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MAJOR ARTICLE

Severity of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Pregnancy in Ontario: A Matched Cohort Analysis

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Background. Pregnancy represents a physiological state associated with increased vulnerability to severe outcomes from infectious diseases, both for the pregnant person and developing infant. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic may have important health consequences for pregnant individuals, who may also be more reluctant than nonpregnant people to accept vaccination.

Methods. We sought to estimate the degree to which increased severity of SARS-CoV-2 outcomes can be attributed to pregnancy using a population-based SARS-CoV-2 case file from Ontario, Canada. Because of varying propensity to receive vaccination, and changes in dominant circulating viral strains over time, a time-matched cohort study was performed to evaluate the relative risk of severe illness in pregnant women with SARS-CoV-2 compared to other SARS-CoV-2 infected women of childbearing age (10–49 years old). Risk of severe SARS-CoV-2 outcomes was evaluated in pregnant women and time-matched nonpregnant controls using multivariable conditional logistic regression.

Results. Compared with the rest of the population, nonpregnant women of childbearing age had an elevated risk of infection (standardized morbidity ratio, 1.28), whereas risk of infection was reduced among pregnant women (standardized morbidity ratio, 0.43). After adjustment for confounding, pregnant women had a markedly elevated risk of hospitalization (adjusted odds ratio, 4.96; 95% confidence interval, 3.86–6.37) and intensive care unit admission (adjusted odds ratio, 6.58; 95% confidence interval, 3.29–13.18). The relative increase in hospitalization risk associated with pregnancy was greater in women without comorbidities than in those with comorbidities (*P* for heterogeneity, .004).

Conclusions. Given the safety of SARS-CoV-2 vaccines in pregnancy, risk-benefit calculus strongly favors SARS-CoV-2 vaccination in pregnant women.

Keywords. SARS coronavirus; pregnancy; COVID-19; epidemiology; respiratory disease; outcomes.

Pregnant individuals represent an important priority population for communicable disease prevention, for several reasons. The pregnant state results in changes in the immune system necessary for immune tolerance of the fetus [1, 2], and that may result in greater severity of some infections [1, 3–5]. Physiological changes associated with pregnancy, including metabolic and hormonal changes, and mechanical reduction in respiratory reserve, make pregnant individuals more vulnerable to respiratory impairment [5, 6]. Management of critical illness in pregnancy is challenging because of the distinct physiology of pregnant people and concerns around the use of some therapeutic agents, whereas critical illness in the pregnant individual may result in fetal demise [5, 7]. Finally, although vaccines in pregnancy, including those that prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, are safe and effective [8], their uptake may be limited because of aversion to pharmaceuticals on the part of both pregnant individuals and care providers [9, 10], as well as informational gaps due to the purposeful exclusion of pregnant individuals from clinical trials. Informed decisions around vaccine acceptance depend on accurate information on the risks of SARS-CoV-2 in the context of pregnancy.

SARS-CoV-2 has infected hundreds of millions of people since the disease emerged in 2019; it has also caused critical illness and death in millions [11]. In the United States, pregnant women have been found to be at a markedly elevated risk of critical illness from SARS-CoV-2 infection, as well as an elevated risk of stillbirth [12–14]. Initial analyses failed to identify an elevated risk of death among pregnant women with SARS-CoV-2 infection, but a subsequent reanalysis identified increased mortality risk, likely because of increased event numbers with the passage of time [13]. Although the per capita incidence of

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SARS-CoV-2-related illness and death has been lower in Canada than in the United States [15, 16], the pandemic has been the cause of tens of thousands of excess deaths in Canada, notwithstanding likely undercounting of SARS-CoV-2 attributable mortality [17]. A multiprovince Canadian surveillance group has reported elevated risk of hospitalization and critical illness associated with SARS-CoV-2 in pregnant individuals in Canada, but this report was published in early June 2021, just as the Delta variant of concern (VOC) was emerging, and relatively early in the Canadian SARS-CoV-2 vaccination effort [18, 19]. Furthermore, this report was largely descriptive, and did not adjust for confounding by VOC, vaccination, age, underlying comorbidity, or healthcare worker status.

The Canadian province of Ontario represents a large (population 14.6 million) and diverse jurisdiction, with high levels of SARS-CoV-2 vaccine coverage (approximately 80% as of December 2021) [20, 21]. Ontario has weathered multiple pandemic waves because of the original circulating variant of SARS-CoV-2, and latterly waves caused by the Alpha (spring 2021) and Delta (summer and autumn, 2021) VOC [22], with the Omicron VOC displacing Delta in December 2021 [23].

The province's rich data sources provide an opportunity for evaluation of the impact of SARS-CoV-2 in pregnant women, relative to other women of childbearing age, and with adjustment for important confounders. Our principal objective was to evaluate the relative morbidity associated with SARS-CoV-2 infection in pregnancy in Ontario. Secondary objectives were to evaluate the impact of infecting VOC and vaccination status on SARS-CoV-2 outcomes.

METHODS

Data Sources

As the likelihood of vaccination, the dominant SARS-CoV-2 variant, and the provincial public health response changed over time, we created a time-matched cohort of women infected with SARS-CoV-2 in pregnancy; nonpregnant controls were individuals with SARS-CoV-2 matched to pregnant women by date of positive laboratory test for SARS-CoV-2. Pregnant individuals and matched nonpregnant controls were identified in the Province's Case and Contact Management database as described elsewhere [24, 25]; we included only cases with a unique "pseudo-health card number," which permitted linkage with the provincial vaccination database. Control selection was limited to women of reproductive age. Because data were available by 10-year age bands, we considered "reproductive age" to encompass individuals aged 10 to 49 years. Data on comorbidities, healthcare worker status, and infecting variant were also available in the Case and Contact Management database. Comorbidities included neurologic disorders, asthma, renal conditions, blood disorders, cancer, cardiovascular conditions, liver conditions, and obesity. We included the period between 1 January 2020 and 4 January 2022 in the analysis.

Population denominators for the population overall and for women aged 10–49 years in Ontario, were obtained from Statistics Canada [20]. We estimated person-time at risk of SARS-CoV-2 infection among pregnant individuals based on reports of 107 855 live births and 482 stillbirths among women of childbearing age in Ontario between 1 January and 31 October 2021 [26]. Person-time at risk was adjusted based on an assumed duration of pregnancy of 40 weeks. To estimate person-time at risk of SARS-CoV-2 infection for nonpregnant women of childbearing age, we subtracted estimated annual person-time at risk among pregnant individuals from the population of women of childbearing age. The person-time at risk among those not classified as women of childbearing age was estimated as the total population size, minus the population of women of childbearing age. Variants were classified as non-variant of concern, N501Y+ variant (including the Alpha, Beta, and Gamma variants), or Delta variant, as described elsewhere [25]. Individuals were considered infected with the Omicron variant (B.1.1.529) if they had been identified as such through viral sequencing, if they were infected with a strain with S-gene target failure on polymerase chain reaction, or with the N501Y mutation, on or after 10 November 2021.

Vaccination information on cases and controls was extracted from the Province's COVaxON dataset [25], which includes dosage dates and vaccines used. To account for time to develop immunity, we considered individuals to have been vaccinated with a first dose of vaccine during time at risk 14 or more days after the date of their first vaccine dose; individuals were considered vaccinated with 2 doses of vaccine during time at risk 14 or more days after their second vaccine dose. A flow diagram outlining creation of the cohort is presented in Figure 1.

Analysis

We explored temporal trends in case incidence overall, in women aged 10–49 years, and in pregnant women, graphically and through calculation of standardized morbidity ratios (SMRs) as described previously [27]. Briefly, SMRs were estimated as incidence in pregnant women, or nonpregnant women of childbearing age, divided by incidence in the population overall. We calculated SMRs for the entire study period and by week. Confidence intervals for proportions were estimated based on standard errors for log-SMRs as previously [27].

We used multivariable conditional logistic regression models to estimate the risk of severe illness among our matched cohort while adjusting for age (treated as a 4-level ordinal variable), comorbidity, healthcare worker status, vaccination status, and infecting variant, all of which were selected a priori. Severe illness was defined as hospitalization or intensive care unit (ICU) admission. We were not able to include death as an outcome because fewer than 5 pregnant individuals died of SARS-CoV-2

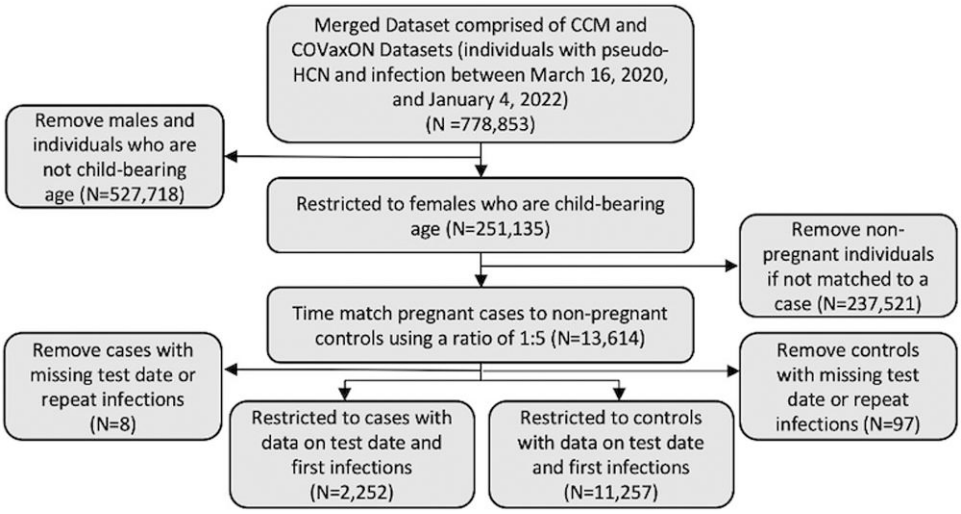

Figure 1. Flow diagram for creation of case-cohort sample. Abbreviations: CCM, Ontario's COVID-19 Contact Case Management Database; COVaxON, Ontario's COVID-19 vaccination database.

in Ontario at the time of analysis. Because of small numbers of adverse outcomes in individuals vaccinated with 3 doses, we treated vaccination as an ordinal variable with 3 levels (ie, unvaccinated, 1 dose, and 2 or more doses).

Because some pregnant individuals infected with SARS-CoV-2 might be hospitalized for monitoring, we performed an additional restriction analysis, in which risk of ICU was evaluated among pregnant and nonpregnant women admitted to hospital. We hypothesized that if pregnant individuals were admitted for precautionary reasons, they would be less likely to be admitted to ICU than nonpregnant controls, and if admission was due to severity of illness, pregnant individuals should be as or more likely than nonpregnant controls to be admitted to ICU. Because of lack of within-stratum variance in healthcare worker status and infecting variant among those admitted to hospital, we adjusted only for age, comorbidity, and vaccination in analyses restricted to hospitalized individuals.

We performed a series of exploratory restriction analyses within each stratum of comorbidity status, age group, vaccination status, or infecting variant variables to evaluate modification of the observed effects by these covariates in pregnant individuals and nonpregnant controls. Because conditional logistic regression models failed to converge for some of these models, we used logistic regression models with time modeled as a cubic term. Heterogeneity in adjusted odds ratios for hospitalization and ICU admission was evaluated using meta-analytic techniques (ie, graphically using forest plots, and statistically using the meta-analytic Q statistic). Our study was conducted in accordance with the STROBE guidelines for observational research [28], and received ethics approval from the Research Ethics Board at the University of Toronto.

RESULTS

Our final cohort consisted of 2252 pregnant women and 11 257 nonpregnant controls, with 5 controls for all but 3 cases (which had 4 matched controls each), with test dates between 16 March 2020, and 4 January 2022. Although the temporal pattern of infection risk in pregnant individuals and nonpregnant women of childbearing age mirrored risk in the population as a whole over time, risk was elevated in nonpregnant women of childbearing age (SMR 1.28) and decreased in pregnant women (SMR 0.43) (Figure 2).

In our matched cohort, pregnant individuals and nonpregnant controls differed significantly according to risk of hospitalization and ICU admission, as well as age distribution, vaccination status, healthcare worker status, and the presence of any significant comorbidity. Pregnant individuals were more likely than nonpregnant controls to have asthma, diabetes, or a diagnosed hematological disorder. There were no differences between pregnant women and nonpregnant controls with respect to infecting variant, likely because we created a time-matched cohort (Table 1).

Conditional logistic regression models for hospitalization and ICU admission are presented in Table 2. After adjusting for potential confounders, we identified a marked increase in risk of admission to hospital (adjusted odds ratio [aOR], 4.94; 95% confidence interval [CI], 3.85–6.34) and ICU admission (aOR, 6.58; 95% CI, 3.29–13.18) in pregnant individuals with SARS-CoV-2 infection compared with nonpregnant controls. We found no significant difference in risk of ICU admission between pregnant and nonpregnant women conditional on hospital admission after adjusting for comorbidity, age, vaccination status, and infecting variant (aOR, 1.30; 95% CI, .70–2.45).

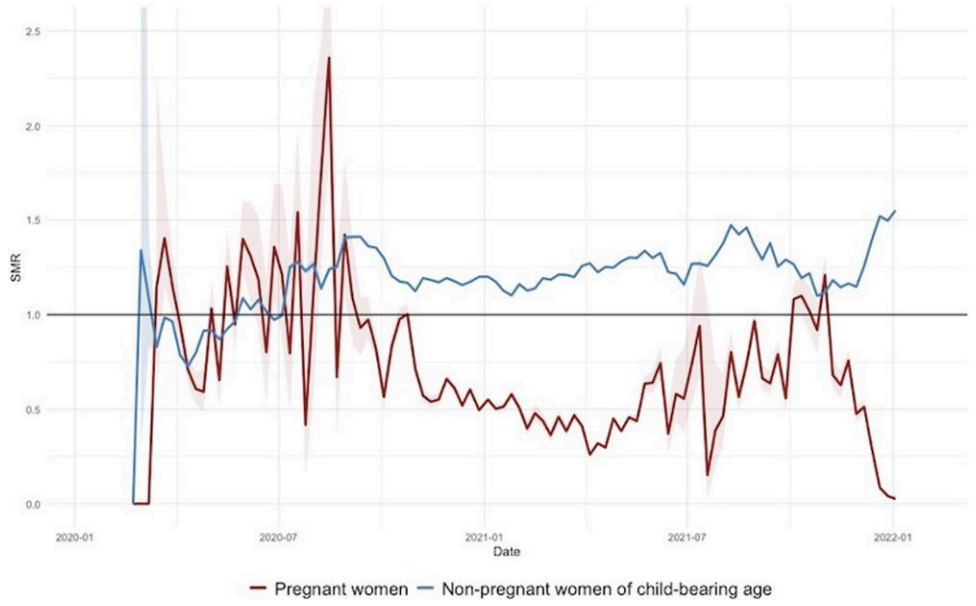

Figure 2. Standardized mortality ratios over time of SARS-CoV-2 cases in pregnant women and nonpregnant women of child-bearing age, Ontario, Canada, January 2020–January 2022. Line of reference at (black) depicts overall Ontario population. Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SMR, standardized mortality ratio.

We performed unmatched logistic regression analyses, with adjustment for time trends and models restricted to individuals with similar comorbidity, vaccination or healthcare worker status, or age group. A summary of the heterogeneity in effect sizes for hospitalizations and ICU admission based on comorbidity status is displayed in Figure 3. The odds of hospitalization among pregnant individuals were significantly greater in analyses restricted to those without recorded comorbidities (aOR, 5.59; 95% CI, 4.34–7.20), compared with analyses restricted to those with comorbidities (aOR, 2.26; 95% CI, 1.28–3.99) (*P* for heterogeneity .029), but no heterogeneity in ICU admission risk by presence of comorbidity (Supplementary Table 1). We did not identify heterogeneity in the effect of pregnancy by infecting variant or vaccination status.

DISCUSSION

In a cohort of pregnant and nonpregnant women in Ontario, Canada, pregnancy was associated with a decreased risk of infection, but a markedly increased risk of severe illness following infection with SARS-CoV-2. We speculate that the decreased risk of infection in pregnant women may derive from greater adherence to public health guidance or avoidance of high-risk transmission settings. The large increase in risk of severe illness in pregnant women, conditional on infection, persisted after adjustment for age, comorbidity, vaccination status, and infecting variant. That pregnant and nonpregnant women were matched by approximate date of infection makes it unlikely that the large increase in hospitalization and ICU risk associated with pregnancy is due to varying propensity to receive vaccination over time or by temporal changes in circulating variants of concern. Furthermore, we did not see a diminished risk of ICU admission in hospitalized pregnant women when they were compared with other hospitalized women, suggesting that pregnant women were likely to have been admitted to hospital for severity of respiratory illness rather than simply for monitoring.

The excess risk associated with pregnancy was less pronounced when analyses were restricted to pregnant and nonpregnant women who had comorbidities, again suggesting that in otherwise healthy women, pregnancy itself is a factor that increases illness severity, whereas in women with comorbidities it becomes 1 of several factors that augments risk. The physiology of increased severity of respiratory virus infection in pregnancy is complex and not fully understood in the context of SARS-CoV-2. Although pregnant women have increased cardiac demand, diminished pulmonary reserve, and physiological impairment of the immune response (which serves to prevent rejection of the developing fetus), and these changes have been linked to worse outcome with pulmonary infection [5, 29], coronavirus disease 2019 (COVID-19) is not simply an infection of the respiratory system. Numerous vascular and hematological abnormalities occur following SARS-CoV-2 infection, and reports of elevated risk of stillbirth in infected individuals [12] and pathological changes reported in the placenta [30], may suggest that some of the excess morbidity we describe here is related to vascular and hematological disease rather than respiratory disease.

Table 1. Characteristics of Matched Study Cohort by Pregnancy Status, Ontario, Canada[a]

	Pregnant Women	(%)	Nonpregnant Controls	(%)	Total	(%)	*P* value
N	2252	…	11 257	…	13 509	…	
Outcome	…	…	…	…	…	…	
Hospitalization	155	6.88	186	1.65	341	2.52	<.001
Intensive care unit admission	26	1.15	28	0.25	54	0.40	<.001
Age group, y	…	…	…	…	…	…	<.001
10–19	33	1.47	1876	16.67	1909	14.13	
20–29	921	40.90	3453	30.67	4374	32.38	
30–39	1208	53.64	3006	26.70	4214	31.19	
40–49	90	4.00	2922	25.96	3012	22.30	
Vaccination status	…	…	…	…	…	…	.004
Unvaccinated	2009	89.21	9756	86.67	11 765	87.09	
Single dose	53	2.35	342	3.04	395	2.92	
≥2 doses	190	8.44	1159	10.30	1313	9.72	
Healthcare worker	295	13.10	1018	9.04	1313	9.72	<.001
Any significant comorbidity	230	10.21	749	6.65	979	7.25	<.001
Asthma	94	4.17	301	2.67	395	2.92	<.001
Hematological disease	46	2.04	121	1.07	167	1.24	<.001
Cardiac disease	21	0.93	114	1.01	135	1.00	.727
Diabetes	57	2.53	123	1.09	180	1.33	<.001
Renal disease	7	0.31	23	0.20	30	0.22	.327
Neurological disease	9	0.40	35	0.31	44	0.33	.500
Obesity	11	0.49	42	0.37	53	0.39	.424
Immune compromised	9	0.40	81	0.72	90	0.67	.088
Infecting variant	…	…	…	…	…	…	.149
Delta variant of concern	345	15.32	1609	14.29	1954	14.46	
N501Y+ variant of concern	433	19.23	2141	19.02	2574	19.05	
Nonvariant of concern	103	4.57	530	4.71	633	4.69	
Unknown variant of concern	1321	58.66	6680	59.34	8001	59.23	
Other variant of concern	25	1.11	96	0.85	121	0.90	
Omicron variant of concern	25	1.11	201	1.79	226	1.67	

[a]Absolute numbers not shown for deaths, or specific comorbidities (liver disease and chronic obstructive pulmonary disease) from concern with identifiability with small cell sizes (N < 5). Differences between pregnant and nonpregnant women were nonsignificant ($P > .50$) for all of these outcomes and characteristics. Proportions compared using χ^2 tests.

Although our primary aim in this study was to evaluate the impact of pregnancy on risk of severe illness with SARS-CoV-2, vaccination, including partial vaccination, was associated with a marked reduction in hospital admission risk and ICU admission in multivariable analyses, notwithstanding that in this case-only analysis, all vaccinated women had, by definition, experienced breakthrough infections. Again, given the safety of these vaccines in pregnancy [8], and the markedly elevated risk of severe illness in pregnancy, risk calculus strongly favors vaccination for pregnant women.

Like any observational study, ours is subject to several limitations. The recent emergence of the Omicron variant makes us unable to explore the relative virulence of this variant in pregnancy in the current paper [23]. Our estimates may also be subject to residual confounding by incompletely ascertained factors, including presence of underlying medical conditions. Comorbidity data were not validated; comorbidities were classified as "present" by the local public health personnel evaluating the case, and as such may have been misclassified in some cases. However, the very large effect size associated with pregnancy means that the magnitude of effect of putative confounding by unmeasured factors needed to explain away these associations would be implausibly large [31]. Furthermore, for pregnancy estimates to be inflated by unmeasured confounding by comorbidity, differential underreporting of comorbidities in pregnant cases would need to have occurred; we would expect that, if anything, pregnancy status would result in more complete ascertainment of medical historical factors. This is consistent with the fact that comorbidities were more commonly reported in pregnant women in our cohort. Because achieving pregnancy may be challenging in individuals with multiple comorbidities, a higher prevalence of comorbidities in pregnant individuals is contrary to expectations and likely suggests increased ascertainment in these individuals.

In summary, we identify a large increase in risk of hospitalization and ICU admission in pregnant women infected with SARS-CoV-2 virus, relative to female controls of childbearing age. This effect was not explained by comorbidity or vaccination status, and indeed, the relative increase in risk with pregnancy was greater when we restricted our analyses to women

Table 2. Results of Multivariable Conditional Logistic Regression Model on Hospitalization and ICU Admission in Pregnant Women Because of SARS-CoV-2 Infection

Covariate	Crude Odds Ratio	LCL	UCL	*P* value	Adjusted Odds Ratio	LCL	UCL	*P* value
				Hospitalization				
Pregnancy	4.46	3.57	5.56	<.001	4.94	3.85	6.34	<.001
Vaccination	…	…	…		…	…	…	…
Unvaccinated (Referent)	1.00	…	…		1.00	…	…	…
1 dose	0.45	0.20	1.01	.054	0.51	0.21	1.24	.137
≥2 doses	0.08	0.03	0.22	<.001	0.07	0.02	0.23	<.001
Age group (per 10-y increase)	1.44	1.27	1.64	<.001	1.69	1.45	1.98	<.001
Healthcare worker	0.42	0.25	0.71	.001	0.34	0.20	0.58	<.001
Comorbidity	3.65	2.58	5.18	<.001	3.59	2.39	5.38	<.001
Infecting variant[a]	…	…	…		…	…	…	…
Delta VOC	1.04	0.62	1.76	.882	0.86	0.47	1.59	.638
N501Y+ VOC	0.90	0.58	1.40	.646	0.82	0.50	1.34	.430
				ICU Admission				
Pregnancy	4.64	2.72	7.92	<.001	6.58	3.29	13.18	<.001
Vaccination	…	…	…		…	…	…	…
Unvaccinated (referent)	1.00	…	…		1.00	…	…	…
1 dose	0.33	0.04	2.62	.295	0.34	0.02	4.87	.424
≥2 doses	0.25	0.03	2.04	.197	0.25	0.02	2.55	.241
Age group	1.53	1.13	2.08	.006	1.71	1.11	2.64	.015
Healthcare worker	0.16	0.03	0.78	.024	0.09	0.02	0.47	.005
Comorbidity	7.91	3.33	18.83	<.001	8.71	2.88	26.36	<.001
Infecting variant[a]	…	…	…		…	…	…	…
Delta VOC	5.06	0.80	32.10	.085	13.50	0.53	343.19	.115
N501Y+ VOC	1.42	0.48	4.20	.522	0.94	0.25	3.45	.920

Abbreviations: ICU, intensive care unit; LCL, 95% lower confidence limit; UCL, 95% upper confidence limit; VOC, variant of concern.

[a]Infection with strains classified as non-VOC, other VOC status (including Omicron VOC), or VOC status unknown used as referent.

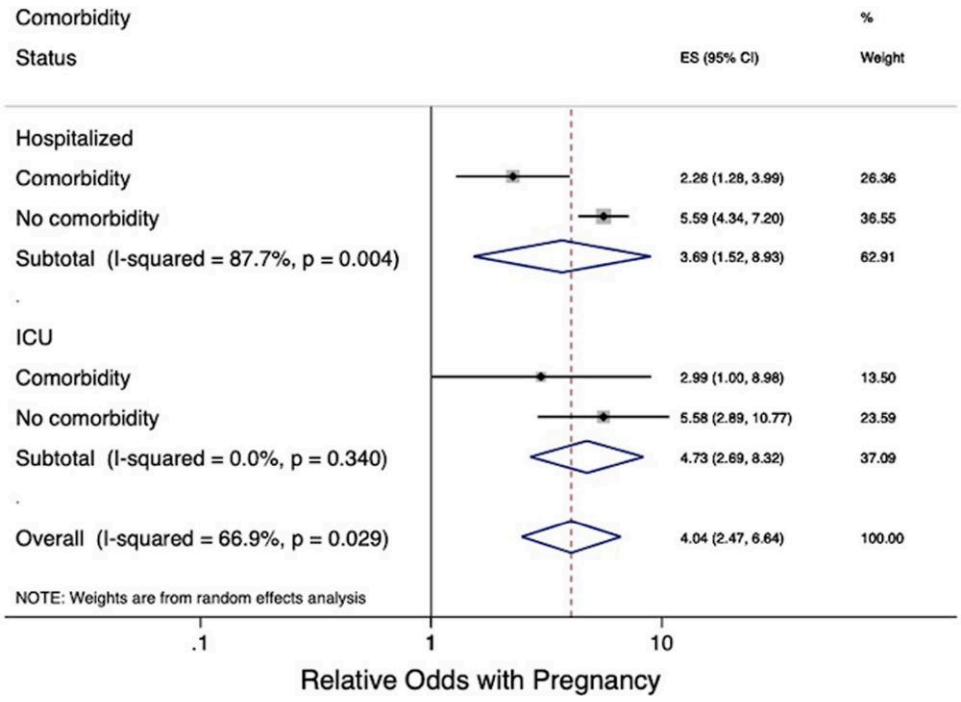

Figure 3. Forest plot summarizing heterogeneity in effect sizes between comorbidity status and severe outcome. Results are stratified on outcome (hospitalization and intensive care unit admission).

without medical comorbidities. Vaccination markedly reduced hospitalization and ICU admission risk in all women, pregnant and nonpregnant, in this study, and should be strongly encouraged in pregnancy.

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.

Notes

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Potential conflicts of interest. D. N. F. has served on advisory boards related to influenza and SARS-CoV-2 vaccines for Seqirus, Pfizer, Astrazeneca, and Sanofi-Pasteur Vaccines, and has served as a legal expert on issues related to COVID-19 epidemiology for the Elementary Teachers Federation of Ontario and the Registered Nurses Association of Ontario. A. R. T. was employed by the Public Health Agency of Canada when this research was conducted. The work does not represent the views of the Public Health Agency of Canada. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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