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Respiratory Syncytial Virus Hospitalization During Pregnancy in 4 High-income Countries, 2010–2016

Annette K. Regan[1,2], **Nicola P. Klein**[3], **Gayle Langley**[4], **Steven J. Drews**[5,6], **Sarah Buchan**[7,8,9], **Sarah Ball**[10], **Jeffrey C. Kwong**[7,8,9,11,12], **Allison Naleway**[13], **Mark Thompson**[4], **Brandy E. Wyant**[10], **Avram Levy**[14,15], **Hannah Chung**[7], **Becca Feldman**[16], **Mark A. Katz**[16,17,18],

PREVENT Group[a]

[1]School of Public Health, Curtin University, Perth, Western Australia, Australia;

[2]Wesfarmers Centre of Infectious Diseases and Vaccines, Telethon Kids Institute, Perth, Western Australia, Australia;

[3]Kaiser Permanente Vaccine Study Center, Kaiser Permanente Northern California, Oakland;

[4]Centers for Disease Control and Prevention, National Center for Immunizations and Respiratory Diseases, Atlanta, Georgia;

[5]Diagnostic Virology, ProvLab Alberta, Alberta Health Services, Edmonton,

[6]Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton,

[7]Institute for Clinical Evaluative Sciences, University of Toronto, Ontario, Canada;

[8]Public Health Ontario, University of Toronto, Ontario, Canada;

[9]Dalla Lana School of Public Health, University of Toronto, Ontario, Canada;

[10]Abt Associates, Cambridge, Massachusetts;

[11]Department of Family & Community Medicine, University of Toronto,

[12]University Health Network, Toronto, Ontario, Canada;

[13]Kaiser Permanente North West, Portland, Oregon;

[14]PathWest Laboratory Medicine WA, Department of Health Western Australia,

[15]Pathology and Laboratory Medicine, University of Western Australia, Perth, Australia;

[16]Clalit Research Institute, Chief Physician's Office, Clalit Health Services, Tel Aviv

Correspondence: A. K. Regan, School of Public Health, Curtin University, GPO Box U1987, Perth, Western Australia 6845, Australia (Annette.Regan@curtin.edu.au).

[a]Members of the PREVENT Group are listed in the Notes section.

Supplementary Data

Supplementary materials are available at *Clinical 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.

[17]School of Public Health, Medical School for International Health, Ben Gurion University, Bersheva, Israel;

[18]University of Michigan School of Public Health, Ann Arbor

Abstract

Few studies have addressed respiratory syncytial virus (RSV) infection during pregnancy. Among 846 pregnant women hospitalized with respiratory illness and tested for RSV, 21 (2%) were RSV positive, of whom 8 (38%) were diagnosed with pneumonia. Despite study limitations, these data can help inform decisions about RSV prevention strategies.

Keywords

pregnancy; respiratory syncytial virus; epidemiology; vaccines; respiratory infections

Respiratory syncytial virus (RSV) is one of the leading causes of lower respiratory tract infections and mortality among infants aged <2 years [1]. Among infants aged <6 months, 1.4 million hospital admissions and 27 300 in-hospital deaths globally were attributed to acute lower respiratory infections from RSV in 2015 [1]. Vaccination during pregnancy has been identified as a potentially effective method of preventing RSV in early infancy, and RSV vaccine clinical trials are currently underway in pregnant women [2].

Although the intention of an RSV vaccine is to provide protection to infants via passive transfer of maternal antibodies, it might also provide benefits for maternal health. Recent studies have suggested that the contribution of RSV to respiratory disease in adults, including pregnant women, has been underappreciated [3, 4]. However, limited data exist describing RSV infections among pregnant women, particularly in high-income settings. The purpose of this study was to describe the characteristics of RSV-associated hospital admissions among pregnant women.

METHODS

The Pregnancy Influenza Vaccine Effectiveness Network (PREVENT) was formed in 2016 as an international collaboration between the Centers for Disease Control and Prevention (CDC), Abt Associates, and sites in 4 countries: Australia, Canada, Israel, and the United States. While the primary aim of this network was to estimate vaccine effectiveness in preventing severe influenza disease during pregnancy, additional data were collected on RSV testing and clinical and birth outcomes.

Four PREVENT sites contributed to this study, including the Institute for Clinical Evaluative Sciences (Ontario, Canada), Kaiser Permanente Northern California, Clalit Health Services (Israel), and the Department of Health Western Australia. In brief, Western Australia identified pregnant women in their state using a perinatal database, and this information was linked with hospital discharge and laboratory testing data (Supplementary Table 1). In Ontario, pregnancies were identified from hospital discharge data and linked to laboratory testing data. In Israel and California, information from electronic medical records was

extracted by each respective healthcare delivery system. These data sources were used to identify pregnant women aged 18–50 years who were admitted to hospital with an acute respiratory infection or febrile illness (ARFI) based on country-relevant *International Classification of Diseases* (ICD) diagnosis codes (9th and 10th edition; Supplementary Table 2) and tested for RSV during the 2010–2011 through 2015–2016 northern hemisphere influenza seasons (Ontario, Israel, and California) and during the 2012 through 2015 southern hemisphere influenza seasons (Western Australia). Western Australia additionally included pregnancies that overlapped any periods of RSV activity that occurred outside the influenza season, based on routinely collected surveillance data (Supplementary Table 3). Women were included in the study if a laboratory test result for RSV by reverse transcription polymerase chain reaction (RT-PCR) was available within 3 days of the date of hospital admission. To ensure that we captured unique episodes of illness, admissions that occurred <14 days from a previous hospital admission were excluded.

Information on date of admission, RSV test result (positive or negative), length of stay, hospital diagnoses, maternal sociodemographics and health conditions, and birth outcomes was obtained from each site (Supplementary Table 2). The status of pregnancy at discharge was also obtained (delivered during ARFI admission vs no delivery). We performed comparisons of categorical variables between RSV-positive and RSV-negative pregnant women using Fisher exact tests and comparisons between all ARFI admissions and RSV-tested admissions using Cochran–Mantel–Haenszel χ^2 tests. Analyses were restricted to women with complete information. The institutional review board or ethics committee at each site approved the study.

RESULTS

Across 4 sites, we identified 1 604 206 women who were pregnant between 2010 and 2016. The study period included 79% of weeks with known RSV activity (Supplementary Table 3). Of the 1 604 206 pregnancies, 15 287 (0.9%) had at least 1 ARFI-related hospitalization; 1593 re-admissions were excluded. Of the 13 694 unique admissions for ARFI, 846 (6%) were tested for RSV (Supplementary Figure 1). Overall, 2.5% (n = 21) of women tested for RSV were positive, all by RT-PCR. The percentage of women who tested positive for RSV ranged from 1.9% (Ontario) to 3.1% (Israel). Percent positivity by year ranged from 0% in 2011–2012 to 4.0% in 2013–2014. All 846 women were tested for influenza, of whom 430 (51%) tested positive; <1% tested positive for both RSV and influenza.

The majority of RSV testing (63%) and detections (67%) occurred in the third trimester of pregnancy (Supplementary Table 4; Table 1). One-third of RSV-positive women (38%) had a preexisting health condition, most commonly asthma (19%). An ICD diagnosis of pneumonia was more common in RSV-positive women compared to RSV-negative women (38% and 19%, respectively; $P = .046$). Ten (48%) RSV-positive women were admitted for ≥3 days.

We observed no difference in preterm, small-for-gestational age, and low birthweight births between RSV-positive and RSV-negative women overall (data not shown). However, among ARFI admissions where no delivery occurred, we did observe an association between RSV

positivity and subsequent preterm birth (RSV-positive women, 29%, and RSV-negative women, 15%; $P = .034$).

DISCUSSION

To our knowledge, this is the largest study of RSV-associated hospitalizations during pregnancy and the only study to investigate RSV infections in a cohort of hospitalized pregnant women across several high-income countries. Our findings suggest that RSV was uncommonly tested for and detected among women hospitalized during pregnancy with an acute respiratory or febrile illness during influenza season. However, in some cases, RSV-associated hospital admission during pregnancy was a clinically significant event. Half of the RSV-positive admissions were severe enough to require ≥3 days of hospitalization and nearly 40% were diagnosed with pneumonia. Furthermore, among women who did not deliver during the ARFI hospitalization, preterm birth occurred more frequently for RSV-positive admissions compared to those who tested negative.

A recent technical review commissioned by the CDC identified major gaps in RSV disease epidemiology, including the need to determine the impact of maternal RSV on pregnancy and maternal health outcomes [5]. The current study, together with a few other recently published studies [6–9], helps to begin to fill this knowledge gap. A US study in 2014 described severe outcomes following RSV infection in 3 pregnant women [6]. All 3 cases were diagnosed in the third trimester of pregnancy, and 2 cases required mechanical ventilation. Three previous studies outside high-income areas have measured RSV infection during pregnancy [7–9]. A recent randomized trial of influenza immunization in Nepal showed that 14/733 (2.0%) of community-based respiratory illness episodes in pregnant women were associated with RSV [7], a percent-positivity similar to that of the current study of hospitalized women. In the Nepal cohort, half of RSV-infected women sought care. Also, similar to our own findings, 29% of RSV-infected women in this cohort had preterm deliveries compared to 13% of uninfected women, although the small numbers precluded the authors from making a statistical comparison. A longitudinal cohort study of human immunodeficiency virus–infected and –uninfected pregnant and postpartum women estimated the burden of RSV to range from 1.9 to 4.3 cases per 1000 person-months [9]. Another prospective cohort study in Mongolia identified 4 RSV cases in pregnant women; however, the study did not provide characteristics of RSV-infected women or information on birth outcomes [8].

Understanding the risk and clinical course of RSV infection in pregnant women is an important step toward understanding the potential benefits of RSV immunization during pregnancy. The burden of RSV infection in young infants, a population that could benefit from passive maternal antibodies from vaccinated mothers, has been more extensively described [1]. Several RSV candidate vaccines are being evaluated in clinical trials [10, 11] with the intention of primarily preventing severe infection in infants [12]. Preventing severe RSV-related disease in pregnant women may be another potential benefit of the vaccine.

This study had several strengths and limitations. This is the first study to focus specifically on severe RSV infection associated with hospitalization during pregnancy in high-income

settings and combines sociodemographic and clinical data from 4 countries. However, case identification was likely incomplete, which may have led to underdetection of RSV cases. The low number of cases was partly due to low testing rates for RSV in our cohort; only 6% of ARFI-hospitalized women were tested for RSV. Another contributing factor may have also been that in 3 of the 4 sites, we only identified pregnant women hospitalized during influenza seasons. Although RSV typically circulates in winter months, it does not always match influenza seasons [9]. To allow more comprehensive capture of RSV cases, future studies should aim to include the entirety of the RSV season. Finally, while these results are useful for high-income countries, they may not be generalizable to other settings.

CONCLUSIONS

Although RSV was uncommonly detected among hospitalized pregnant women, our findings suggest that RSV-associated ARFI hospitalization during pregnancy can result in severe infection. This information adds to our knowledge about the clinical outcomes of RSV in pregnant women and could be useful for understanding the potential benefits of maternal RSV vaccines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclaimer.

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Potential conflicts of interest.

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Members of the PREVENT workgroup in addition to the named authors include the following: Centers for Disease Control and Prevention (Eduardo Azziz-Baumgartner), Abt Associates (Pat Shifflet, Rebecca V. Fink), Institute for Clinical Evaluative Sciences (ICES) (Deshayne Fell), Clalit Research Institute (Dan Riesel), Central Virology Laboratory, Israel Ministry of Health (Michal Mandelboim), Israel Center for Disease Control, Israel Ministry of Health (Aharona Glatman-Freedman), Department of Health Western Australia (Paul Effler), and Kaiser Permanente Northern California (Ned Lewis).

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Table 1.

Characteristics of Women Hospitalized With an Acute Respiratory Infection During Pregnancy and Tested for Respiratory Syncytial Virus—California, Israel, Ontario, and Western Australia, 2012–2016

	RSV Negative		RSV Positive		
Characteristic	**n**	**% (95% CI)**	**n**	**% (95% CI)**	***P* Value[a]**
Sociodemographic characteristics					
Age <35 years	654/825	79 (76–82)	14/21	67 (43–85)	.175
Low socioeconomic status	271/785	34 (31–38)	9/19	47 (24–71)	.329
Urban residence	97/682	14 (12–17)	6/16	37 (15–65)	**.021**
Pregnancy characteristics					
Parity ≥2	316/825	38 (35–42)	11/21	52 (30–74)	.256
Third trimester	517/825	63 (59–66)	14/21	67 (43–85)	.821
Pregnancy complication	399/825	48 (45–52)	13/21	62 (38–82)	.271
Health conditions					
≥1 preexisting health condition	287/825	35 (32–38)	8/21	38 (18–62)	.818
Clinical characteristics					
Primary diagnosis of acute respiratory or febrile illness	377/825	46 (42–49)	8/21	38 (18–62)	.516
Pneumonia diagnosis	158/825	19 (16–22)	8/21	38 (18–62)	**.046**
Sepsis	31/825	4 (3–5)	0/21	0 (0–16)	1.000
Respiratory failure	90/825	11 (9–13)	0/21	0 (0–16)	.154
Length of stay ≥3 days	422/825	51 (48–55)	10/21	48 (26–70)	.827

Where data were unavailable or missing, we restricted analysis to include only women with complete information. Comparisons that were significant at $P < .05$ are shown in bold. Abbreviations: CI, confidence interval; RSV, respiratory syncytial virus.

[a] *P*- value for Fisher exact test for differences.