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Antenatal Respiratory Syncytial Virus and Human Metapneumovirus Illness Rates Among Pregnant Women in Thailand and the Association Between Antenatal Respiratory Syncytial Virus and Perinatal Outcomes: A Prospective Cohort Study

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Disclaimer.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US CDC, US Public Health Service, US Department of the Army, US Department of Defense, or the US Government. Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The investigators have adhered to the policies for protection of human subjects as prescribed in AR 70–25. US CDC–affiliated authors were involved in study design; data collection, analysis, and interpretation; report writing; and the decision to submit the manuscript for publication.

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Potential conflicts of interest.

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Abstract

Background. We estimated respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) illness incidences among pregnant women and examined the association between antenatal RSV illness and preterm birth and small-for-gestational-age (SGA) infant.

Methods. Pregnant women aged ≥ 18 years were contacted twice weekly until the end of pregnancy to identify illness episodes with ≥ 1 of the following: myalgia, cough, runny nose/nasal congestion, sore throat, or difficulty breathing. Midturbinate nasal swabs were collected and tested for RSV and hMPV by real-time reverse transcription polymerase chain reaction. Incidences were calculated. Cox proportional hazards regression was used to estimate hazard ratios (HRs) comparing participants with and without RSV illnesses for preterm birth (live birth before 37 weeks' gestation) and SGA infant.

Results. Among 2764 participants, the median age was 29 years (IQR, 24–34), and the median enrollment gestational age was 10 weeks (IQR, 7–14). Overall, 71 (3%) and 29 (1%) cases of RSV and hMPV illnesses were identified, respectively. Among these, 30 (42%) and 10 (34%) participants sought medical care. Incidence rates per 10 000 pregnant woman–months were 57 (95% CI, 44–72) for RSV illnesses and 23 (95% CI, 16–33) for hMPV illnesses. Antenatal RSV illness in the third trimester conferred an increased risk of preterm birth (adjusted HR, 2.50; 95% CI, 1.04–6.00) but not SGA infant (adjusted HR, 0.79; 95% CI, .29–2.16).

Conclusions. Antenatal RSV illness was associated with some adverse antenatal outcomes. Pregnant women had a 0.4%–0.7% risk of RSV illness per pregnancy month, of which one-third resulted in medical visits.

Keywords

hMPV; pregnancy; preterm; RSV; small-for-gestational-age

Respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) are known to cause severe illness in older adults and young children, but there are limited data on their impact during pregnancy. Understanding the burden of antenatal RSV and hMPV illnesses and the potential effects on perinatal outcomes is important for informing prevention strategies, including vaccine development. In August 2023, the Food and Drug Administration approved Abrysvo for pregnant women to prevent RSV-related lower respiratory tract disease in infants aged < 6 months through maternal antibody transfer [1, 2]. The US Advisory Committee for Immunization Practices recommends a single dose of Abrysvo for pregnant women at 32 to 36 weeks of gestation [3], although it is approved for use as early as 24 weeks in some countries [4]. For hMPV, vaccines are still in development, with no licensed vaccines available yet.

Data on antenatal RSV incidence are scarce [5], and available information suggests that it is usually mild but may lead to lost productivity and negative outcomes for pregnant women. A prior meta-analysis found associations between antenatal RSV illness and certain adverse perinatal outcomes [5]. This study used data from a prospective cohort in Thailand with surveillance for acute respiratory illness (ARI), employing broad case definition and midturbinate nasal swabs. We estimated RSV and hMPV incidences among pregnant women

over 2 respiratory viral seasons and examined whether antenatal RSV illness was associated with preterm birth and small-for-gestational-age (SGA) infants. The findings aim to expand evidence to inform prevention strategies in Thailand and other low- and middle-income countries regarding the use of RSV and hMPV vaccines during pregnancy.

METHODS

Setting and Study Design

This analysis included pregnant women from 2 hospitals in Thailand participating in the Pregnancy and Influenza Multinational Epidemiologic (PRIME) study, a cohort study conducted in 2017 and 2018 across India, Peru, and Thailand to estimate antenatal influenza illness incidence and its association with adverse perinatal outcomes [6]. In Thailand, the influenza season coincides with the circulation period of RSV and hMPV, providing an opportunity to study these viruses among pregnant women in the cohort [7, 8].

Pregnant women were enrolled from 10 weeks before the anticipated start of the influenza season through the first 4 weeks of the season. Eligibility criteria included being ≥ 18 years old, having an estimated delivery date that allowed for ≥ 8 weeks of observation during the influenza season, planning to deliver at study hospitals, and consenting to biweekly symptom surveillance throughout pregnancy [6]. At enrollment, participants who did not yet have an ultrasound received one for gestational age dating. All participants completed in-person structured interviews to gather demographic and baseline clinical data.

Study staff contacted participants twice weekly throughout their pregnancies to monitor for ARI, defined as the sudden onset or worsening of ≥ 1 symptom within the past 7 days (myalgia, cough, runny nose/congestion, sore throat, or difficulty breathing). Participants were encouraged to contact the study staff if they experienced ARI episodes between scheduled contacts. Symptomatic participants were asked to self-collect midturbinate nasal specimens for influenza virus testing. In Thailand, these specimens were also tested for RSV and hMPV. The performance of self-collection for the detection of respiratory viruses was validated [9]. Participants resumed symptom surveillance when illness resolved, defined as 48 hours without symptoms or ≥ 13 days after illness onset, whichever occurred first. Any new or worsening symptoms after resolution or ≥ 13 days following a previous illness were considered a new episode.

Neonatal birth weights were recorded by study-approved scales, as close to delivery as possible but no later than 48 hours afterward. Participants completed in-person interviews about pregnancy complications, prenatal care, and delivery/perinatal outcomes within 7 days of delivery. Medical records were reviewed to confirm prenatal care, pregnancy course, and delivery/perinatal outcomes.

Laboratory Testing

Midturbinate nasal specimens were tested for RNase P to assess quality and for RSV and hMPV by real-time reverse transcription polymerase chain reaction per the protocol of the US Centers for Disease Control and Prevention. Participants with respiratory symptoms

meeting the study case definition and testing positive for RSV or hMPV were classified as having RSV or hMPV illness, respectively.

Data Analysis

Characteristics and illnesses of fully enrolled study participants (those with ≥ 1 surveillance contact) were summarized as frequencies or medians. Incidences were calculated from enrollment to the end of pregnancy, focusing on episodes of antenatal RSV and hMPV illnesses.

The impact of antenatal RSV illness was assessed for preterm birth and SGA infants. Only fully enrolled participants with singleton pregnancies and live births were included. The effect of hMPV illness was not assessed due to a small sample size. Preterm birth was defined as a live birth at <37 weeks of gestation, determined by the earliest available ultrasound. The INTERGROWTH-21 Project Standards were used to assess SGA status [10]. Participants with influenza or hMPV illness were excluded from the analyses. Additionally, participants were excluded if they had RSV and hMPV coinfection ($n = 1$) or RSV followed by hMPV illness ($n = 1$).

Cox proportional hazards regression models were used to estimate hazard ratios for the 2 outcomes, comparing participants with antenatal RSV illness against those without RSV illness (reference group). The time scale began at enrollment and ended at 36 weeks' gestation for preterm birth analysis or at delivery for the SGA analysis. The exposure of interest was antenatal RSV illness, with participants considered to have had RSV exposure starting from the date of a positive midturbinate nasal swab result through the end of pregnancy. Associated 95% CIs were obtained by robust SEs. Data were analyzed in Stata version 16 (StataCorp). Two-tailed P values $<.05$ were considered statistically significant.

Ethical Approval

The study was approved by the institutional review boards (IRBs) of Abt Associates, Walter Reed Army Institute of Research, and the local ethical review committees. The US Centers for Disease Control and Prevention's IRB relied on the determination of Abt Associates' IRB. Written informed consent was obtained from all study participants.

RESULTS

Participants' Characteristics

Of 2764 fully enrolled participants (Supplementary Figure 1), 1230 were enrolled in 2017 and 1534 in 2018 (Supplementary Table 1). At enrollment, 75% were aged 20 to 35 years, and 24%, 62%, and 13% were in the first, second, and third trimesters, respectively, while 1% had missing trimester data. Overall, 11% self-reported chronic medical conditions, and 8% had preterm deliveries while 7% delivered SGA infants.

During follow-up, 3% had ≥ 1 episode of RSV illness, and 1% had hMPV illness. Among them, 1 participant had repeat RSV illness, 1 had RSV and hMPV during the same episode, and 1 had RSV followed by hMPV. A total of 71 RSV cases and 29 hMPV cases occurred (Supplementary Figure 2). Among RSV cases, 8% patients reported fever, 27% could not

complete daily activities, 42% sought medical care, and 1% were hospitalized (Table 1). The median RSV illness duration was 11 days. For hMPV cases, 21% had fever, 34% could not complete daily activities, 34% sought medical care, and none were hospitalized. The median hMPV illness duration was 10 days.

RSV and hMPV Incidences

Participants contributed 12 468 person-months of observation. RSV incidences were 47 per 10 000 person-months in 2017 (95% CI, 31–70) and 64 in 2018 (95% CI, 47–86; Table 2), with no significant difference between years ($P = .24$). Trimester-specific RSV incidences were 24.3 (first), 53.2 (second), and 61.8 (third) per 10 000 person-months, with no significant differences across trimesters ($P > .05$). For hMPV, the incidences were 40 per 10 000 person-months in 2017 (95% CI, 25–61) and 10 in 2018 (95% CI, 4–21), significantly higher in 2017 ($P < .01$). Trimester-specific hMPV incidences were 24.3 (first), 20.9 (second), and 25.0 (third) per 10 000 person-months, with no significant differences across trimesters ($P > .05$).

Association Between Antenatal RSV Illness and Perinatal Outcomes

In the RSV–preterm birth analysis, 192 (9%) participants had preterm deliveries, and 41 (2%) had RSV illnesses. Adjusting for maternal age, chronic heart conditions, gestational hypertension, and history of SGA infants, RSV illnesses in the third trimester were associated with preterm birth (adjusted hazard ratio [aHR], 2.50; 95% CI, 1.04–6.00; $P = .04$). No significant effect was observed in the second trimester (aHR, 2.01; 95% CI, .70–5.72; $P = .193$), and first trimester data were too limited for analysis. In the RSV–SGA analysis, 193 (9%) participants delivered SGA infants, and 51 (2%) had RSV illnesses. No significant difference in the likelihood of delivering an SGA infant was found between those with and without RSV illnesses (aHR, 0.79; 95% CI, .29–2.16; $P = .64$).

DISCUSSION

Among >2700 cohort women, antenatal RSV illness was associated with an increased risk of preterm birth but not SGA in term singleton pregnancies. Pregnant women had a 0.4%–0.7% monthly risk of RSV illness and 0.2%–0.3% risk of hMPV illness. Although most RSV and hMPV illnesses were mild, over a third of affected women sought medical care. With 130 to 140 million global births annually, these relatively low rates could impose a significant burden on public health systems, if care seeking patterns are similar in other low- and middle-income countries.

Few studies reported on antenatal RSV and hMPV illness incidences, largely due to limited clinical testing, emphasizing the need for more surveillance. We used data from a multinational influenza cohort study in Thailand to estimate RSV and hMPV incidences, where these viruses cocirculate. Our incidence estimates for RSV and hMPV align with existing research (10–133 per 10 000 person-months for RSV and 7–13 per 10 000 person-months for hMPV) [11–13]. This and other studies show that antenatal RSV and hMPV incidences vary by season and geography, as expected for respiratory viruses.

During certain seasons, antenatal RSV and hMPV illness incidence may be comparable to antenatal influenza rates, particularly when influenza circulation is lower than usual. For instance, influenza illness incidence was 37 per 10 000 person-months in Thailand and 42 per 10 000 person-months across all 3 countries in 2018 [6]. While RSV and hMPV illnesses were mostly mild, they were often linked to lost productivity, including disruption of daily activities and the need for outpatient medical care.

Although data on antenatal RSV and hMPV incidences are limited, even fewer studies examined their impact on pregnancy and perinatal outcomes. Assessing the association between respiratory viral illnesses and outcomes requires careful data collection to minimize bias. Previous research on RSV and pregnancy outcomes has shown mixed results. For example, Chu et al found a trend toward preterm birth among pregnant women with RSV illnesses [14], while Madhi et al found no association [11]. A recent meta-analysis, which included data from this study, suggested an association between antenatal RSV and preterm birth [5]. Our study expands on this by reporting the effect of antenatal RSV on preterm birth.

This study was a single-country analysis over 2 respiratory viral seasons. However, the findings suggest that further research is needed to explore the association between RSV (and other non-influenza respiratory viral illnesses) and adverse perinatal outcomes. Additionally, these data could inform cost analysis for RSV vaccination, considering potential savings from preventing respiratory illnesses and complications such as adverse birth outcomes. Maternal RSV vaccination currently focuses on late pregnancy to optimize antibody transfer for infant protection, not to prevent antenatal RSV. If other studies confirm an association between antenatal RSV and adverse perinatal outcomes, this could inform optimal timing for vaccination strategies.

This analysis has several strengths, including the use of prospective active ARI surveillance with systematic molecular testing for RSV and hMPV among pregnant women during 2 seasons, as well as standardized measurement of gestational age at birth and birth weight. We employed a broad study case definition, prompting respiratory specimen collection from participants with illness symptoms consistent with these infections. Our sample size was, however, insufficient to examine the association between RSV or hMPV illness and pregnancy loss, a rare but significant outcome. The prospective cohort design likely identified mostly mild ARI, not severe cases with higher potential for adverse birth outcomes [15]. Finally, this single-country study conducted over 2 seasons may not be generalizable to pregnant women in other settings, highlighting the need for further research on the burden and impact of RSV and hMPV in this population.

This study found that antenatal RSV illness was associated with preterm birth but not to SGA infants. Incidences of RSV and hMPV were comparable to previously published influenza incidences from the same and a larger multinational cohort during seasons with lower influenza circulation. These findings may help assess the costs and potential impact of RSV and hMPV prevention strategies in pregnant women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1. Illness Characteristics Among Participants Who Had ≥ 1 Surveillance Contact, Reported Symptoms Meeting the Study Case Definition, and Tested Positive for RSV or hMPV: Pregnancy and Influenza Multinational Epidemiologic Study, Thailand (N = 2764)

	RSV			hMPV		
	2017	2018	2017 and 2018	2017	2018	2017 and 2018
No. of illness episodes ^a						
No.	26	45	71	22	7	29
% ^b	2	3	3	2	0	1
Had body temperature $>100.4^{\circ}\text{F}$						
No.	1	5	6	5	1	6
% ^c	4	11	8	23	14	21
Stopped routine daily activities						
No.	8	11	19	10	0	10
% ^c	31	24	27	45	0	34
Sought medical care						
No.	10	20	30	9	1	10
% ^c	38	44	42	41	14	34
Hospitalized						
No.	0	1	1	0	0	0
% ^c	0	2	1	0	0	0
Illness duration, days						
Median	11	9	11	11	9	10
IQR	7–13	7–13	7–13	9–13	7–11	8–13

The study case definition was new onset or sudden worsening of ≥ 1 of the following symptoms within the past 7 days: myalgia, cough, runny nose or nasal congestion, sore throat, or difficulty breathing.

Abbreviations: hMPV, human metapneumovirus; RSV, respiratory syncytial virus.

^a Infection was confirmed by real-time reverse transcription polymerase chain reaction. For the purpose of this study, participants who reported respiratory symptoms that met the study case definition and tested positive for RSV or hMPV were considered to have RSV or hMPV illness (ie, the identified virus was assumed to be the cause of their illnesses).

^b The denominator was the number of participants who had ≥ 1 surveillance contact.

^c The denominator was the number of illness episodes.

Table 2. Incidence Rates of RSV and hMPV Illnesses per 10 000 Pregnant Person-Months Among Participants Who Had ≥ 1 Surveillance Contact: Pregnancy and Influenza Multinational Epidemiologic Study, Thailand (N = 2764)

Pathogen ^a : Study Year	No. of Illness Episodes	Person-Months	Incidence	95% CI	
				Lower Bound	Upper Bound
RSV					
2017	26	5473	47	31	70
2018	45	6994	64	47	86
2017 and 2018	71	12 468	57	44	72
hMPV					
2017	22	5473	40	25	61
2018	7	6994	10	4	21
2017 and 2018	29	12 468	23	16	33

Abbreviations: hMPV, human metapneumovirus; RSV, respiratory syncytial virus.

^aInfection was confirmed by real-time reverse transcription polymerase chain reaction. For the purpose of this study, participants who reported respiratory symptoms that met the study case definition—specifically, new onset or sudden worsening of ≥ 1 of the following symptoms: myalgia, cough, runny nose or nasal congestion, sore throat, and/or difficulty breathing within the past 7 days—and who tested positive for RSV or hMPV were considered to have RSV or hMPV illness (ie, the identified virus was assumed to be the cause of their illnesses).