Human metapneumovirus infection in pregnant and postpartum women: Clinical characteristics, risk factors and severity

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Abstract

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Epidemiology

Background: Since its isolation in 2001, Human Metapneumovirus (hMPV) has emerged as a cause of respiratory illness worldwide. While hMPV incidence varies based on location and time of year, it has been found responsible for an estimated 1.5-10.5% of respiratory infections among adults. To our knowledge, hMPV's risk factors, clinical manifestations and severity have never been described among pregnant and postpartum women; this thesis seeks to address this research gap.

Methods: As part of a community-based randomized controlled trial of seasonal influenza vaccination in rural southern Nepal, pregnant women were enrolled and visited weekly through six months postpartum. If an episode of respiratory illness with fever occurred in the prior week, a mid-nasal swab was collected. Risk factors

were assessed using a multivariate Cox regression model. To assess severity, a 1-point score was assigned to each symptom (fever, cough, sore throat, rhinorrhea, myalgia); a Wilcoxon rank-sum test was used to compare the severity scores and symptom duration between groups.

Results: During the 3-year study period, 56 of 3693 women enrolled (1.5%) had hMPV detected. The overall incidence of hMPV in the study sample was 15 cases/1000 person-years; this represents 26 cases (1.3% incidence) among pregnant women and 30 cases (1.8% incidence) among postpartum women. HMPV incidence peaked between September 2011 and January 2012. Maternal education duration was significantly associated with hMPV, with additional years of education associated with decreased risk (HR 0.93; 95% CI 0.87, 0.99). Overall, the most common symptom was cough (64.2%), followed by myalgia (60.7%). While the severity score did not differ significantly between groups, pregnant women experienced longer duration of symptoms (6.5 days vs 4.5 days; p = 0.03).

Conclusion: HMPV is a significant cause of respiratory illness in pregnant and postpartum women in rural Nepal. Women with fewer years of education experienced greater risk of infection. Pregnant women experienced significantly increased symptom duration compared to postpartum women.

Background

Respiratory infections are a significant cause of illness and mortality worldwide [1,2]. In 2001, researchers from the Netherlands identified a novel virus of the Paramyxoviridae family, in the same subfamily as respiratory syncytial virus (RSV) [3]. This newly identified virus, human metapneumovirus (hMPV), was suspected to be the major cause of what had previously been referred to as "non-RSV bronchiolitis" [3]. Since its isolation, hMPV has been identified as a cause of upper and lower respiratory illness and associated complications among both children and adults [1,4].

HMPV is estimated to be responsible for 5-25% of respiratory infections among infants and children [5-8], and 1.5-10.5% among adults [9-14]. Due to the presence of multiple genotypes and an incompletely protective immune response conferred by infection with hMPV, reinfection is common, though repeat infections tend to be less severe than primary infections [14,14]. While hMPV has been described in several geographic settings, its epidemiological and clinical impact among adults has never been described in a rural south Asian setting. Furthermore, the majority of existing studies describe patients who seek care in a clinic or hospital setting; few studies have been performed in community-based settings using active home-based surveillance.

Common complications of hMPV include bronchiolitis (59-66%) and pneumonia (8-14%) [6,7]. One study enrolling pediatric patients presenting for care for severe pneumonia in Kathmandu, Nepal found that 1.4% of all pneumonia cases and 4.8% of virus-positive cases were positive for hMPV [15]. In children and adults,

hMPV can also exacerbate preexisting conditions such as asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis, and can lead to severe infections in immunocompromised patients and those with congenital heart disease [12,14].

While hMPV has been thoroughly documented among children, less research exists on hMPV in previously healthy adults. A challenge study of hMPV in adults found that 43% of subjects were infected with the virus, and peak viral shedding occurred 7-9 days after infection [16]. A longitudinal study by Okamoto et al. found that 16.9% of healthy adults were infected with hMPV during the five-year study period; younger adults (age 20-39) were found to be at greater risk for hMPV infection compared with middle-aged adults (age 40-65) [17]. Similarly, 2003 study by Falsey et al. found that hMPV illness rates were highest among young adults, particularly those sharing a household with children [9]. In this study, 4.5% of respiratory illnesses were associated with hMPV infection [9].

Identifying risk factors for hMPV infection and severe illness may help care providers to identify, prevent and/or address complications. While risk factors have been addressed in several studies, to our knowledge none have addressed risk among pregnant women [18]. There is reason to hypothesize that pregnant women are at greater risk for severe hMPV infection. Pregnancy is known to have an immunomodulating effect, and pregnant women are at elevated risk for complications of both seasonal and pandemic influenza [19,20]. A global pooled analysis of risk factors for severe H1N1 found that pregnant women had approximately seven times the risk of hospitalization and two times the risk of

death when compared with non-pregnant women with H1N1 [21]. In contrast, little has been published on the morbidity of other respiratory viral infections (parainfluenza, RSV, etc.) during pregnancy. This project therefore represents a valuable opportunity to describe the clinical manifestations and severity of hMPV among pregnant women.

Overall, this study represents an opportunity to study the impact of hMPV in pregnant and postpartum women in rural south Asia. Given the aforementioned literature gaps, the specific aims for this study are as follows:

- Aim 1a: To describe the incidence and the demographic characteristics of human metapneumovirus (hMPV) infection among pregnant and postpartum women in a rural population in Sarlahi, Nepal.
- Aim 1b: To describe the risk factors for hMPV infection among pregnant and postpartum women.
- Aim 2: To compare clinical characteristics and disease severity of hMPV infection in pregnant versus postpartum women.

Methods

Study Design: This retrospective cohort study is a secondary analysis using data from two consecutive community-based, placebo-controlled, individually randomized trials of seasonal influenza vaccination among pregnant women in a rural population in Sarlahi, Nepal.

Study Setting: Enrollment for this study took place in 9 Village Development Committees (VDCs) in Sarlahi, Nepal (Dhungre Khola, Karmaiya, Hariaun, Ghurkauli,

Sasapur, Netraganj, Lalbandi, Jabdi, and Raniganj). Sarlahi is located in the southern plains of Nepal [22]; the area is characterized by rural Hindu culture and consists largely of peasant famers (58%), laborers (26%), and their families [23]. The study area is mostly comprised of members of the Vaiysha caste, ethnic Hindus who are traditionally classified as merchants but often work as farmers and laborers [24]. The majority of inhabitants are from two ethnic groups: the Pahadis, who are from the hill regions of Nepal, and the Madheshis, who are of north Indian origin [22].

Study Subjects: The study population included all married women 15-40 years of age identified as pregnant with gestational age between 17 and 34 weeks during the study period (4/2011-9/2013). Women were enrolled in the study only one time; subsequent pregnancies in the same woman were not enrolled.

Exclusion criteria for enrollment were as follows: woman did not intend to deliver child within study area; woman had already received current influenza vaccine; woman allergic to any component of vaccine; woman refused to provide consent; woman later than 34 weeks gestation at time of identification. Women were also excluded from the dataset if they delivered their child less than two weeks following receipt of the vaccine or placebo.

Data Collection: Upon initiation of the primary study, a door-to-door census was conducted in the study area to identify married women of reproductive age. Informed consent was obtained using a verbal consent process from households where women of reproductive age resided. After the consent process, information on household structure, demographic information and socioeconomic status were obtained. Women identified as pregnant during this household census were

individually consented and enrolled.

After the baseline census, follow-up occurred every five weeks at households where women of reproductive age resided, in order to determine if a woman had become pregnant. At pregnancy enrollment, information regarding medical history, pregnancy history and anthropomorphic measurements were collected. From the time of enrollment of the woman through six months postpartum, a Field Interviewer (FI) visited the household to conduct a morbidity interview for each day in the prior week. Temperature was recorded during this weekly visit, and during the intervening days by the participant using a digital thermometer provided by the study team. If a participant had an episode of respiratory illness (reported fever >38°C and one or more of the following symptoms: cough, sore throat, rhinorrhea/nasal congestion or myalgia), a mid-nasal swab was collected and tested by real-time reverse transcription PCR; cycle threshold (CT) values were also measured to quantify viral load [25].

US-based investigators traveled regularly to Nepal for project oversight. Quality control procedures were emphasized during project-specific training and were reviewed on a regular basis by study investigators. Data were collected on paper forms in Nepali, translated into English, and entered into a secure database in Nepal. All data are kept on a locked password protected drive. Coded data were used for the purposes of these analyses.

IRB approval for the randomized controlled trial was received from the Johns Hopkins University Bloomberg School of Public Health, Seattle Chidren's Hospital, Cincinnati Children's Hospital, the Institute of Medicine at Tribhuvan University, and

the Nepal Health Research Council. Approval for this secondary analysis was received from the University of Washington IRB.

Data Analysis:

Aim 1. Descriptive statistics were used to summarize the characteristics of pregnant and postpartum women with and without hMPV infection. Gestational age at time of hMPV infection was estimated using date of birth minus the last menstrual period (LMP). Mother's smoking captured whether cigarettes or bidi (a hand-rolled cigarette common in Southeast Asia) were smoked in the past 30 days. Ethnic group was dichotomized as Pahadi vs. Madheshi. Caste was categorized as Brahmin/Chhetri (higher caste), Vaiysha (working caste), Shudra (lowest caste) and Muslim; this categorization has been used in previously published research from the study area [24]. Household size was defined as number of people sharing a cookstove; household density was defined as number of people per room (excluding kitchen and storerooms).

Incidence rates were calculated using person-weeks generated from weekly surveillance visits. Individuals began contributing person-weeks beginning with their first weekly surveillance visit at ≥17 weeks gestation, through their final surveillance visit at ≤6 months postpartum.

For the assessment of risk factors, the exposure of interest was hMPV infection. HMPV infection was defined as virologic diagnosis of hMPV with a mid-nasal swab tested by real-time reverse transcription PCR with symptoms of a respiratory illness (reported or measured fever >38°C plus at least one additional symptom, including cough, myalgia, rhinorrhea, or sore throat). Episodes of

respiratory illness must be separated by 7 or more days without symptoms. Potential risk factors for hMPV infection evaluated included household density, number of children <5 years in the household, caste, ethnic group, maternal education and smoking; potential confounding factors included trimester and season, both included in the model as time-varying covariates. Univariate and multivariate Cox regression analyses were performed; variables with a univariate p-value ≤0.1 and potential confounding factors were considered for inclusion in the multivariate model. The role of socioeconomic status in hMPV risk was also assessed through an exploratory analysis of covariates including caste, mother's education and latrine type.

Because the majority of hMPV cases occurred over a 19-week period (09/2011-01/2012), the primary analysis was limited to this hMPV season. The season was defined as the period in which ≥1 hMPV+ swab was collected each consecutive week, with no intervening swab-free weeks. A sensitivity analysis including the entire surveillance period and controlling for hMPV season was also performed; in this analysis, hMPV season was included as a binary, time-varying covariate (hMPV season vs. not hMPV season).

Aim 2. HMPV symptoms among pregnant and postpartum women were assessed using weekly surveillance visits. Any symptoms separated from the positive swab by one symptom-free week were excluded; these symptoms were considered to be part of a separate illness episode.

To assess differential severity of infection between pregnant vs. postpartum participants, a 1-point score was assigned to each of the following symptoms: fever,

cough, sore throat, rhinorrhea/nasal congestion, myalgia; this methodology has been used in previously published research [16-18,26]. Proportion of women experiencing each individual symptom was also assessed between pregnant vs. postpartum women using a chi^2 statistic. A Wilcoxon rank-sum test was used to compare the severity score between pregnant and postpartum women and to compare the total days with symptoms between the two groups. To assess whether illness was more severe during later stages of pregnancy, the aforementioned analyses were also conducted comparing women in their second trimester with women in their third trimester.

All analyses were performed using Stata version 13.1 (Stata Corp., College Station, Texas, USA).

Results

From 04/2011 to 09/2013, 3693 eligible women were enrolled in the study; weekly surveillance visits continued through 05/2014. Median overall follow-up time from enrollment through the end of postpartum surveillance was 52 weeks (IQR 46-57). Among cases, median follow-up time was 51 weeks (IQR 45-56); among non-cases, median follow-up time was 52 weeks (IQR 46-57).

During this three-year period, 56 women had an hMPV illness episode; no repeat infections occurred.

Among pregnant women, mean gestation at time of infection was 32.0 weeks. Median age at enrollment was similar among cases and non-cases, at 22.0 (IQR 19.0-20.0) and 23.0 (IQR 20.0-26.0) years, respectively (Table 1). Members of the Pahadi ethnic group comprised the majority of both cases and non-cases (58.2% among

hMPV+ women, 56.7% among hMPV- women) (Table 1). Among cases, 16.7% were of the upper-class Brahmin and Chhetri castes, while 18.5% were of the lower-class Shudra caste. Among non-cases, 23.4% were Brahmin or Chhetri while 13.0% were Shudra (Table 1). Median household density was 4.0 people/room (IQR 2.3-6.0) among cases and 3.0 people/room (IQR 2.0-5.0) among non-cases; median number of children <5 in the household was 1.0 among both cases (IQR 1.0-2.0) and non-cases (IQR 0-2.0) (Table 1). Median education duration was 0 years (IQR 0-8.0) among cases and 5 years (IQR 0-10.0) among non-cases; 52.9% of cases and 60.3% of non-cases were literate (Table 1). Three (5.4%) of cases and 108 (3.1%) of non-cases had smoked in the 30 days prior to enrollment (Table 1).

Aim 1: A total of 832 nasal swabs were collected from 636 women over 3596.7 person-years of follow-up. The overall incidence of hMPV in the study sample was 15 cases/1000 person-years; this represents 26 cases (1.3% incidence) among pregnant women and 30 cases (1.8% incidence) among postpartum women (Table 2). Among 832 nasal swabs collected, 56 (6.7%) were hMPV+ (Table 2).

In univariate analysis limited to hMPV season, no covariates were significantly associated with hMPV infection, although household density neared the threshold of p=0.1, with a HR of 1.05 (95% CI 0.98-1.12, p=0.19) (Table 3). In univariate analysis of the entire study period, maternal education duration was significantly associated with hMPV risk, with additional years of education associated with decreased risk (HR 0.93, 95% CI 0.87-0.99, p=0.02) (Table 3). Brahmin/Chhetri vs. Shudra neared the threshold of p=0.1 (HR 2.07, 95% CI 0.84-5.10, p=0.11 for Shudra when compared to Brahmin/Chhetri), but no other caste

reached this level of significance (Table 3). In multivariate analysis controlling for trimester and season, the HR for education duration remained significant at 0.93 (95% CI 0.87-0.99, p=0.02) (Table 4).

In the exploratory analyses of the role of socioeconomic status indicators in hMPV risk, the HR and 95% CI for mother's education remained constant, when caste was added to the model, while HRs for caste shifted considerably from the univariate estimate (Table 5). To In analysis of latrine presence and hMPV risk, women in households with no latrine had a HR of 0.44 (95% CI 0.23-0.83) when compared with women in households with latrines (Table 5).

Aim 2. The most common symptom among participants with hMPV infection was cough (64.3%), followed by myalgia (60.7%); all cases had fever, as this symptom was required for a mid-nasal swab to be taken (Table 6). No significant difference in the presence of any individual symptom was observed between pregnant and postpartum women. While a larger proportion of pregnant women appeared to have rhinorrhea/nasal congestion compared with postpartum women (65.4% and 43.3%, respectively), this difference was not significant (p=0.10) (Table 6). Median severity score was 3.5 points (IQR 2.0-4.0) among pregnant women and 3.0 points (IQR 2.0-4.0) among postpartum women (p=0.45) (Table 6).

Median duration of symptoms overall was 5.0 days (IQR 3.0-14.0). Median duration was significantly longer among pregnant vs. postpartum women, 6.5 days (IQR 4.0-23.0) vs. 4.5 (IQR 3.0-10.0) (p = 0.02) (Table 6). However, the duration of fever did not vary significantly between the groups, with a median duration of 3.0 days (IQR 2.0-4.0) among pregnant women and 2.0 days (IQR 2.0-4.0) among

postpartum women (p=0.31)(Table 6). While the duration of cough did not differ significantly between pregnant and postpartum women, women in their third trimester experienced significantly longer cough compared with women in their second trimester, with median duration of 4.5 days (IQR 1.0-6.0) and 0 days (IQR 0-2.5) respectively (p=0.02).

Among women with hMPV, median CT value was 36.9 (IQR 35.6-38.3); CT values were similar among pregnant and postpartum women (Table 6). Twenty-two (39.3%) women experienced coinfections; rhinovirus was the most common (23.2%), followed by coronavirus (8.9%) and parainfluenza (5.4%). One pregnant woman was coinfected with both rhinovirus and coronavirus.

Eighteen pregnant women (72.0%) and 21 postpartum women (70.0%) received medical care during the period of their hMPV+ illness episode; the most common types of care received by pregnant or postpartum women included visits to a medicine shop or local doctor, visits to a community health volunteer or sub health post, or visits to a primary care clinic. One pregnant woman (4.6%) and two postpartum women (6.3%) visited the hospital during the period of their hMPV illness episode; no participants died due to hMPV.

Discussion

In our study, hMPV was an important cause of symptomatic febrile respiratory illness among pregnant and postpartum women in a study using active-home based surveillance in rural Nepal. HMPV was found to be highly seasonal, with the virus detected largely between the months of September 2011 through January 2012 over three seasons. Higher levels of maternal education were associated with

lower likelihood of infection. Household density was not found to be associated with increased risk of infection.

While previous estimates of adult hMPV incidence range from 15 to 53/1000 person-years [9-14], accurate estimates of hMPV incidence are difficult to obtain; many individuals with hMPV infections do not present for care, and among those who do, many are not tested for viral infections [14]. The proportion of respiratory swabs positive for hMPV (6.7%) aligned with the Walsh et al. study, which found that hMPV infections in adults ranged from 3.0-7.1% of total respiratory infections during four consecutive winters [27]. The proportion documented in this cohort was higher than the 4.5% documented by Falsey et al. [9] and the 2.6% documented by Widmer et al. [12], but lower than the 8.3% documented by Zimmerman et al. [11]. However, these studies focused on medically attended respiratory infections, rather than infections identified through household surveillance.

The seasonality demonstrated by this study (September 2011-January 2012) is somewhat earlier than the seasonality documented in other settings, which found that most cases occurred in January through April [7,9,14,18,28-31]. While the majority of this research occurred in temperate climate zones (United States, Austria, Germany), one study took place in New Delhi, India, which shares Nepal's subtropical climate. However, the New Delhi study focused on hospitalized children rather than adults, with the majority of infections occurring prior to 24 months of age [31]. The presence of only one hMPV season over the three-year study period suggests that hMPV may be cyclical in nature in this setting; this cyclic pattern has been documented in previous research [30,32].

While no risk factor for hMPV infection was found to be significant in the analysis limited to hMPV season, this may have been due to insufficient statistical power; by limiting the analysis to this 19-week period, only 46 of the 56 total hMPV cases were included. In analyses encompassing the entire study period, the primary risk factor for hMPV infection was maternal education duration, with additional years of education associated with decreased risk. Education is routinely included in analyses as a proxy for socioeconomic status. Women's education not only impacts the socioeconomic status of the family (increasing household resources), but is also a contributor to sustained economic development of the geographic area [33]. Education is a risk factor for individual-level health outcomes [34], and mother's education is a risk factor for her children's health outcomes, including respiratory virus morbidity and mortality [35,36]. The HR for mother's education did not change when caste was added to the multivariate exploratory model, suggesting that caste was not a confounder in the relationship between mother's education and hMPV risk.

The hypothesis that socioeconomic status may be a factor in hMPV risk is supported by the exploratory analysis of latrine presence and hMPV risk, which found that women in households with latrines (particularly more advanced brick and cement/mud latrines) were at reduced risk for hMPV compared to those with no latrines in the household. While the presence of a latrine is not believed to play a direct role in hMPV risk, access to infrastructure including improved sanitation facilities is sometimes used as a proxy for socioeconomic status, and thus might indicate that women with higher socioeconomic status or greater access to

infrastructure may experience lower hMPV risk [37].

Pregnant and postpartum women were both symptomatic with hMPV infection. However, pregnant women did experience 45% longer symptom duration when compared to postpartum women. Increased symptom duration during pregnancy may also be related to decreased cardiopulmonary reserve, particularly in the third trimester. Indeed, women in their third trimester experienced longer duration of cough compared with women in their second trimester.

Because of the construct of our study, afebrile or asymptomatic hMPV illness episodes were not detected. However, it is known that adults with respiratory viruses are often afebrile. Thus the true incidence of hMPV in pregnancy is likely much higher. Definitions of hMPV disease vary across studies, limiting the ability to directly compare this thesis's findings to other studies [18-20]. While clinic visits are sometimes used as a surrogate for illness severity or a component in severity score calculations, in this area of the country clinic visits are heavily confounded by factors such as location and socioeconomic status, so they were not included as a factor in severity score calculation. This also limited our ability to assess whether lower respiratory complications, such as bronchiolitis or pneumonia, varied between pregnant and postpartum women. Future research should investigate lower respiratory complications and longer-term sequelae of hMPV in pregnant and postpartum women.

This study has several limitations. First, the study was confined to one rural district, which may have limited the variation in risk factors such as caste and education, and may compromise the generalizability to other areas of Nepal and

worldwide. However, few studies of hMPV risk factors and clinical presentation have been conducted in resource-limited settings. This is important because the presentation and clinical outcomes of disease may differ in regions of the world with high rates of household density, malnutrition, and indoor air pollution.

An additional limitation relates to the study's geography. Within the study area, location of the household was not addressed in this analysis; if household location was correlated with risk factors such as education/socioeconomic status, and if hMPV infection occurred in clusters, location may confound the relationship between risk factors and infection.

To our knowledge, this is the first study to describe the risk factors and clinical outcomes associated with hMPV in pregnant and postpartum women. The knowledge that symptomatic infection may last longer among pregnant women may help providers to make decisions about their care. Furthermore, to our knowledge this the first study to assess hMPV in a large prospective study using active home-based surveillance in a rural south Asian setting; this is of particular importance due to the shortfalls in passive surveillance in this area. HMPV seasonality in Nepal may not follow patterns observed in previous settings; prevention and control efforts should take this into account. Furthermore, as attempts to develop a vaccine, antibody or antiviral therapy for hMPV are currently underway, the identification of risk factors for infection and for severe disease is critical in order to identify groups that would benefit most from these advances, and to help develop targeted prevention strategies [17-19].

Tables and Figures

Table 1. Baseline demographic characteristics of pregnant and postpartum women with and without hMPV infection in Sarlahi, Nepal

Characteristic	hMPV+ N=56	hMPV- N=3637
Maternal age at enrollment, years	22.0 (19.0, 26.0)	23.0 (20.0, 26.0)
Maternal smoking, past 30 days	3 (5.4)	108 (3.1)
Ethnic group		
Pahadi	32 (58.2)	2007 (56.7)
Madeshi	23 (41.8)	1532 (43.3)
Caste		
Brahmin & Chhetri	9 (16.7)	824 (23.4)
Vaiysha	31 (57.4)	1958 (55.5)
Shudra	10 (18.5)	460 (13.0)
Muslim	4 (7.4)	287 (8.1)
Household size		
No. children <5 years	1.0 (1.0, 2.0)	1.0 (0.0, 2.0)
Density (people/room)	4.0 (2.3, 6.0)	3.0 (2.0, 5.0)
Maternal education duration, y	0.0 (0.0, 8.0)	5.0 (0.0, 10.0)
Maternal literacy	27 (52.9)	2033 (60.3)
Weeks gestation at infection*	32.0 (22.0, 36.0)	N/A
Delivered during hMPV season	18 (32.1)	642 (17.7)

*n=25
Data presented as median (IQR) or n(%)
Missing values not included in percentages

Table 2. Incidence of hMPV infection among pregnant and posptpartum women in Sarlahi, Nepal

Measure	Estimate
Incidence rate (total)	16/1000 person-years
Incidence rate (pregnant)	13/1000 person-years
Incidence rate (postpartum)	18/1000 person-years
Proportion of nasal swabs hMPV+	6.7% (56/832 swabs)

Table 3. Univariate hazard ratio (HR) estimates for hMPV infection among pregnant and postpartum women in Sarlahi, Nepal

Characteristic	hMPV season only*		All seasons	
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**
Household size				
Children ≤5 years	0.88 (0.69, 1.13)	0.32	0.97 (0.79, 1.19)	0.76
Household density (people/room)	1.05 (0.98, 1.12)	0.19	1.03 (0.96, 1.10)	0.38
Mother's education (continuous)	0.96 (0.90, 1.03)	0.25	**0.93 (0.87, 0.99)**	**0.02**
Mother's education (categorical)				
None	ref	ref	ref	ref
1-9 years	1.24 (0.63, 2.42)	0.53	0.93 (0.50, 1.72)	0.82
10+ years	0.57 (0.24, 1.36)	0.21	**0.39 (0.17, 0.89)**	**0.03**
Mother's Smoking	1.94 (0.60, 6.24)	0.27	1.65 (0.52, 5.29)	0.40
Caste				
Brahmin/Chhetri	ref		ref	
Vaiysha	1.23 (0.58, 2.62)	0.59	1.49 (0.71, 3.14)	0.29
Shudra	1.26 (0.45, 3.55)	0.66	2.07 (0.84, 5.10)	0.11
Muslim	1.05 (0.28, 3.88)	0.94	1.35 (0.42, 4.38)	0.62

*hMPV season defined as week 38, 2011 through week 5, 2012 (09/2011-01/2012)

Table 4. Multivariate analysis of the association between mother's education and hMPV infection, adjusted for trimester

Covariates included in model	hMPV season only*		All seasons	
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**
Mother's education, trimester, hMPV season				
Mother's education	0.96 (0.90, 1.03)	0.24	**0.93 (0.87, 0.99)**	**0.02**
2nd trimester	0.98 (0.44, 2.16)	0.95	0.87 (0.42, 1.82)	0.71
3rd trimester	1.03 (0.51, 2.08)	0.94	0.97 (0.51, 1.84)	0.92
Postpartum	ref	ref	ref	ref
hMPV season	N/A	N/A	1.83e+16	N/A

Table 5. Exploratory analysis of the association between socioeconomic status covariates and hMPV risk

Covariates included in model	hMPV season only*		All seasons	
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**
Mother's education, caste				
Mother's education	0.95 (0.87, 1.02)	0.18	**0.92 (0.85, 0.99)**	**0.03**
Brahmin/Chhetri	ref	ref	ref	ref
Vaiysha	0.82 (0.34, 1.99)	0.66	0.87 (0.37, 2.04)	0.75
Shudra	0.88 (0.27, 2.83)	0.83	1.07 (0.38, 3.06)	0.90
Muslim	0.67 (0.16, 2.85)	0.58	0.68 (0.18, 2.53)	0.57
Latrine (categorical)				
None	ref	ref	ref	ref
Brick & Cement/Mud	**0.37 (0.18, 0.76**	**0.007**	**0.36 (0.19, 0.68)**	**0.002**
Pit	0.99 (0.24, 4.14)	0.99	1.26 (0.39, 4.07)	0.70
Latrine (binary)	**0.44 (0.23, 0.83)**	**0.01**	**0.43 (0.24, 0.77)**	**0.005**

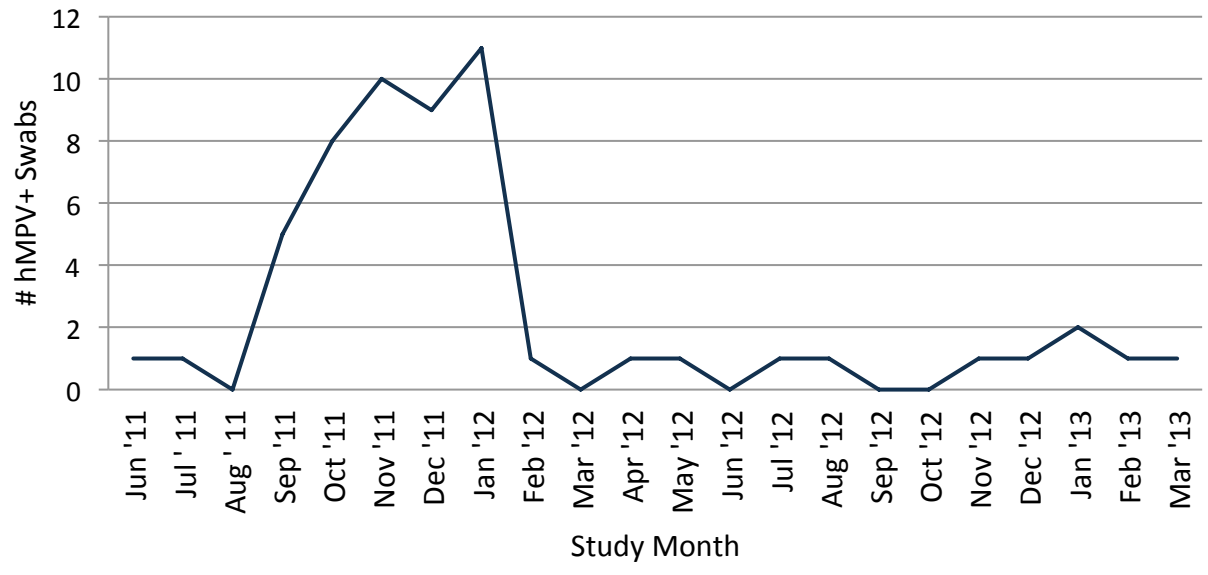
Table 6. Proportion of hMPV infections with selected symptoms and illness severity among pregnant and postpartum women

Measure	Total (%) N=56	Pregnant (%) N=26	Postpartum (%) N=30	p-value
Symptom				
Fever*	56 (100%)	26 (100%)	30 (100%)	n/a
Cough	36 (64.3%)	17 (65.4%)	19 (63.3%)	0.87
Sore throat	24 (42.8%)	11 (42.3%)	13 (43.3%)	0.83
Rhinorrhea /nasal congestion	30 (53.6%)	17 (65.4%)	13 (43.3%)	0.10
Myalgia	34 (60.7%)	16 (61.5%)	18 (60.0%)	0.91
Visit for care	39 (70.9%)	18 (72.0%)	21 (70.0%)	0.87
Severity Measure				
CT value	36.9 (35.6, 38.3)	36.7 (32.3, 38.0)	37.2 (36.1, 38.8)	0.15
Severity score	3.0 (2.0, 4.0)	3.5 (2.0, 4.0)	3.0 (2.0, 4.0)	0.45
Fever duration (days)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	2.0 (2.0, 4.0)	0.31
Cough duration (days)	2.0 (0.0, 5.0)	2.5 (0.0, 5.0)	2.0 (0.0, 5.0)	0.61
Symptom duration (days)	**5.0 (3.0, 14.0)**	**6.5 (4.0, 23.0)**	**4.5 (3.0, 10.0)**	**0.03**

Data presented as n (%) or median (IQR)

*Documented fever required for nasal swab collection

Figure 1. hMPV-positive swabs, by month



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