Burden of respiratory syncytial virus-associated acute respiratory infections during pregnancy

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Abstract

Introduction With the licensure of maternal RSV vaccines in Europe and USA, data are needed to better characterize the burden of respiratory syncytial virus (RSV)-associated acute respiratory infections (ARI) in pregnancy. This study aims to determine among pregnant individuals the proportion of ARI testing positive for RSV and RSV incidence rate, RSV-associated hospitalizations, deaths, and perinatal outcomes.

Methods We conducted a systematic review following PRISMA 2020 guidelines using five databases (Medline, Embase, Global Health, Web of Science and Global Index Medicus) and included additional unpublished data. Pregnant individuals with respiratory infections who had respiratory samples tested for RSV were included. We used a random-effects meta-analysis to generate overall proportions and rate estimates across studies.

Results Eleven studies with pregnant individuals recruited between 2010 and 2022 were identified, most of which recruited pregnant individuals in community, inpatient and outpatient settings. Among 8126 pregnant individuals, the proportion with respiratory infections that tested positive for RSV ranged from 0.9% to 10.7%, with a meta-estimate of 3.4% (95% CI: 1.9; 54). The pooled incidence rate of RSV infection episodes among pregnant individuals was 26.0 (15.8; 36.2) per 1000 person-years. RSV hospitalization rates reported in two studies were 2.4 and 3.0 per 1000 person-years. Of five studies that ascertained RSV-associated deaths among 4708 pregnant individuals, no deaths were reported. Three studies comparing RSV-positive and RSV-negative pregnant individuals found no difference in odds of miscarriage, stillbirth, low birth weight, and small for gestational age. RSV-positive pregnant individuals had higher odds of preterm delivery (odds ratio 3.6 [1.3; 10.3]).

Conclusion Data on RSV-associated hospitalization incidence rates are limited but available estimates are lower than those reported in older adults and young children. As countries debate

whether to include RSV vaccines in maternal vaccination programs, which are primarily intended to protect infants, this information could be useful in shaping vaccine policy decisions.

Background

Respiratory syncytial virus (RSV) is a major respiratory pathogen that can cause acute respiratory infections (ARI) in people of all ages and can infect people multiples times throughout their lives. Severe manifestations disproportionately affect those at the extremes of age, causing a significant disease burden in these population groups [1-3]. Pregnant individuals, with their inherent immunological changes, could be at an increased risk of severe RSV infection, but RSV infections in pregnant individuals remain poorly characterized [4]. During pregnancy, maternal RSV antibodies are actively transferred across the placenta to the fetus and later provide some immunity to infants in the first few months after birth [5, 6]. Higher titers of maternal antibodies, especially against F protein in prefusion (preF) conformation reduce the risk of severe disease in infants [7]. Passive immunization during pregnancy has been used successfully to protect young infants from diseases such as tetanus, pertussis, influenza, and SARS-CoV-2 [8-11]. Maternal immunization also provides direct benefits to the pregnant individuals by reducing risk of infection and associated complications during the pregnancy and postpartum periods [8-12]. RSV vaccines for pregnant individuals have recently been licensed in USA and Europe. While the primary goal of antenatal RSV vaccination is focused on providing protection to young infants, antenatal vaccination could also have protective benefits for pregnant individuals and the pregnancy as has been documented for other maternal immunizations [8, 12]. We conducted a systematic review and meta-analysis of studies that included pregnant individuals with ARI who underwent testing for RSV infection to estimate the proportion of ARI episodes that tested positive for RSV, incidence rates of antenatal RSV infection, and numbers of RSV-associated hospitalizations and deaths. We also characterized RSV-associated perinatal outcomes.

Methods

We searched articles in 5 databases: Medline (Ovid), Embase (Ovid), Global Health (Ovid), Web of Science, and Global Index Medicus. Search terms that broadly included RSV and pregnant individuals are provided in Supplementary table 1. The database searches included the period from January 1, 1996 to November 24, 2022 without any language restriction. We also manually searched the reference list of eligible studies identified from databases to identify additional eligible studies. When published data were insufficient for meta-analysis or when data collection continued after publication, we contacted pharmaceutical companies and observational study authors to obtain additional unpublished data pertinent to our review. We decided a priori that if two or more published reports were from the same study or if the unpublished data overlapped with the published report, then the dataset which provided data for the maximum length of time or which provided the most details would be included in the analysis. We registered the systematic review on the international prospective register of systematic reviews (PROSPERO) database (CRD42022372847) and followed the PRISMA 2020 reporting guidelines while conducting the review [13].

We included data from observational studies related to pregnant individuals with study-defined ARI who had been tested for RSV by culture, antigen, and molecular testing (Supplementary table 2). The definition of ARI varied from study to study. Given the scarcity of data on RSV in pregnant individuals, we broadened our clinical definition criteria and included influenza like illness (ILI) and severe acute respiratory infections (SARI). We excluded studies not focused on pregnant individuals, studies where clinical specimens were not laboratory tested for RSV, conference abstracts, reviews, and case reports. We developed and piloted a data extraction template. The literature search, study selection and data extraction were carried out independently by two reviewers (HM and SK). Any disagreements were resolved through mutual discussion or with the help of an arbiter (HN).

Risk of bias and data analysis

The risk of bias in the included studies was assessed using the Joanna Briggs Institute scale (Supplementary table 3). Data analyses were conducted using R version 4.0.3 software [14]. We used a random-effects meta-analysis to estimate the proportion of pregnant individuals with ARI who tested positive for RSV and the RSV incidence rate among pregnant individuals. When necessary, we converted the incidence rates from person-months to person-years by multiplying the person-months by 12. Subgroup analyses were performed based on the case identification settings and whether the study period was seasonal or throughout the year. Seasonal studies were defined as those conducted during RSV epidemic periods, which typically occur from October to May in temperate regions and at different times in tropical regions [15]. An evaluation of publication bias was conducted using funnel plot asymmetry and a weighted Egger's regression test with a threshold of 0.05 [16]. For proportion positive among pregnant individuals with ARI, we did a sensitivity analysis which involved excluding one study at a time to evaluate its influence on the overall outcome [17]. We described in pregnant individuals the RSV-associated hospitalization rate, the proportion hospitalized of pregnant individuals with RSV-associated ARI, the proportion with RSV infection of pregnant individuals with ARI-associated hospitalizations, and the number of RSV-associated deaths among those with ARI. We used random-effects meta-analysis to determine the proportions of specific perinatal outcomes among pregnant individuals with RSV-associated ARI: preterm birth (birth before 37 weeks' gestational age), low birth weight (<2500 g), stillbirth, and miscarriage. The cut-off point for miscarriage and stillbirth was 20 weeks gestational age, with miscarriage defined as spontaneous loss of pregnancy before 20 weeks and stillbirth as death of the fetus at or after 20 weeks. We also estimated using random-effects meta-analysis the association between RSV infection and perinatal outcomes.

Results

Study selection

A search of databases yielded a total of 630 records (Supplementary figure 1). Among these, 602 were excluded as they did not meet the eligibility criteria, leaving 28 full-text articles for further assessment. Out of these 28 studies, 22 were excluded and 2 additional records were identified through citation searching. We did not include any unpublished data from the placebo arm of recent Phase II/III RSV maternal vaccine trials as they did not follow up pregnant individuals for ARI or test them for RSV (Pfizer PF-06928316); the Phase III trials were conducted during the COVID-19 pandemic when RSV activity in general was very low across most sites (Pfizer and Glaxo SmithKline RSV MAT-009); and recruitment was halted midway following a recommendation by the independent data monitoring committee (GSK). We also did not include data from Phase III Novavax RSV M-301 as ascertainment of RSV disease in the pregnant individuals was passive and the number of individuals positive for RSV-ARI was in the low single digits. Unpublished data were made available by the authors of 3 additional observational studies. We excluded one previously published article that met the inclusion criteria due to its overlap with unpublished data [18]. Finally, a total of 11 studies (8 published and 3 unpublished) were included in the analysis for this systematic review [19-26].

Studies characteristics

The recruitment period of pregnant individuals in the included studies ranged from 2010 to 2022 (Supplementary table 4). Except for RSV-associated deaths, all other estimates are based on data collected during the pre-COVID-19 pandemic era. Of all 11 included studies, eight were cohort studies, while the remaining three were cross-sectional studies. Six studies were conducted in high-income countries (Australia, Canada, Israel, Panama, and the United States); four in lower-middle-income countries (El Salvador, Kenya, Mongolia, and Nepal); and two in upper-middle-income

148 countries (South Africa and Thailand). Four studies were conducted year-round, lasting between
149 two and six years, and seven were conducted seasonally, lasting from one to eight seasons. One
150 study reported data exclusively among outpatients, two studies exclusively among inpatients, and
151 three studies exclusively in the community. In studies with a combination of settings three were in
152 the community, outpatients, and inpatients and 2 were in outpatients and inpatients. Seven studies
153 used ARI as the primary definition for inclusion. Meanwhile, other studies employed varying
154 definitions which included criteria like RSV-positive, limiting to only febrile patients with ARI or
155 including specific sub-populations, such as those living with human immunodeficiency virus (HIV)
156 infection. The RSV diagnostic test used in most of the studies was polymerase chain reaction (PCR)
157 (9 studies), with other methods including culture, antigen tests, and rapid diagnostic tests. Of
158 studies that provided information about clinical specimen types four collected nasal swabs, three
159 nasopharyngeal swabs, and one oropharyngeal swab. Of five studies with gestational age reported,
160 one included pregnant individuals in all 3 trimesters, three in the second and third trimesters, and
161 one in the first and second trimesters.

162 **Risk of bias of included studies**

163 The cohort studies presented a low risk of bias, with all studies achieving scores of 82% or more
164 according to JBI assessment tools (Supplementary table 5) [19-21, 24-26]. Cross-sectional studies
165 by Hause (2018) and Hause (2021) also displayed low risk of bias, with scores of 88% and 75%,
166 respectively (Supplementary table 6) [22, 23].

167 **Proportion of pregnant individuals with RSV-positive acute respiratory infections**

168 Supplementary table 7 reports the proportion of pregnant individuals with ARI who tested positive
169 for RSV among studies that tested in the community, outpatient, or in-patient settings. These
170 studies were conducted in Africa (Kenya and South Africa) [24, 25], Central America (El Salvador,
171 Panama), North America (United States) [19, 22, 23], South-East Asia (Nepal and Thailand) [21],

and the Western Pacific (Mongolia) [20]. There were 203 cases of RSV infection among 8126 pregnant individuals tested, with the proportion of positive cases ranging from 0.9% in HIV-uninfected persons in South Africa to 10.7% in an unpublished study in Thailand. The pooled proportion of RSV positivity in pregnant individuals with ARI was 3.4% (95% confidence interval (CI): 1.9; 5.4) (Fig 1). After removing each study sequentially from the meta-analysis, the overall estimates ranged from 2.2% (95% CI: 1.3 to 3.2) to 4.1% (95% CI: 2.1 to 6.2) (Supplementary table 8). The Egger's test indicated publication bias (p=0.046). A visual inspection of the funnel plot did not reveal marked asymmetry to conclusively support the Egger's test result (Supplementary figure 2). In studies conducted during RSV seasons, the prevalence was 4.4% [95% CI: 0.8; 10.1], while in year-round studies, the prevalence was 2.5% [95% CI: 1.3; 4.0], with a statistically significant difference (p<0.001) (Supplementary figure 3). The proportion of pregnant individuals positive for RSV was 9.8% [95% CI: 4.3; 18.5] among outpatients, 5.5% [95% CI: 0.6; 14.0] among community participants, 3.6% [95% CI: 0.3; 8.8] among outpatients and inpatients, and 1.7% [95% CI: 0.8; 2.7] among community, outpatient, and inpatient participants (Supplementary figure 4).

Incidence rate of RSV in pregnant individuals

Supplementary table 9 presents the incidence rate of RSV among pregnant individuals. The included studies were conducted in Kenya [25], South Africa [24], Thailand, and Mongolia [20]. All studies identified pregnant individuals across community, inpatient and outpatient settings, except unpublished data by Dawood where participants were identified only in the community in Thailand. The incidence rate of RSV varied from 0.2 per 1000 person-months among pregnant individuals in an unpublished study from Thailand to 24.0 per 1000 person-months in Mongolia. The RSV incidence rate meta-estimate in pregnant individuals diagnosed with ARI was 2.1 (95% CI: 1.3; 3.0) per 1000 person-months. The incidence rate was 1.7 (95% CI: 1.0; 2.3) per 1000

196 person-months in seasonal studies and 4.9 (95% CI: 0.3; 9.5) per 1000 person-months in year-
197 round studies, with a statistically significant difference (p=0.170) (Fig 2).

198 **RSV-associated hospitalizations in pregnant individuals**

199 RSV-associated hospitalizations in pregnant individuals were provided in ten studies, two reported
200 hospitalization rates [19] (Dawood, unpublished data), five the proportion hospitalized among
201 those with RSV-associated ARI episodes [21, 22, 24, 25] (Frivold, unpublished data), and three the
202 proportion of ARI hospitalizations that were associated with RSV infection [20, 26] (Dawood,
203 unpublished data).

204 One study conducted in El Salvador reported RSV hospitalization rate of 3.0 per 1000 person-years
205 among pregnant individuals (Supplementary table 10) [19]. In an unpublished study from Thailand,
206 a single case of RSV hospitalization was observed in a pregnant person and when extrapolated to
207 the cohort population resulted in a hospitalization rate of 2.4 [0.4; 17.3] per 1000 person-years.

208 In a study by Hause and colleagues in the United States, out of 8 pregnant individuals with
209 outpatient, medically attended ARI who tested positive for RSV, one required hospitalization
210 (Supplementary table 11) [22]. In other studies, from South Africa [24], Kenya [25], Nepal [21],
211 and the United States (Frivold, unpublished data), where 6853 individuals were tested, 86 were
212 RSV-positive and no RSV-positive pregnant individuals were hospitalized.

213 Three studies report data on the proportion of pregnant individuals hospitalized with ARI who
214 tested positive for RSV (Supplementary table 12) [20, 26]. These studies reported data from
215 Mongolia, Thailand, and a multicountry study across Australia, Canada, Israel, and the United
216 States. The RSV positivity among pregnant individuals hospitalized with ARI ranged from 0% in
217 the study in Mongolia to 9.1% in the unpublished study in Thailand.

218 **RSV-associated deaths in pregnant individuals with acute respiratory infections**

We included 5 studies (from Mongolia, Nepal, United States, and Kenya) that reported data on 4708 pregnant individuals tested for RSV of which 203 were RSV-positive [20, 21, 26] (Frivold, unpublished data; Havers, unpublished data) (Supplementary table 13). No deaths were reported amongst these pregnant individuals.

Perinatal outcomes in pregnant individuals with RSV-associated acute respiratory infections

Three studies conducted in Nepal, Thailand, and South Africa reported data on perinatal outcomes among pregnant individuals who tested positive for RSV [21, 24] (Dawood, unpublished data) (Figure 3 and Supplementary table 14). The RSV-positive pregnant individuals had seven infants with low birth weight (6.0%; 95% CI: 1.0; 13.4) and 12 preterm births (12.3%; 95% CI: 5.4; 20.8). Two of these studies provided data on small for gestational age births, stillbirths, and miscarriages. Of the pregnant women who tested positive for RSV in these studies, five of them delivered small for gestational age infants (5.1%; 95% CI: 0.4; 13.0), but no miscarriages or stillbirths were reported. Stillbirths, small for gestational age, miscarriage, and low birth weight did not differ by antenatal RSV infection status in three studies. There was significant difference in odds of preterm birth between RSV-positive and RSV-negative pregnant individuals (OR = 3.6 [1.3; 10.3]); however these are based on data from single study (Dawood, unpublished data).

Discussion

This is the first study to summarize available evidence and quantify RSV-associated ARI burden among pregnant individuals, a population subgroup in whom RSV burden is poorly understood. We found that 3.4% (95% CI: 1.9; 5.4) of ARI episodes among pregnant individuals were associated with RSV infection. The estimated incidence rate of antenatal RSV infection was 2.1 (95% CI: 1.3; 3.0) per 1000 person-months or 26.0 (95% CI: 15.8; 36.2) per 1000 person-years. RSV-associated hospitalizations were uncommon, and no RSV-associated deaths were observed. Based on limited data from three studies, the odds of stillbirths, miscarriage, low birth weight, and

small for gestational age did not differ between pregnant individuals who had antenatal RSV infection compared to those who did not, but antenatal RSV infection was associated with increased odds of preterm delivery (3.6 [1.3; 10.3]).

The paucity of data about the epidemiology of RSV among non-pregnant adults of reproductive ages limits comparisons of RSV incidences rates between non-pregnant and pregnant individuals. We estimated that the incidence of RSV was 26.0 per 1000 person-years in pregnant individuals, which is comparable to incidence rates reported among adults aged ≥18 years with underlying medical conditions or older adults aged ≥60 years [27, 28]. For adults ≥18 years with cardiopulmonary diseases, the incidence rate of RSV during the epidemic period was 19.1 cases per 1000 person-years [27]. In immunodeficient patients aged ≥18 years, a higher incidence rate was observed when studies covered the whole year (36.8 cases per 1000 person-years) which increased seven folds when restricted to the epidemic period (260.8 cases per 1000 person-years). The proportion of pregnant individuals with ARI who were RSV-positive was found to be 3.4%, which is similar to previous studies conducted in adults aged ≥16 years [28-30]. Based on these numbers, proportion of ARI cases positive for RSV among pregnant individuals lies between adults aged ≥16 years with community-acquired pneumonia (2%; 95% CI=1-3) and adults with comorbidities (11%; 95% CI=7-16) [27, 31].

Limited data on RSV-associated hospitalizations suggests hospitalization rates of 2.4 and 3.0 per 1000 person-years, which is substantially higher than rates for the 50-64-year age group in both high-income and low- and middle-income countries (0.2 and 0.3 per 1000 person-years, respectively) [31]. However, limited data and different testing and hospital admission practices among pregnant individuals compared with non-pregnant individuals may lead to biased estimates.

Among prospective studies included in this meta-analysis, only a single hospitalization event was observed among RSV-positive pregnant individuals with ARI which align closely with those over 60 years (0.1%) and was substantially lower than in RSV infected adults aged ≥18 years with comorbidities (32%; 95% CI: 23-43) and RSV infected immunodeficient patients aged ≥18 years (38.3%; 95% CI: 29-48) [27, 32]. The proportion of RSV-positive cases among hospitalized pregnant individuals with ARI varied broadly from 0% to 9.1%, aligning with proportions among elderly individuals in high-income countries (6.1%) [2].

There were no reported deaths in the five contributing studies on RSV during pregnancy, which is lower than previous meta-analyses that demonstrated varying case fatality rates among adults aged ≥18 years or adults with comorbidities, which ranged between 1.4% and 11.0% [2, 27, 28, 32]. In addition, observational studies have also shown cases of RSV-related deaths in hospitalized young adults [33-35].

Severe illnesses from respiratory infections like COVID-19 and influenza in pregnant individuals, particularly those requiring hospitalization, have been associated with an increased risk of numerous adverse outcomes [36-41]. Specifically, in the case of severe COVID-19 illness, there is an increased risk of preterm birth, fetal growth restriction, postpartum hemorrhage, and stillbirth [36, 38, 39, 41]. Similarly, severe illness from influenza during pregnancy, especially pandemic A/H1N1 influenza, is linked with a greater risk of adverse perinatal outcomes such as preterm birth [37, 40]. In this meta-analysis, among RSV infected during pregnancy, adverse perinatal outcomes include low-birth-weight infants (6.0%; 95% CI: 1.0; 13.4), preterm infants (12.3%; 95% CI: 5.4; 20.8) and small-for-gestational-age infants (5.1%; 95% CI: 0.4; 13.0), however the rates were comparable to those in the general population of the countries where the studies were conducted

[42-44]. The only exception was observed in the Nepal study, where preterm births among people with RSV in pregnancy exceeded the rate seen in the general population [45].

It is important to view the interpretation of these findings within the context of several limitations. Seven out of eleven studies only tested for RSV during the epidemic months and one was confined to a single season. Some were not explicitly oriented towards the RSV season, while others were aimed at the influenza season, which does not always coincide with the RSV season and thus might not fully capture RSV disease burden [46, 47]. Also, in most regions, RSV has seasonal circulation patterns and studies conducted during the perceived RSV season are expected to yield a higher proportion positive [48]. The limited number of studies, reflected in publication bias, coupled with their small sample sizes may lead to potentially imprecise estimates. Notably, we lack adequate data to stratify our estimates by income region, study settings, clinical definition of ARI, or gestational age. We acknowledge the scarcity of consistent data on pregnant individuals with and without RSV or lower respiratory tract infection and the absence of a comparable non-pregnant control group of the same age. The varied methodologies and risk factors across the included studies raise concerns about the potential for coincidental similarities in outcome frequencies. In this analysis, we were unable to control for potential confounders such as age, socioeconomic status, and smoking exposure which could be explored in an individual patient data meta-analysis if data on potential confounders were available. Limitations also arose from laboratory testing, as most included studies relying solely on PCR testing of one type of upper respiratory tract specimen, which could underestimate the true RSV burden, indicating the need for including serology tests in future research [49, 50]. The clinical case definitions for ARI used in the individual studies, along with the exclusion of non-febrile cases in some studies, could lead to further underestimation

of RSV prevalence [51]. RSV proportion might also be underestimated due to the lack of clarity surrounding standard of care testing practices in pregnant individuals.

Our current understanding of RSV in pregnant individuals is based on a limited number of studies and participants, indicating the need for more studies. Placebo arms of future phase III maternal RSV vaccine trials could provide valuable RSV burden data through comprehensive prospective disease surveillance of pregnant individuals as well as their infants (as opposed to infants alone). Post-licensure studies of RSV vaccine effectiveness could also offer valuable insights into RSV-associated outcomes among unvaccinated pregnant individuals. Alongside increased testing for RSV in pregnant individuals with ARI, these approaches are crucial to capturing both the burden of RSV and the potential public health impact of maternal vaccines accurately. The adoption of standardized case definitions, testing, and reporting criteria through improved surveillance will facilitate more robust estimates of RSV disease burden in pregnant individuals. Further research could examine multiple pathogens, which would allow differentiation between RSV monoinfections and codetection with other viruses. This advancement seems achievable given the broader adoption of multiplex testing in response to the COVID-19 pandemic.

Conclusion

The RSV incidence rates in pregnant individuals may be comparable to those observed in adults aged 18-49 years with comorbidities. Compared with older adults or young children, incidence of RSV-associated severe disease, particularly hospitalizations in pregnant individuals, appears to be lower. For an accurate and reliable assessment of both RSV-associated hospitalizations and deaths in pregnant individuals, more comprehensive research in this area is critical given the limited data available. Without further analyses comparing RSV-positive vs RSV-negative or ARI vs non-ARI groups, we are unable to draw conclusions from our findings at this point for potential correlations between RSV infection during pregnancy and perinatal outcomes. With the rollout of maternal

RSV vaccines due to begin this autumn, these results underscore the need for ongoing research to ensure a comprehensive understanding of the burden of RSV in pregnant individuals.

Legend

Fig 1: Proportion positive for RSV in pregnant individuals with acute respiratory infections

Fig 2: Incidence rate of RSV in pregnant individuals

ARI: Acute respiratory infections; HIV: human immunodeficiency virus; ILI: Influenza-like illness; NA: Not available; PM: person-months; RSV: Respiratory syncytial virus; T1: First trimester; T2: Second trimester; T3: Third trimester; wGA: weeks' gestational age

Fig 3: Perinatal outcomes among pregnant individuals with and without RSV.

For Chu et al., 2016, low birth weight was available for 5 babies born in RSV-positive groups and 2736 babies born in RSV-negative groups. Preterm birth was available for 7 babies born in RSV-positive groups and 3612 babies born in RSV-negative groups.

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