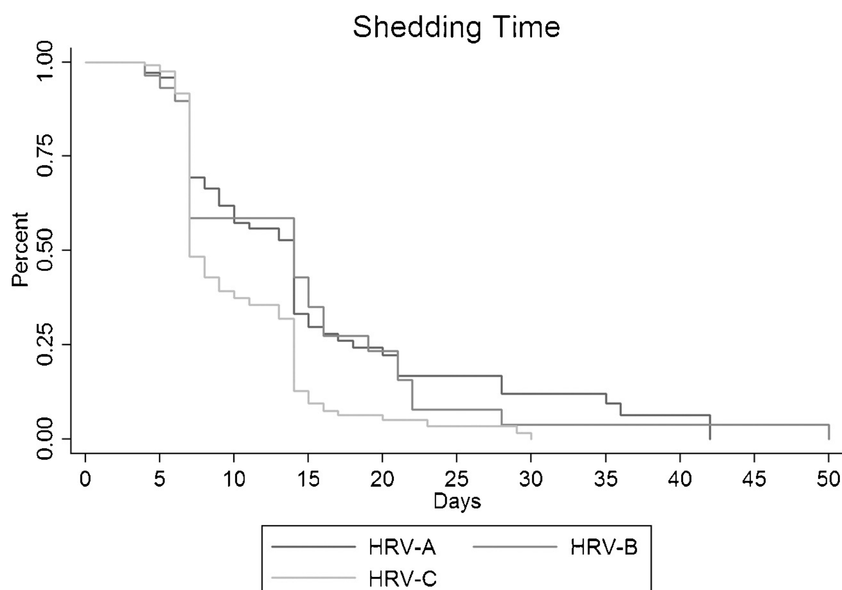

Fig. 1. Median shedding time by type of human rhinovirus (HRV). HRV A, B and C combined: 9 days (95% confidence interval [CI]: 7–13); HRV A: 14 days (95% CI: 9–14); HRV B: 14 days (95% CI: 7–16); and HRV C: 7 days (95% CI: 7–9). Log-rank test (all HRV types): $p = 0.0003$; log-rank test (HRV-A *vs* HRV-B): $p = 0.94$; log-rank test (HRV-A *vs* HRV-C): $p = 0.0002$; log-rank test (HRV-B *vs* HRV-C): $p = 0.012$.

However, these timings are based on data limited to HRV species and, as different types of HRV can circulate simultaneously [13,14], prolonged detection could be due to consecutive new infections caused by different types. A more precise evaluation of shedding is needed in order to clarify the real clinical significance of HRV, optimize infection control measures, and study the pathogenesis of HRV infection. Moreover, it is not clear whether different HRV species and types play different pathogenic roles.

2. Objectives

Although the incidence of HRV infection is highest in young, no study has yet been published concerning the types of HRV circulating in this population, the incidence of asymptomatic and symptomatic infections due to the different types, or the real duration of shedding [1]. The main aim of this study was to try to fill this gap.

3. Study design

3.1. Study population

This prospective study. which was conducted by the Pediatric Highly Intensive Care Unit of the University of Milan's Department of Pathophysiology and Transplantation and approved by the Ethics Committee of the Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico (Milan, Italy), involved a cohort of healthy children aged <2 years of age, who were enrolled between 15 and 30 October 2013, and followed up by means of weekly household visits from 1 November 2013 to 28 February 2014.

A letter explaining the nature of the study was sent to 150 families with children born in our institution during the previous two years in which it was specified that only healthy, full-term infants could be enrolled and that any child with a severe chronic disease diagnosed after birth would be excluded. It was also stated that the family would need to remain in the Milan area throughout the study period and accept weekly household visits. The 93 families expressing interest were invited to attend a first hospital appointment with their child at which demographic, socio-economic and medical information was collected, and the final selection was made after having obtained the written informed consent of a parent or legal guardian.

The 93 enrolled children were followed up by means of weekly household visits by field-workers at which the parents/guardians were interviewed and a record was made of the date of onset, duration and specific symptoms of URTIs, LRTIs or other acute infections occurring during the preceding week. At each visit, nasopharyngeal (NP) secretions were collected using a flexible pernasal flocked swab (Eswab 490 CE.A, Copan Italia, Brescia, Italy), which was immediately placed in a mini-tube containing 1 mL of transport medium (Enat medium, Copan Italia), taken to the research laboratory, and stored at −70 °C until being analysed for the presence of HRVs. All of field-workers were trained in data and sample collection and recognising respiratory signs and symptoms by means of workshops and reviews of educational material prepared for the World Health Organization's Integrated Management of Childhood Illnesses (IMCI) protocol [15].

3.2. 4HRV identification

Viral nucleic acids were extracted from the nasopharyngeal swabs using a Nuclisens EasyMAG automated extraction system (Biomeriéux, Craponne, France), and the HRVs were identified by means of a RT-polymerase chain reaction (PCR) assay (iAg-Path-ID one-step RT-PCR Kit Applied Biosystems, Foster City, CA). The primers and probe sequences were those reported by Lu et al. [16].

The hypervariable part of the 5' non-coding region (NCR), the entire VP4 gene and the 5' terminus of the VP2 gene in the HRV-positive samples were amplified by means of a RT-PCR, as previously described [2,17], and the newly determined sequences were edited using Sequencher software and aligned using the ClustalW program integrated in the MEGA package, version 5.0 [18]. The HRV in each sample was determined on the basis of the phylogenetic tree and by comparing it with all of the available HRV reference prototypes encoding VP4/VP2 protein retrieved from GenBank (http://www.ncbi.nlm.nih.gov). The phylogenetic tree was reconstructed using the neighbor-joining method and parameters selected by the MEGA model test program. The genetic

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