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ORIGINAL PAPER

Human metapneumovirus infections—biannual epidemics and clinical findings in children in the region of Basel, Switzerland

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Abstract Human metapneumovirus (hMPV) epidemics vary in time and severity. We report findings for PCR for hMPV and respiratory syncytial virus (RSV) performed on nasopharyngeal aspirates (NPA) of hospitalized and outpatient children with respiratory tract infections between October 2004 and April 2008. A total of 3,934 NPAs were tested for hMPV and 3,859 for RSV. Of these, 198 (5%) were hMPV positive and 869 (23%) were RSV-positive. Median age was 17 months and 9 months for hMPV and RSV, respectively. Fifty-nine percent of hMPV and 58% of RSV patients were hospitalized. Proportions of hMPV positive samples for the four winter seasons were 0.4%, 11%, 0.2%, and 14%. For RSV, they were 28%, 15%, 28%, and 28%. HMPV epidemics follow a biannual variation in our area. Major epidemics were observed in winter seasons starting in odd years (2005/06 and 2007/08), minor epidemics in those starting in even years (2004/05 and 2006/07). RSV epidemics usually follow a reciprocal biannual pattern, leading to annually alternating major RSV and hMPV epidemics.

Keywords Human metapneumovirus · Respiratory syncytial virus · Biannual · Children · Epidemic

Introduction

Human metapneumovirus (hMPV), a paramyxovirus first discovered in the Netherlands in 2001 [29], causes acute respiratory tract infections (RTI) in children and adults worldwide [2, 4, 8, 9, 13–17, 20–24, 26–28, 33].

Since October 2004, nasopharyngeal aspirates (NPA) from in- and out-patients with RTI have been tested for hMPV by a reverse-transcriptase-polymerase chain reaction (RT-PCR) as part of a broad panel of multiplex-PCR in our laboratory [19], and clinical characteristics of patients have been obtained [3]. Our initial observations revealed that only a few nasopharyngeal samples tested positive for hMPV in the first winter season, followed by an epidemic in the next winter season. In the meantime, epidemiological observations in Austria, Germany and Sweden have suggested that hMPV activity appears to follow a biannual cycle [1, 25, 31] similar to previous findings with respiratory syncytial virus (RSV) in Europe [10, 11]. Here, we present the results from our continuous ongoing surveillance and provide further evidence that hMPV causes biannual major epidemics.

Materials and methods

Study subjects

Procedures were similar as in previous studies by our group [3, 19]. Specifically, nasopharyngeal aspirates (NPA) were obtained from patients hospitalized with RTI on a routine basis. Further, NPA were collected from ambulatory patients with RTI presenting to the emergency room of

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our children's hospital or to pediatricians in private practices in close vicinity.

Clinical characteristics (age, gender, prematurity, underlying chronic diseases, onset of symptoms, duration of illness, clinical signs and symptoms, medication, and final clinical diagnosis information) in hospitalized patients with hMPV infections were abstracted from their medical records. Informed consent was not deemed necessary by the ethics committee for this procedure. In ambulatory patients, the same data was obtained by use of standardized questionnaires sent to the treating physicians and informed consent was obtained from the patients' parents. All patients with respiratory tract infection and a nasopharyngeal specimen obtained for virus detection were included. Patients without parental agreement for study participation were excluded from analyses.

Laboratory investigations

Details have been described before [3]. Briefly, from October 2004 onwards, RT-PCR for hMPV was performed by use of a one-tube reaction (Titan One Tube RT-PCR System, Roche Diagnostics GmbH Mannheim, Germany) and a primer pair comprising hMPV L-L Hex-labeled (5′ CAT GCC CAC TAT AAA AGG TCA G 3′) and hMPV L-R1 (5′ CAC CCC AGT CTT TCT TGA AA 3′), amplifying a fragment of 170 bp in the polymerase gene as described by van den Hoogen et al. [30]. In addition, a second primer pair hMPV N-L1 (5′ GCA TGC TAT ATT AAA AGA GTC TCA 3′) and hMPV N-R FAM-labeled (5′ ATC TCA GCA GCA TAT TTG TA 3′) was used for amplification of a highly conserved fragment of 157 bp in the nucleoprotein gene. These primers were slightly modified based on those previously described by Maertzdorf et al. [18]. The two hMPV RT-PCRs were integrated in the existing in-house RT-multiplex-PCR as follows: primers for hMPV N gene were combined with those for RSV, influenza viruses A and B (block 1) and primers for HMPV L gene were combined with those for adenoviruses and parainfluenza type 1 and type 3 viruses (block 2).

After careful internal validation, PCR technique was changed to a one-step RT-PCR with TaqMan (Applied Biosystems 7500 Real Time PCR System) in October 2007 according to the manufacturer's instructions (TaqMan One-Step RT-PCR Master Mix Reagents, Applied Biosystems, Roche, Branchburg, New Jersey, USA). This RT-PCR amplifies the hMPV NL-N gene by use of a primer pair comprising 5′-CATATAAGCATGCTATTAAAAGAGTCT C-3′ and 5′-CCTATTTCTGCAGCATATTTGTAATCA G-3′ specific to all hMPV subtypes, and a 5′-FA M-TGYAATGA TGAGGGTGTCACTGCGGTTG-TAMR A-3′ primer. Until December 2007, hMPV L-Gen was amplified as before but disregarded thereafter due to its suboptimal sensitivity [3, 7].

Statistical methods

Data were entered into a database and statistical analyses were performed using SPSS (version 13.0, SPSS, Inc., Chicago, IL, USA). Clinical characteristics and laboratory variables were compared by Student's *t*-test, Mann–Whitney *U* test, Fisher's exact test, chi-squared test, or odds ratio analysis as appropriate. A two-sided *P* value of <0.05 was considered significant.

The study protocol was approved by the University of Basel Ethics Committee.

Results

Epidemiological characteristics

Findings from the first study period, comprising 2,582 NPA received between October, 11, 2004 and February 28, 2006, have been published before [3]. Here, we present results for the extended period until May 31, 2008 from a total of 5,057 NPA. Based on the physicians' orders for detection of viruses from multiplex-PCR blocks 1 and 2, 3,934 (77.8%) NPA were tested for hMPV and 198 (5.0%) specimens were positive. For RSV, 3,859 NPA were tested and 869 (22.5%) were positive.

Only 20 (0.2%) of 1,003 NPA obtained during the three warm study seasons (April to September) were positive for hMPV. Similarly, three of 691 (0.4%) and two (0.2%) of 897 NPA tested for hMPV in the winter seasons October 2004 to March 2005 and October 2006 to March 2007, respectively, were positive for hMPV. In contrast, major hMPV epidemics occurred during the alternating winter seasons 2005/2006 and 2007/2008 with 64 (11.4%) of 560 and 109 (13.9%) of 783 NPA positive (Fig. 1). During the peaks of the epidemics, up to 30% of all RTI were caused by hMPV (Fig. 2).

In comparison, major RSV epidemics occurred early during the winter seasons 2004/2005 and 2006/2007 (i.e., in alternating years compared to hMPV epidemics) and one minor and one major RSV epidemic occurred late during the winter seasons 2005/2006 and 2007/2008, respectively (Figs. 1 and 2).

Seventeen (8.6%) of 198 hMPV-infected patients were documented to be coinfected with other respiratory pathogens: 11 with RSV, four with *M. pneumoniae*, and two with adenovirus.

Clinical characteristics

Informed consent could be obtained from the parents of all ambulatory children infected with hMPV during the second study period. Basic characteristics of patients were remark-

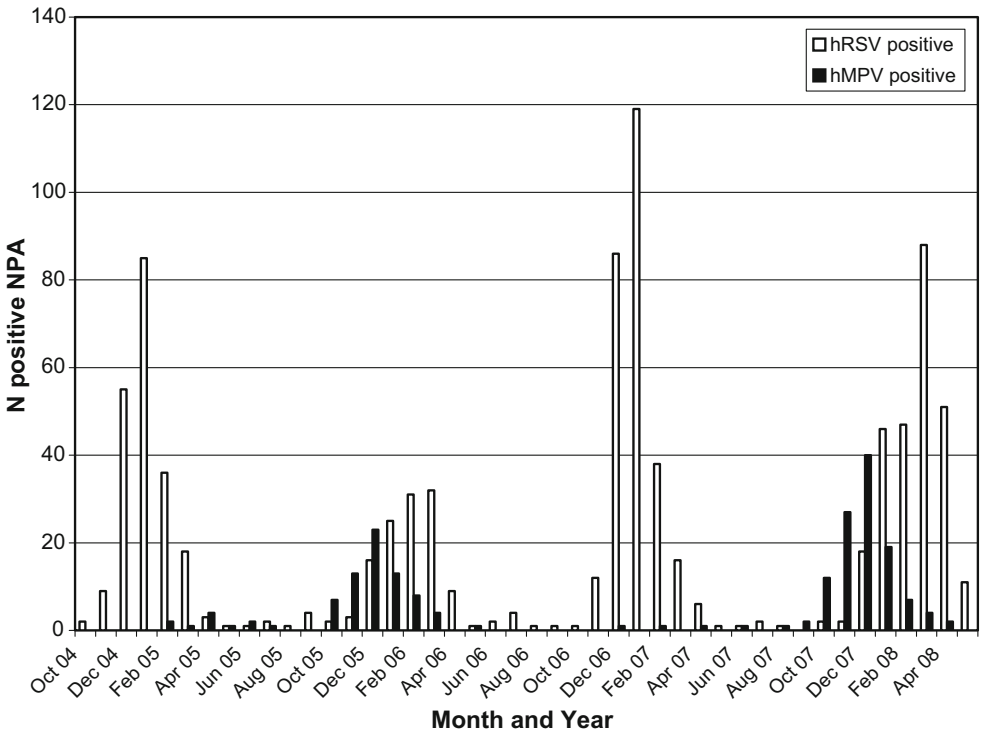

Fig. 1 Seasonal distribution of hMPV and RSV detected by PCR in nasopharyngeal aspirates from patients with respiratory tract infections

ably similar compared to the first period with mean age of 32 (first period) and 32 months (second period) and median age of 15 (first period) and 17 months (second period), respectively. In comparison, RSV-positive patients had a mean age of 16 and 16 months and median age of 9 and 8 months, respectively.

Overall, more males than females had hMPV and RSV infections (both 59%).

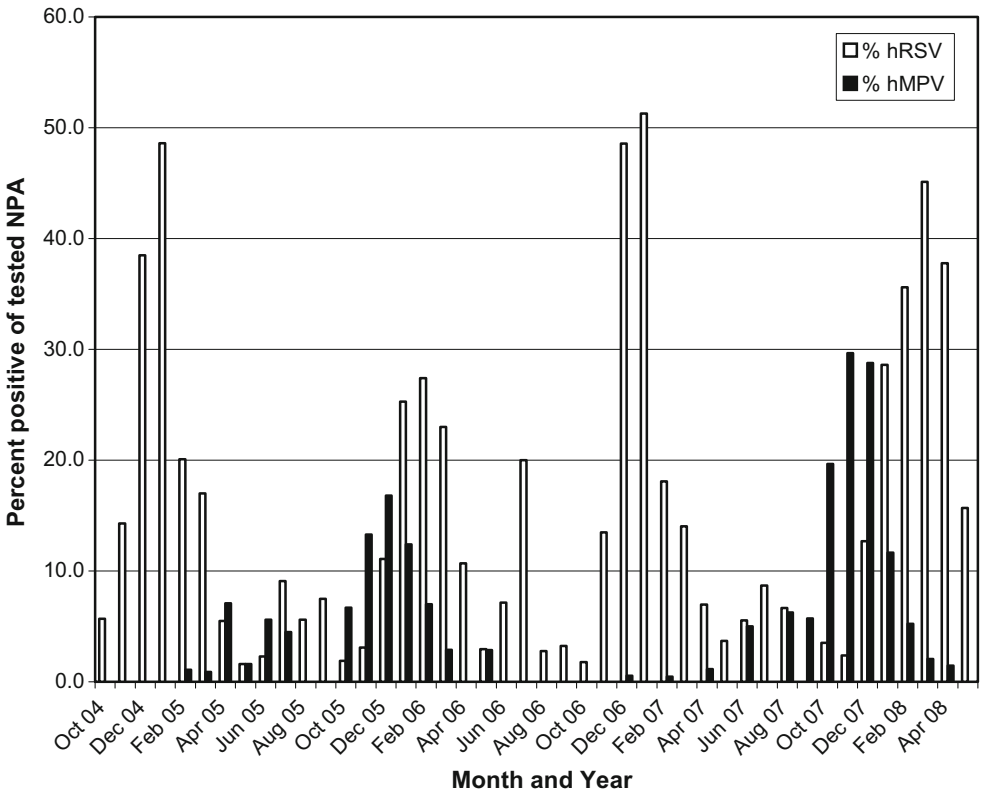

Fig. 2 Proportion of hMPV and RSV detected by PCR in nasopharyngeal aspirates from patients with respiratory tract infections

The following comparative analyses of clinical characteristics comprise 111 hMPV and 558 RSV-positive patients during the second study period without co-infections. Of patients with hMPV infection, 48 (43%) were infants including one (0.9%) newborn (<1 month of age) compared to 343 (61%; OR 0.48, 95% confidence interval 0.31–0.74, $p<0.001$) infants and 35 (6.3%; OR 0.15, 95% CI 0.01-0.92; $p=0.03$) newborns among RSV-positive patients. Hospitalization rates were 59% ($n=65$) for hMPV and 58% ($n=326$) for RSV infections; intensive care treatment was required due to imminent respiratory failure in five (4.5%) and 39 (7.0%; $p=0.33$) patients with hMPV and RSV infections, respectively.

A summary of clinical characteristics of hMPV infections and a comparison between hospitalized children and out-patients are demonstrated in Table 1. Dyspnea, diarrhea, pneumonia, feeding difficulties, and use of corticosteroids were more frequently among hospitalized children who also tended to be younger than out-patients (31.4±45.8 months versus 33.9±32.9 months, $p=0.06$). The majority of patients had LRTI (73%; out-patients: 70%, in-patients: 75%). Further, mean duration of hospitalization was 4.2±3.2 days (median 3 days, range 1–20 days) and thus shorter than during the first study period (mean 6.6±8.9 days; median 4). The difference in age distribution between hospitalized patients (median 25 months; range 3–148) and out-patients (15 months; 1–207) was not significant ($p=0.06$).

Thirty-two (29%) of 111 hMPV-infected children had some form of underlying chronic disease. Eighteen (56%) of them were hospitalized compared with 47 (59%) of 79 primary healthy children ($p=0.75$).

Signs and symptoms of hMPV infection were not different whether the disease occurred during the warm (April to September) or cold (October to March) study seasons (data not shown).

Discussion

Human metapneumovirus is a member of the *Paramyxoviridiae* family and was first isolated from young children with RTI [29]. We report findings from our extended ongoing surveillance of hMPV, which comprises 198 cases and is one of the most comprehensive case series so far.

In the first two study years, we had observed only few hMPV infections in the winter of 2004/2005 whereas a

Table 1 Clinical characteristics in 46 out-patients and 65 hospitalized patients with hMPV infections

Variables	Total N/known (%)	Out-patients N/known (%)	In-patients N/known (%)	*p* value	Odds ratio[a] (95% CI)
Male gender	62/111 (56)	30/46 (65)	32/65 (49)	0.096	0.5 (0.2–1.2)
Prematurity (<37 weeks)	23/108 (21)	8/46 (17)	15/62 (24)	0.393	1.5 (0.5–4.4)
Body temperature					
38.5–38.9°C	22/107 (22)	9/42 (21)	13/65 (20)	0.858	0.9 (0.3–2.7)
≥39°C	55/107 (52)	17/42 (40)	38/65 (58)	0.069	2.1 (0.9–4.9)
Cough	107/111 (96)	46/46 (100)	61/65 (94)	–	–
Dyspnea	50/111 (45)	10/46 (22)	40/65 (62)	≤0.001	9.6 (3.5–27)
Rash	10/109 (9)	4/46 (9)	6/63 (10)	0.882	1.1 (0.3–4.2)
Oral fluid intolerance	54/106 (51)[b]	12/46 (26)	42/60 (70)	≤0.001	6.6 (2.8–15.6)
Vomiting	33/107 (31)[c]	11/46 (24)	22/61 (36)	0.178	1.8 (0.8–4.2)
Diarrhea	23/107 (21)[c]	4/46 (9)	19/61 (31)	0.005	4.7 (1.5–15.1)
URTI	95/111 (85)	40/46 (87)	55/65 (85)	0.729	0.8 (0.3–2.5)
Conjunctivitis	10/111 (9)	2/46 (4)	8/65 (12)	0.149	3.1 (0.6–15.3)
Rhinitis	93/111 (84)	40/46 (87)	53/65 (82)	0.446	0.7 (0.2–1.9)
Pharyngitis	55/111 (50)	17/46 (37)	38/65 (58)	0.026	2.4 (1.1–5.2)
Acute otitis media	19/109 (17)	8/46 (17)	11/63 (17)	0.993	4.7 (0.4–2.7)
LRTI	81/111 (73)	32/46 (70)	49/65 (75)	0.496	1.3 (0.6–3.1)
Pneumonia	33/111 (30)	5/46 (11)	28/65 (43)	≤0.001	6.2 (2.2–17.7)
Bronchitis	59/111 (53)	28/46 (61)	31/65 (48)	0.171	0.6 (0.3–1.3)
Bronchiolitis	7/111 (6)	4/46 (9)	3/65 (5)	0.384	0.5 (0.1–2.4)
Treatment					
Antibiotics	38/111 (34)	15/46 (33)	23/65 (35)	0.762	1.1 (0.5–2.7)
Corticosteroids	19/111 (17)	3/46 (6)	16/65 (25)	0.004	4.7 (1.2–22)
Inhaled broncho-dilators	44/111 (40)	16/46 (35)	28/65 (43)	0.379	1.4 (0.6–3.3)
Oxygen supplementation	37/111 (33)	0/46 (0)	37/65 (57)	0.001	–

[a] Odds ratios were calculated where meaningful

[b] Five patients excluded because of concomitant rotavirus infection ($n=4$) and oral tube feeding ($n=1$)

[c] Four patients excluded because of concomitant rotavirus infection

major epidemic of hMPV infections occurred in the following winter. At that time, we had speculated that this observation could represent a pattern of biannual major epidemics similar to those observed with RSV [3]. Continued surveillance now supports the assumption of a biannual pattern and in the meantime three other groups came to the same conclusion [1, 25, 31]. In a retrospective RT-PCR-based study from Sweden, hMPV was found in 143 of 4,989 specimens from patients of all ages with respiratory tract infection [25]. The proportion of positive samples (2.9%) was similar to our findings (5.0%), where the higher proportion in our study probably reflects the fact that it was restricted to children. In accordance, in the respiratory pathogen surveillance in children in Germany, with more than 12,000 specimens between 2002 and 2006, hMPV was also recovered in 5.0% [31]. In addition, the selection of PCR primers may have played a role. In the Swedish study, only L gene primers were used which have been shown to be less sensitive than N gene primers [7]. Further, in a single-center study over a 7 year period from Vienna, Austria, 109 (6.8%) of 1,612 NPA specimens in children under 2 years of age were positive for hMPV [1].

Interestingly, the biannual hMPV epidemics in Sweden occur in even years (e.g., 2004/2005) [25] whereas in Switzerland (our study), Germany [31], and (based on a 2 year surveillance) possibly also in Italy [6], they occur in odd years (e.g., 2005/2006). However, in all of these countries hMPV epidemics are anti-cyclical to RSV epidemics. No plausible explanations have been offered for these peculiar epidemiological findings. In the study from Austria, the biannual pattern refers to the peaks of hMPV activities which alternate between spring and winter whereas the proportions of positive hMPV specimens by no means were as different from year to year as in our study [1].

Our original clinical observations on the first 74 patients [3] have now been substantiated with a total cohort of almost 200 patients with documented clinical course of hMPV infection. In summary, signs and symptoms of hMPV infection are similar to those of RSV infection although patients with hMPV infections are significantly older than RSV infected patients. The clinical presentation of both hospitalized and out-patients with hMPV respiratory tract infection comprise cough, rhinitis, and dyspnea as the major findings.

Approximately 50% of patients were treated with antibiotics for suspected bacterial infection during their illness in the first study phase and this percentage was reduced to 34% in the second phase. Further, duration of stay in hospitalized patients decreased from a mean of 6.6 days to 4.2 days. These changes reflect the current trend towards a preference for ambulatory care and a more stringent use of antibiotics, respectively.

Proportions of hMPV-infected patients with chronic underlying diseases (30% versus 29%) and a history of prematurity (11% versus 21%) were comparable in both study phases and also similar to previous observations [5, 12, 30, 32]. These rates are high compared to the normal population and either indicate an increased susceptibility for infection or a bias towards a greater likelihood for diagnostic tests in these high-risk patients.

In conclusion, hMPV infections lead to upper and lower respiratory tract disease in primary healthy children but also in patients with underlying disease. The clinical course is usually uncomplicated and the observed seasonality with biannual early winter epidemics, anti-cyclical to those caused by RSV, allows assumptions on the expected burden for the health care system in the ambulatory and clinical setting year by year.

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Conflict of interest None.

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