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

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Background

RSV vaccines for pregnant individuals (PI) 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 PI and the pregnancy similar with other maternal immunizations [1, 2]. Scarce data are available about the burden of RSV infection among PI or the association between antenatal RSV and adverse perinatal outcomes [3]. We conducted a systematic review and meta-analysis of studies that reported laboratory tested RSV among PI to estimate the proportion of ARI episodes that are positive for RSV, incidence rates of antenatal RSV infection, and number of RSV-associated hospitalizations and deaths. We also characterized RSV-associated perinatal

Methods

We searched articles in 5 databases: Medline (Ovid), Embase (Ovid), Global Health (Ovid), Web of Science, and Global Index Medicus. We contacted observational study authors to obtain additional unpublished data pertinent to our review. We included data from studies related to PI with ARI who had been tested for RSV by culture, antigen, serology, and molecular testing. We used random-effects meta-analysis to estimate the proportion of PI with ARI who were positive for RSV; the RSV incidence rate; the RSVassociated hospitalization rate; and the association between RSV infection and perinatal outcomes: preterm birth (birth before 37 weeks' gestational age), low birth weight (<2500 g), stillbirth, and miscarriage [4]. PROSPERO registration: CRD42022372847

Results

Included studies identification (see Figure 1)

Database search: 6 studies; citation search: 2 studies; and unpublished Data: provided by authors of 3 observational studies.

Included studies characteristics

- Data collection period: 2010 to 2022
- Study locations: High-income countries (6 studies): (Australia, Canada, Israel, Panama, and United States), Uppermiddle-income countries (2 studies): (South Africa and Thailand), and Lower-middle-income countries (4 studies): (El Salvador, Kenya, Mongolia, and Nepal)
- Study duration: Year-round (4 studies): duration: 2-6 years and Seasonally (7 studies): duration: 1-8 seasons
- Gestational age details (5 studies): all 3 trimesters: 1 study, second and third trimesters: 3 studies, and first and second trimesters: 1 study



Figure 1: Study selection

Study	RSV-Positive	Total tested			Proportion positive (%)	95% CI	Weight
Africa							
Madhi et al., 2018_HIV-infected_South Africa	3	194			1.55	[0.32; 4.45]	8.2%
Madhi et al., 2018_HIV-uninfected_South Africa	18	2116	+		0.85	[0.50; 1.34]	9.9%
Nyawanda et al., 2022_HIV-infected_Kenya	19	517			3.68	[2.23; 5.68]	9.3%
Nyawanda et al., 2022_HIV-uninfected_Kenya	33	2360	+		1.40	[0.96; 1.96]	9.9%
Random effect meta-analysis		5187	\diamond		1.63	[0.77; 2.77]	37.2%
Heterogeneity: I^2 = 82.9% [56.4%; 93.3%], τ^2 = 0.001	1, <i>p</i> = 0.0005						
America							
Azziz-Baumgartner et al., 2022_El Salvador	11	149			7.38	[3.74; 12.83]	7.8%
Azziz-Baumgartner et al., 2022_Panama	3	47			6.38	[1.34; 17.54]	5.2%
Frivold et al., Unpub_USA	6	93			6.45	[2.40; 13.52]	6.8%
Hause et al., 2018_USA	8	81			- 9.88	[4.36; 18.54]	6.5%
Hause et al., 2021_USA	25	1057			2.37	[1.54; 3.47]	9.7%
Random effect meta–analysis		1427			5.79	[2.45; 10.30]	36.0%
Heterogeneity: $I^2 = 79.4\%$ [51.3%; 91.3%], $\tau^2 = 0.006$	2, <i>p</i> = 0.0006						
South-East Asia							
Chu et al., 2016_Nepal	7	733			0.95	[0.38; 1.96]	9.5%
Dawood et al., Unpub_Thailand	66	614		+	10.75	[8.41; 13.47]	9.4%
Random effect meta-analysis		1347			- 4.61	[0.00; 18.65]	18.9%
Heterogeneity: $I^2 = 98.6\%$ [97.1%; 99.4%], $\tau^2 = 0.027$	'0, <i>p</i> < 0.0001						
Western Pacific							
Chaw et al., 2016_Mongolia	4	165			2.42	[0.66; 6.09]	7.9%
Overall random effect meta–analysis		8126	\langle		3.49	[1.91; 5.47]	100.0%
Prediction interval						[0.00; 12.87]	
Heterogeneity: $l^2 = 93.1\%$ [89.8%; 95.4%], $\tau^2 = 0.005$	6, <i>p</i> < 0.0001						
Test for subgroup differences: $\chi_2^2 = 7.34$, df = 3 ($p = 0$.0617)		0 5 10	D 15			

Proportion of pregnant individuals with RSV-positive acute respiratory infections

- Total tested: 8126; total RSV cases: 203; RSV positivity range [0.9%-10.7%]
- Pooled RSV positivity (see Figure 2): 3.4% (95% CI: 1.9; 5.4)
- RSV positivity by study timing (p<0.001): during RSV seasons: 4.4% (95% CI: 0.8; 10.1) and year-round studies: 2.5% (95% CI: 1.3; 4.0)
- RSV positivity by case ascertainment settings: outpatients: 9.8% (95% CI: 4.3; 18.5), community participants: 5.5% (95% CI: 0.6; 14.0), outpatients & inpatients: 3.6% (95% CI: 0.3; 8.8), and community, outpatient, & inpatient participants: 1.7% (95% CI: 0.8; 2.7)

Figure 2: Proportion positive for RSV in pregnant individuals with acute respiratory infections

				Study	Study period	Gestational age	Population	Incidence rate (per 1000 PN	1) 95%-Cl Weight	
 Incidence rate of RSV in pregnant individuals RSV incidence rate range: [0.2; 24.0] per 1000 person-months Pooled RSV Incidence rate (see Figure 3): 2.1 [CI 95%: 1.3; 3.0] per 1000 person-months Incidence rate by study timing (p<0.01): seasonal studies: 1.7 [CI 95%: 1.0; 2.3] per 1000 person-months and year-round studies: 4.9 [0.3; 9.5] per 1000 person-months 				Seasonal Chaw et al., 2016 Chaw et al., 2016 Chaw et al., 2016 Dawood et al., Unpub Dawood et al., Unpub Madhi et al., 2018	$ \begin{array}{c} \longrightarrow 24.00 \ [12.00; 45.00] 0.3\% \\ 3.00 \ [3.00; 9.00] 4.0\% \\ \hline 9.00 \ [6.00; 15.00] 2.5\% \\ 0.21 \ [0.01; 1.04] 7.8\% \\ 0.20 \ [0.01; 1.00] 7.8\% \\ 1.06 \ [0.39; 2.34] 7.3\% \\ 2.03 \ [1.03; 3.62] 6.8\% \\ 2.12 \ [1.07; 3.77] 6.7\% \\ 3.25 \ [1.92; 5.17] 6.2\% \\ 1.06 \ [0.39; 2.34] 7.3\% \\ 2.03 \ [1.03; 3.62] 6.8\% \\ 0.85 \ [0.27; 2.04] 7.4\% \\ 0.81 \ [0.26; 1.96] 7.4\% \\ 5.30 \ [3.10; 8.90] 4.1\% \\ \end{array} $					
Study or Subgroup	RSV–positive RSV–negative Events Total Events Total OR [95% CI]		RSV-associated hospitalizations and deaths in pregnant	Madhi et al., 2018 Madhi et al., 2018 Random effects mod Heterogeneity: <i>I</i> ² = 77%, Year-round Nyawanda et al., 2022	Mai/2017-Jul/2012 Mar/2012-Jul/2012 Mar/2012-Jul/2012 el $\tau^2 = 1.2141, p < 0.01$ Feb/2015-Jan/2019 Feb/2015-Jan/2019	NA NA NA T1, T2 T1, T2	ARI, HIV-uninfected	d	$\begin{array}{rcrcrcr} 1.50 & [0.10; 0.30] & 4.1\% \\ 1.50 & [0.60; 4.00] & 6.1\% \\ \hline 6.50 & [2.10; 20.20] & 0.8\% \\ 1.70 & [1.00; 2.39] & 89.3\% \\ \end{array}$	
Low birth weight Chu et al., 2016_Nepal Dawood et al., Unpub_Thailand Madhi et al., 2018_South Africa Random effect meta-analysis Heterogeneity: Tau ² = 1.1387; Chi ² = 1	$\begin{array}{cccccccccccccccccccccccccccccccccccc$		 Individuals RSV hospitalization rate in PI: El Salvador study (3.0 per 1000 person-years) (Azziz-Baumgartner et al., 2022) and 	Random effects mode Heterogeneity: $I^2 = 85\%$, Random effects mode Heterogeneity: $I^2 = 82\%$, Test for subgroup differen	$\tau^{2} = 9.3656, p = 0.01$ el $\tau^{2} = 2.3286, p < 0.01$ nces: $\chi^{2}_{1} = 1.90, df = 1 (p$	= 0.17)			4.95 [0.38; 9.52] 10.7% 2.17 [1.32; 3.02] 100.0%	
Miscarriage Chu et al., 2016_Nepal Dawood et al., Unpub_Thailand	0 7 8 3686 28.85 [1.52; 546.16] 0 66 0 548		Unpublished study from Thailand (2.4 [CI 95%: 0.4; 17.3] per 1000 person-years) (Dawood et al.)	Figure 3: Incidence rate of RSV in pregnant individuals						
Preterm birth Chu et al., 2016_Nepal Dawood et al., Unpub_Thailand Madhi et al., 2018_South Africa Random effect meta-analysis Heterogeneity: Tau ² = 0.3644; Chi ² = 5	$2 7 469 3612 2.68 [0.52; 13.86] \\8 66 8 548 9.31 [3.37; 25.73] \\2 18 181 1980 1.24 [0.28; 5.45] \\91 6140 3.68 [1.31; 10.37] \\5.25, \ df = 2 \ (P = 0.0726); \ I^2 = 61.9\% [0.0\%; 89.1\%]$		 No deaths (203 RSV+ among 4708 PI; n= 5 studies). 		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					
Small for gestational age Chu et al., 2016_Nepal Dawood et al., Unpub_Thailand Random effect meta-analysis Heterogeneity: Tau ² = 2.3300; Chi ² = 2	$1 7 1495 3686 0.24 \ [0.03; 2.03] \\ 4 66 4 548 8.77 \ [2.14; 35.96] \\ \hline 73 4234 1.76 \ [0.15; 20.50] \\ \hline 7.61, df = 1 \ (P = 0.0058); \ I^2 = 86.9\% \ [48.2\%; 96.7\%]$		 Perinatal outcomes in pregnant individuals with RSV-associa Outcomes not impacted by antenatal RSV infection: stillbirths, sm 	ited acute all for gesta	respirat tional add	ory inf	ections arriage, l	(see Figure ow birth weig	e 4) aht	
Stillbirth Chu et al., 2016_Nepal Madhi et al., 2018_South Africa Random effect meta-analysis Heterogeneity: Tau ² = 0; Chi ² = 0.15, c	$\begin{array}{cccccccccccccccccccccccccccccccccccc$		 Difference in odds of preterm birth: Significant difference between CI: 1.3; 10.3]; (3 studies) 	n RSV-positi	ve vs. RS	SV-negat	tive PI; (Odds Ratio (0	OR): 3.6 [95%	

Figure 4: Perinatal outcomes among pregnant individuals with and without RSV

0.01 0.1 1 10 100

✤RSV incidence rates in PI 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 PI, appears to be lower;

Few data available on the burden (hospitalizations and deaths) of RSV in PI;

* Few studies have been conducted on potential correlations between RSV infection during pregnancy and perinatal outcomes.

*As the quest for passive immunization with a safe and effective maternal RSV vaccine continues, these results underscore the need for ongoing research to ensure a comprehensive understanding of the RSV infection effects during pregnancy.



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