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A Cross-sectional Surveillance Study of the Frequency and Etiology of Acute Respiratory Illness Among Pregnant Women

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(See the Editorial commentary by Englund and Chu, on pages 512–5.)

Background. Other than influenza, little is known about the consequences of viral acute respiratory illness (ARI) on pregnant women and fetuses. Our objectives were to determine the frequency of ARI due to respiratory viruses and the associated clinical outcomes during pregnancy.

Methods. Pregnant women in their second or third trimester were enrolled if they reported having symptoms of ARI or were healthy within the preceding 2 weeks. Nasopharyngeal secretions were evaluated for respiratory viruses by molecular diagnostic assays. Clinical outcomes were evaluated at enrollment and via a follow-up telephone-based questionnaire 2 weeks later.

Results. There were 155 pregnant participants, with 81 ARI cases and 91 healthy controls. Acute lower respiratory tract illness (ALRTI) was identified in 29 cases (36%). Human rhinovirus (HRV), respiratory syncytial virus (RSV), and influenza virus accounted for 75% of virus-positive cases of ALRTI. Cases with ALRTI often reported a longer duration of illness, history of allergies, symptoms of wheezing, shortness of breath, or chest pain, and use of prescription medication. Two cases with ALRTI reported decreased fetal movement; a third case with ALRTI was hospitalized.

Conclusions. In over one third of ARI cases, participants had symptoms consistent with ALRTI. Infection with HRV, RSV, or influenza virus was commonly detected in patients with ALRTI. Viral ALRTI during pregnancy appears to be common and is associated with significant morbidity.

Keywords. Maternal respiratory viral infection; respiratory tract infection; maternal vaccination; respiratory syncytial virus; influenza; rhinovirus.

Respiratory viruses are a major cause of morbidity and mortality worldwide [1]. Persons at risk for severe acute respiratory illness (ARI) include young children and older adults, presence of comorbid conditions, poor nutrition, exposure to environmental pollutants, low access to healthcare services, and impoverished circumstance [2–4]. Less well documented is the impact of respiratory viruses during pregnancy.

Pneumonia is an important cause of morbidity and mortality in pregnant women [5]. The incidence of pneumonia is 1.5 cases per 1000 pregnancies [6]. The physiologic and immunologic changes that occur during pregnancy make pregnant women at increased risk for serious viral respiratory illness [7]. The consequences of pneumonia include risk to the mother's health, including death and pregnancy-related complications [8], and risk to the infant's health, such as premature birth and small size for gestational age [6, 8]. In pregnant women, pneumonia is more likely to be diagnosed in those with comorbidities or recent respiratory tract infections [8].

ARI and pneumonia may be the result of infection with viruses and/or bacteria. In a recent review, the consequences of influenza virus infection during the first, second, and third trimesters of pregnancy were well documented [9]. The clinical significance of infection with respiratory viruses other than influenza virus during pregnancy is limited. Only recently was respiratory syncytial virus infection shown to result in severe respiratory disease and hospitalization, as reported by a case-series study [10]. In addition, human metapneumovirus (HMPV) infection and febrile human rhinovirus (HRV) infection in mothers have been associated with infants that are small for gestational age and infants with a low birth weight, respectively [11, 12].

In this single-site study, we enrolled both healthy pregnant women and those with symptoms of an ARI during their regular prenatal and sick visits, to better understand the frequency

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and clinical outcomes of infection with respiratory viruses during the second and third trimesters of pregnancy.

METHODS

Patient Enrollment

Patients were enrolled at an outpatient obstetric (for routine and high-risk obstetric care) and gynecologic clinic in the Houston, Texas, area between 1 October and 10 May to coincide with the 2015–2016 respiratory virus season. Pregnant women in their second trimester (13–27 weeks of gestation) or third trimester (>27 weeks of gestation) of pregnancy were enrolled as cases if they reported having symptoms of ARI (rhinorrhea, sore throat, cough, shortness of breath, or wheezing) at the time of or ≤7 days before their clinic visit. Healthy pregnant women in their second or third trimester were enrolled as healthy controls if they reported no signs of illness during the 2 weeks before their clinic visit. Women were allowed to reenroll in the study; cases could reenroll if they became ill again or were healthy at a subsequent clinic visit, and healthy controls were allowed to reenroll if they developed symptoms of ARI later in the respiratory season.

After obtaining written informed consent, a questionnaire was used to record demographic characteristics, current obstetric history, recent vaccination history, past medical history, and current respiratory and nonrespiratory symptoms. Nasopharyngeal secretions were obtained from both the case and healthy control groups by a combined throat and nasal swab and evaluated for respiratory viruses by real-time reverse transcription–polymerase chain reaction (RT-PCR). Clinical outcomes, prescription and over-the-counter medication use, and complications of ARI illness were obtained by telephone interview, using a standardized form for telephone-based collection of illness data, 2 weeks after the initial visit for both healthy women and those with ARI.

Ethical Review

This study was approved by the Institutional Review Board of Baylor College of Medicine. The objectives of the study were introduced by the women's obstetrician and explained by the study staff, and written informed consent was provided by the pregnant women before study participation.

Inclusion Criteria

Women who were in their second or third trimester of pregnancy, were aged ≥18 years, were otherwise healthy, were available to complete a follow-up questionnaire by telephone 2 weeks after enrollment, and provided written informed consent were eligible for the study. Those with symptoms of ARI were enrolled as cases, and those who were healthy during the previous 2 weeks were enrolled as healthy controls.

Exclusion Criteria

Excluded were pregnant women who were in their first trimester of pregnancy, were aged <18 years, received blood or blood products ≤3 months before enrollment, required use of oral steroids or other immunosuppressant or immunomodulatory therapy for a chronic health condition (eg, chronic inflammatory bowel disease, chronic renal disease, chronic heart disease, chronic liver disease, chronic lung disease, systemic lupus erythematosus, rheumatoid arthritis, and other connective tissue diseases), had another chronic health condition (ie, heart or liver disease), were infected with human immunodeficiency virus, or had a primary immunodeficiency. Not excluded were women with asthma treated with inhaled steroid therapy or women with thyroid disease.

Case Definitions

All signs and symptoms were self-reported by the patient as having occurred at the time of or ≤7 days before enrollment. Included were signs and symptoms related to an ARI, gastrointestinal illness (ie, vomiting or diarrhea), pregnancy-related complications (ie, vaginal bleeding, ruptured membranes, decreased fetal movement, and preterm labor), self-reported fever, decreased activity, loss of appetite, and chest pain. Acute upper respiratory tract illness (AURTI) was defined as the presence of any of the following: rhinorrhea, sore throat, or cough. Acute lower respiratory tract illness (ALRTI) was defined as the presence of any of the following: difficulty breathing or shortness of breath, wheezing, or cyanosis.

RNA Extraction and Real-Time RT-PCR

All real-time RT-PCR assays were 1-step, singleplex assays performed as previously described in a Clinical Laboratory Improvement Amendments of 1988 (CLIA)–certified respiratory virus diagnostic laboratory (CLIA identifier 45D0919666) to detect genomic material of the following respiratory pathogens: RSV A and B; HRV; influenza virus types A and B; human coronaviruses (HCoVs) NL-63, HKU1, OC43, and 229E; parainfluenza virus (PIV) types 1, 2, and 3; HMPV; adenovirus; bocavirus; *Mycoplasma pneumoniae*; and *Bordetella pertussis* [13, 14].

Statistical Analyses

Sample size was estimated on the basis of a reported frequency of community-acquired RSV ARI of 5%–15% among adults. To show a 5% difference in the frequency of RSV ARI between RSV-infected pregnant women and healthy pregnant women at a power of 80% and an α of 0.05, 150 or 71 subjects per group were required for 5% or 10% frequency of RSV infection, respectively. Frequencies of demographic and clinical data, as well as PCR findings, were determined for ARI and healthy control groups. The χ^2 or Fisher exact test was performed to compare frequency distributions between groups. To compare mean or median values of continuous demographic and clinical data between groups, an independent *t* test or Kruskal-Wallis test was conducted. The results of the statistical tests are reported as *P* values. All statistical analyses were performed using Stata software, version 14.2 [15].

RESULTS

Comparison of ARI Cases and Healthy Controls

A total of 155 pregnant women were enrolled during the 7-month season of respiratory virus illness, from 1 October through 10 May. During that interval the obstetric practice saw an estimated 500 women in their second or third trimester of pregnancy. At the initial enrollment, 65 and 90 pregnant women were enrolled as cases and healthy controls, respectively (Supplementary Figure 1). Twelve healthy controls had ARI and were enrolled a second time, as cases; and 1 case was enrolled again, as a healthy control. Two cases were enrolled as cases 2 more times each. For this reason, there were 172 unique events, of which 81 involved cases and 91 involved healthy controls.

When comparing demographic characteristics and medical history, information provided upon the first enrollment visit was used. Data for all demographic variables were comparable between the 2 groups (Table 1). Data collected on medical history of the current pregnancy were also comparable between cases and healthy controls (Table 2). Seasonal influenza vaccination was reported by less than half of women, while vaccination with the tetanus, diphtheria, and acellular pertussis vaccine(Tdap) was reported by approximately 10%. Complications reported during the current pregnancy were similar for cases and healthy controls, with the most common being placental complications (including subchorionic hemorrhage, polyhydramnios, and placenta previa), urinary tract infection, and diabetes.

Comparison of the AURTI and ALRTI Groups

Cases were classified as AURTI or ALRTI (Table 3). One case not included in Table 3 met neither case definition, reporting fever and malaise without respiratory symptoms. Overall, AURTI was more common (64% of cases) than ALRTI (36% of cases). The median time from onset of symptoms to study enrollment was similar for both case groups, but cases with ALRTI reported a longer duration of illness (16 vs 13 days), although it was not significantly different. Major presentation for AURTI included rhinorrhea (86% of cases with AURTI), sore throat (78%), and cough (76%). For ALRTI, presentation included rhinorrhea (90% of cases with ALRTI), difficulty breathing or shortness of breath (83%), cough (83%), sore throat (72%), chest pain (41%), and wheezing (41%). Of cases with ALRTI, 97% also reported at least 1 symptom of AURTI. Decreased activity was significantly associated with ALRTI (P = .04). Fever, vaginal bleeding, and fetal distress were all infrequent and comparable in frequency for both ARI groups. The detection of a respiratory pathogen by real-time RT-PCR was similar among cases with AURTI (67%) and cases with ALRTI (59%).

Viral Etiology of ARI

For this analysis, each case or healthy control enrollment was treated as a unique event. Among 81 cases, 52 respiratory pathogens were detected, with HRV, HCoV, and RSV being the most common (Table 4). A single coinfection with RSV/A and HRV was detected in the ARI group. Ten respiratory viruses were detected among 91 healthy controls, with HRV being the most common. HRV, HCoV, and RSV were detected significantly more frequently in cases.

Table 1. Demographic Characteristics and Medical History at Initial Enrollment Among Pregnant Women With (Cases) and Those Without (Controls) Acute Respiratory Illness

Medical History	Cases (n = 65)	Controls (n = 90)	*P*
Age, y, mean ± SD	31 ± 5	30 ± 5	.22
Gestational age of fetus, wk	27 (14)	28 (9)	.98
Weight, kg	73 (27)	69 (24)	.46
Height, cm	160 (10)	163 (10)	.63
Race			.58
White	51 (78)	65 (72)	
Black	6 (9)	13 (14)	
Asian	7 (11)	8 (9)	
Other	1 (2)	4 (4)	
Hispanic or Latino	26 (40)	33 (37)	.67
Asthma	5 (8)	5 (6)	.74
Allergies	30 (46)	42 (47)	.95
Comorbidities[a]			
Any	9 (14)	21 (23)	.14
Thyroid disease	4	10	
Diabetes	1	4	
Chronic lung disease	0	0	
Chronic heart disease	0	1	
Chronic IBD	2	2	
Chronic liver disease	0	1	
Neuromuscular disease	1	4	
Other chronic disease	4	1	
Pregnancies, no.	2 (1)	2 (2)	.76
Births, no.	1 (0)	1 (2)	.98
Abortions, no.	0 (1)	0 (1)	.32
Complications in past pregnancies[b]			
Any	26 (53)	25 (40)	.16
Diabetes	4	4	
Hypertension	6	6	
Hypothyroidism	3	1	
Gallstones	1	1	
Urinary tract infection	1	1	
Hematologic	1	2	
Placental	1	4	
Fetal distress	2	1	
Preterm labor	3	3	
Fetal demise	2	1	
Spontaneous abortion or miscarriage	2	3	
Chromosomal anomaly	3	0	
Emergent cesarean section	3	4	
Other	0	0	

Data are no. or no. (%) of participants or median value (interquartile range), unless otherwise indicated.

Abbreviation: IBD, inflammatory bowel disease.

[a]Five women (3 cases and 2 controls) had 2 comorbidities.

[b]One hundred twelve women (49 cases and 63 controls) had prior pregnancies. Eleven women (6 cases and 5 controls) had >1 complication in a prior pregnancy.

Table 2. Current Pregnancy–Associated Medical History at Initial Enrollment Among Pregnant Women With (Cases) and Those Without (Controls) Acute Respiratory Illness

Medical History	Cases (n = 65)	Controls (n = 90)	*P*
Received prenatal vitamins	63 (97)	85 (94)	.70
Received influenza vaccine	24 (37)	41 (46)	.29
Received Tdap	6 (9)	10 (11)	.70
Prior sinus infection	3 (5)	7 (8)	.52
Prior acute upper respiratory tract illness	26 (40)	39 (43)	.69
Prior cough	20 (31)	28 (31)	.96
Prior pneumonia	2 (3)	0	.17
Complications during current pregnancy[a]			
Any	11 (17)	24 (27)	.15
Diabetes	1	3	
Hypertension	0	2	
Hypothyroidism	1	2	
Gallstones	1	1	
Urinary tract infection	2	2	
Hematologic	1	2	
Placental	4	4	
Fetal distress	0	1	
Preterm labor	1	1	
Chromosomal anomaly	0	1	
Other	2	8	

Data are no. or no. (%) of participants.

Abbreviation: Tdap, tetanus, diphtheria, and acellular pertussis vaccine.

[a]Four women (2 cases and 2 controls) had >1 complication.

The relationship between respiratory pathogen and type of respiratory illness was examined in cases (Figure 1). The most common pathogens detected in AURTI cases, with or without fever, were HRV and HCoV. In addition, HRV was the most common pathogen detected among cases without fever in the ALRTI group. Of 7 cases with fever in the ALRTI group, 3 were positive for influenza virus, 3 were positive for RSV (1 had HRV coinfection), and 1 was positive for HRV. Of 4 cases with detectable influenza virus, 2 had received seasonal influenza vaccine, with AURTI in one and ALRTI in the other. Of cases in whom no respiratory pathogen was detected, 17 had AURTI, and 12 had ALRTI.

Allergies as a Potential Risk Factor for ALRTI

Cases were stratified into those with and those without a history of allergies, to determine whether bias of noninfectious causes of ARI could be identified between the 2 groups (Table 5). Detection of a respiratory pathogen occurred in approximately two thirds of cases, independent of history of allergies. Lower respiratory tract symptoms were more frequently observed among those with (46%) than among those without (28%) a history of allergies, but the difference was not significant. A history of asthma was similarly infrequent for both groups.

Table 3. Signs and Symptoms at Enrollment Among Pregnant Women With Acute Respiratory Illness (ARI), by ARI Classification

Sign or Symptom	AURTI (n = 51)	ALRTI (n = 29)	Overall (n = 80[a])	*P*
Duration of illness, d[b]	13 (8)	16 (9)	14 (10)	.09
Time to enrollment, d	5 (7)	6 (7)	5 (7)	.29
Congestion or rhinorrhea	44 (86)	26 (90)	70 (88)	.74
Sore throat	40 (78)	21 (72)	61 (76)	.54
Cough	39 (76)	24 (83)	63 (79)	.58
Difficulty breathing or shortness of breath	0	24 (83)	24 (30)	<.01
Wheezing	0	12 (41)	12 (15)	<.01
History of fever	7 (14)	7 (24)	14 (18)	.24
Gastrointestinal symptoms	8 (16)	9 (31)	17 (21)	.11
Chest pain	6 (12)	12 (41)	18 (23)	<.01
Loss of appetite	17 (33)	15 (52)	32 (40)	.11
Decreased activity	27 (53)	22 (76)	49 (61)	.04
Pregnancy-related symptoms	1 (2)	2 (7)	3 (4)	.30
Positive respiratory pathogen	34 (67)	17 (59)	51 (64)	.47

Data are no. (%) of cases or median value (interquartile range).

Abbreviations: ALRTI, acute lower respiratory tract illness; AURTI, acute upper respiratory tract illness.

[a]Of 81 cases of ARI, 1 involved no ARI symptoms.

[b]Data are for 48 cases with AURTI and 77 overall because 3 cases with AURTI were lost to follow-up.

Health Status During the 2-Week Follow-up Period

Outcomes of illness were described by respiratory illness classification (Table 6). Complications to pregnancy were infrequently reported in the case and healthy control groups. Among cases, complications included decreased fetal movement (2 cases).

Table 4. Respiratory Pathogens Identified by Real-Time Reverse-Transcription Polymerase Chain Reaction in Pregnant Women With (Cases) and Those Without (Controls) Acute Respiratory Illness

Pathogen Detected	Cases, No. (%) (n = 81)[a]	Controls, No. (%) (n = 91)	*P*
Human rhinovirus	22 (27)	6 (7)	<.01
HCoV	14 (17)	2 (2)	<.01
HCoV HKU1	6 (7)	1 (1)	
HCoV NL63	6 (7)	0	
HCoV OC43	2 (2)	1 (1)	
Respiratory syncytial virus	8 (10)	0	<.01
Group A	7 (9)	0	
Group B	1 (1)	0	
Influenza virus	4 (5)	0	
A(H3N2)	2 (2)	0	
A(H1N1)pdm09	2 (2)	0	
Human metapneumovirus	2 (2)	0	
Parainfluenza virus 1	1 (1)	0	
Bordetella pertussis	1 (1)	0	
Bocavirus	0	1 (1)	
Adenovirus	0	1 (1)	
None	30 (37)	81 (89)	<.01

Abbreviations: A(H1N1)pdm09, 2009 pandemic influenza A(H1N1) virus; HCoV, human coronavirus.

[a]One case positive for RSV group A was also positive for human rhinovirus.

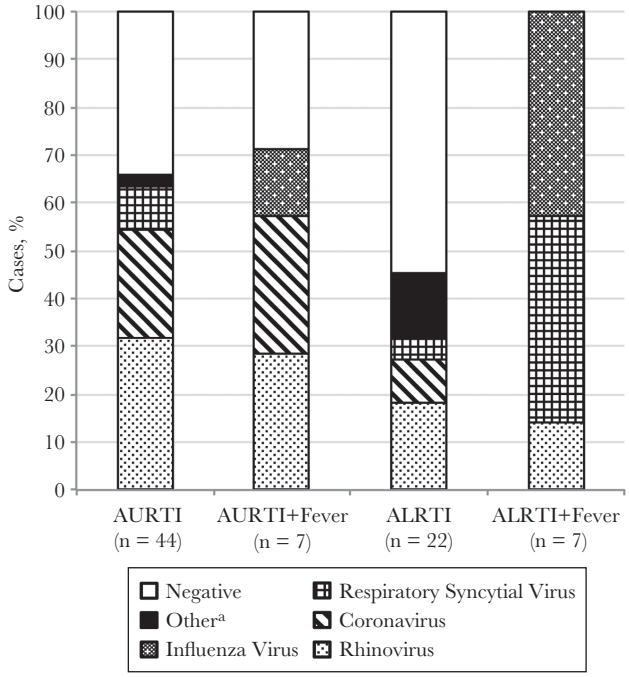

Figure 1. Results of real-time reverse-transcription polymerase chain reaction analysis to detect respiratory pathogens, by acute upper respiratory tract illness (AURTI) or acute lower respiratory tract illness (ALRTI) status, with or without self-reported fever. [a]Human metapneumovirus, *Bordetella pertussis*, or parainfluenza virus.

Two cases (one with AURTI and another with ALRTI) attended the emergency department within 2 weeks after enrollment. One case with ALRTI was hospitalized for 3 days, presenting with uterine contractions and fever, and treated with antibiotics. She developed respiratory symptoms during her stay and was enrolled in the study the week following hospitalization and had detectable RSV.

The use of prescription medications was more common but not significant among cases with ALRTI (38%) than among those with AURTI (22%). The most common prescription medication among cases was antibiotics; asthma therapy was observed only in the ALRTI group. The percentage of cases still reporting symptoms when contacted 2 weeks after enrollment was significantly greater in the ALRTI group (59%), compared with the AURTI group (23%).

The use of medication and the presence of ARI symptoms 2 weeks after enrollment were significantly greater among cases as compared to healthy controls. Of the 91 healthy controls, 11 developed ARI during follow-up: 8 reported symptoms consistent with AURTI, and 3 reported symptoms consistent with ALRTI. Of these, 4 had detectable virus present at study enrollment (3 had HRV detected, and 1 had bocavirus detected). One healthy control who developed ARI attended the emergency department for decreased fetal heart rate. Among the healthy controls who did not develop ARI within the 2-week follow-up period, complications of pregnancy were uncommon (n = 3); 1 healthy control was admitted to the hospital for foodborne illness.

Table 5. Outcomes of Acute Respiratory Illness (ARI) Among Pregnant Women, by History of Allergies

Outcome	History, No. (%) (n = 37)	No History, No. (%) (n = 44)	*P*
Respiratory pathogen positivity by real-time RT-PCR	22 (59)	29 (66)	.55
Acute lower respiratory tract illness	17 (46)	12 (28)[a]	.09
History of asthma	4 (11)	2 (5)	.40
Any complications to pregnancy	4 (11)	1 (2)	.173
Any emergency department visit	2 (5)	0	.21
Any hospitalization	0	1 (2)	
Any over the counter medications for illness	24 (65)	22 (50)	.18
Any prescription medications for illness	13 (35)	9 (20)	.14
ARI symptoms at 2 weeks of follow-up	15 (41)	13 (32)[b]	.42

[a]Data are for 43 cases because 1 had fever with malaise without respiratory symptoms.
[b]Data are for 41 cases because 3 were lost to follow-up.

DISCUSSION

Viral ARI was commonly identified in pregnant women during the fall and winter months and was associated with significant morbidity. Approximately one third of cases went on to develop ALRTI. These individuals were significantly more likely to report chest pain and decreased activity and to continue to experience symptoms at their 2-week follow-up call. A healthy control group was included for comparison to determine the role of the respiratory viruses detected in the cases. Compared with healthy controls, HRV, HCoV, and RSV were detected at a significantly greater frequency among cases. Importantly, 10% of cases had RSV identified as a pathogen. This proportion is the highest reported in recent studies, although different inclusion criteria were used in these respiratory surveillance studies [16, 17]. In addition to RSV, our data support the role of HRV and HCoV as causing ARI in pregnant women during the second and third trimesters of pregnancy.

Among healthy controls, we identified 11 women who developed symptoms of ARI, 4 of whom tested positive for a respiratory virus at enrollment. Seven additional healthy controls also reported symptoms at 2 weeks of follow-up but tested negative for respiratory pathogens at enrollment. It is likely that some of these virus-positive healthy controls remained truly asymptomatic. Likewise, some healthy controls who developed symptoms of ARI may have been infected with a respiratory virus during the 2-week follow-up period.

Table 6. Outcomes of Respiratory Illness at Enrollment and Follow-up Among Pregnant Women With Acute Respiratory Illness (ARI; Cases), by ARI Classification, and Those Without ARI (Controls)

Outcome	Cases (n = 80[a])				
	AURTI (n = 51)	ALRTI (n = 29)	*P*, AURTI vs ALRTI	Controls[b] (n = 91)	*P*, Cases vs Controls
Complications to pregnancy					
Any	3 (6)	2 (7)	>.99	4 (4)	.74
Obstetric/gynecologic	3	0		1	
Fetal distress	0	2		2	
Other	0	1		1	
Emergency department visit					
Any	1 (2)	1 (3)	>.99	1 (1)	.60
For obstetric/gynecologic reason	1	0		0	
For fetal distress	0	0		1	
Other	0	1		0	
Hospitalization					
Any	0	1 (3)	.36	1 (1)	>.99
For respiratory illness	0	1		0	
For foodborne illness	0	0		1	
Over-the-counter medications					
Any	28 (55)	17 (59)	.75	7 (8)	<.01
For cold	20	11		4	
For pain	12	7		4	
Other/vitamins	1	0		0	
Prescription medications					
Any	11 (22)	11 (38)	.12	0	<.01
For cold	1	0		0	
For pain	1	0		0	
Oseltamivir	1	2		0	
Antibiotics	10	9		0	
For asthma	0	3		0	
For gastrointestinal reason	0	1		0	
Reported ARI symptoms at 2 wk follow-up	11 (23)[c]	17 (59)	<.01	11 (12)[d]	<.01

Data are no. or no. (%) of participants.

Abbreviations: ALRTI, acute lower respiratory tract illness; AURTI, acute upper respiratory tract illness.

[a]Data are for 80 cases because 1 had fever with malaise without respiratory symptoms.

[b]Includes 8 cases who developed AURTI and 3 who developed ALRTI.

[c]Data are for 48 cases with AURTI because 3 were lost to follow-up.

[d]Data are for 89 controls because 2 were lost to follow-up.

HRV was the most common pathogen detected among cases and healthy controls, but it was detected significantly more often in cases. Approximately 40% of cases had detectable HRV. This is not unexpected, because HRV is the most common respiratory pathogen in otherwise healthy adults [18]. The presence of HRV among healthy controls may be explained by asymptomatic infection or prolonged viral shedding, both of which are common to HRV [19, 20]. HRV is commonly associated with upper respiratory tract infections, but among vulnerable populations, such as infants, young children [14], and elderly individuals, infection with HRV may involve the lower respiratory tract [21]. It is interesting to note that a number of women with detectable HRV reported symptoms consistent with lower respiratory tract infection.

Most studies on ARI in pregnant women focus either on influenza or limit inclusion criteria to influenza-like illness, which includes fever. Because fever was not an inclusion criterion for this study, we were able to capture a range of respiratory illnesses, as well as respiratory viruses not commonly associated with fever. A little over one third of cases were classified as having ALRTI. While chest pain and decreased activity were significantly associated with ALRTI, history of fever was not. Over half of cases with ALRTI without fever did not have any detectable respiratory pathogen. It is possible that the individuals developed secondary infections due to pathogens for which we did not test. For febrile ALRTI, the most common viruses were influenza virus and RSV. Although infection with influenza virus has been associated with poor pregnancy outcomes [9], complications in pregnancy were uncommon in our study.

Maternal immunization coverage in this study was low overall. Among study participants, 42% received seasonal influenza vaccine, and 10% received Tdap. Receipt of either vaccine was

not associated with enrollment status, because both healthy controls and cases had similar rates of both seasonal influenza vaccine and Tdap receipt. During the 2016–2017 influenza season, a Centers for Disease Control and Prevention–led study found that 53.6% of pregnant women had received a seasonal influenza vaccine [22]. Similarly, a 2015 national surveillance study reported maternal Tdap coverage to be 54% [23]. Many women in the study were not yet in the recommended time frame to receive Tdap. It is possible that, because seasonal influenza vaccine was not offered during regular obstetric visits, vaccine coverage in our patient population was lower than the national average.

Among cases, a history of allergies was identified as a possible risk factor for developing ALRTI. When stratified with respect to a history of allergies, those with a history of allergies more frequently developed ALRTI, although the difference was not statistically significant. However, detection of respiratory pathogens was similar among cases with and those without a history of allergies. Among children, infection with HRV or RSV has been associated with the development of long-term wheeze and asthma [24, 25]. The reason for this association is possibly related to childhood sensitization to a respiratory virus that exacerbates later infections [26]. Children with detectable HRV and a positive result of an immunoallergy assay are more likely to develop a subsequent wheeze [18, 27]. Similar studies in adults have found a relationship between exposure to indoor allergens, detection of respiratory viruses, and hospitalization with asthma [28]. It is possible that a similar mechanism is at work for the pregnant women in our study.

Our study had several limitations. As a single-site study that enrolled participants during 1 respiratory season (October through May), our population size was limited, and our study cohort might not be comparable to patients at other obstetrics and gynecology clinics. Also, because the study was powered to capture a 10% frequency for RSV, less frequent respiratory viruses may not have been captured. Additionally, we did not capture the impact of viruses with summer seasonality. Because we only enrolled pregnant women seen at a clinic, compared with those at an emergency care facility, we were less likely to capture individuals with severe disease. However, this ambulatory study could have captured more individuals with ARI than those seen in an emergency center. Because some patients were enrolled later during their illness course, it is possible that the infecting virus was no longer present, resulting in a false-negative test result.

In summary, respiratory viruses were frequently detected among pregnant women with ARI, over one third of whom had symptoms consistent with ALRTI. By not restricting the inclusion criteria to influenza-like illness, we were able to capture a broader range of respiratory viruses and their associated respiratory illnesses. Although HRV was the most commonly detected respiratory virus, RSV or influenza virus were the most common viral pathogens among cases with ALRTI with fever. History of allergies might be a predisposing factor for virus-induced wheezing during pregnancy. Despite the availability of a seasonal influenza vaccine, maternal vaccine coverage in this population was low. A maternal RSV vaccine is currently in evaluation and would theoretically prevent illness in both infants and mothers. However, vaccine coverage in this vulnerable population must improve for these maternal vaccines to be truly effective.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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