



## Original article

# Vaccination against SARS-CoV-2 in pregnancy during the Omicron wave: the prospective cohort study of the Italian obstetric surveillance system

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## ABSTRACT

**Objectives:** Evidence on the effects of the SARS-CoV-2 Omicron variant on vaccinated and unvaccinated pregnant women is sparse. This study aimed to compare maternal and perinatal outcomes of women infected with SARS-CoV-2 during the Omicron wave in Italy, according to their vaccine protection.

**Methods:** This national prospective cohort study enrolled pregnant women with a positive SARS-CoV-2 nasopharyngeal swab within 7 days of hospital admission between 1 January and 31 May, 2022. Women who received at least one dose of vaccine during pregnancy and those who completed the vaccine cycle with the first booster were considered protected against moderate or severe COVID-19 (MSCD). A multivariable logistic regression model evaluated the association between vaccine protection and disease severity. Maternal age, educational level, citizenship, area of birth, previous comorbidities, and obesity were analysed as potential risk factors.

**Results:** MSCD was rare (41/2147, 1.9%; 95% CI, 1.4–2.6), and the odds of developing it were significantly higher among unprotected women (OR, 2.78; 95% CI, 1.39–5.57). Compared with protected women ( $n = 1069$ ), the unprotected ( $n = 1078$ ) were more often younger, with lower educational degrees, and foreigners. A higher probability of MSCD was found among women with previous comorbidities (OR, 2.86; 95% CI, 1.34–6.12) and those born in Asian countries (OR, 3.05; 95% CI, 1.23–7.56). The percentage of preterm birth was higher among women with MSCD compared with milder cases (32.0% [8/25] versus 8.4% [161/1917],  $p < 0.001$ ) as well as the percentage of caesarean section (52.0% [13/25] versus 31.6% [606/1919],  $p = 0.029$ ).

**Discussion:** Although severe maternal and perinatal outcomes were rare, their prevalence was significantly higher among women without vaccine protection. Vaccination during pregnancy has the potential to protect both the mother and the baby, and it is therefore strongly recommended. **Edoardo Corsi Decenti, Clin Microbiol Infect 2023;29:772**

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## Introduction

During the SARS-CoV-2 pandemic, pregnant women had an increased risk of severe COVID-19 compared with the general population [1,2]. Mother-to-child transmission in utero was documented to be rare [3,4], and infected mothers showed a good immunological response with a substantial transfer of anti-SARS-CoV-2 antibodies to the newborn [5].

Although multiple studies describe a robust maternal antibody response to vaccination against SARS-CoV-2 and no safety concerns [6], the vaccine uptake during pregnancy remains lower compared with the general population [7]. Overall, the duration of the protection against severe disease, estimated to last 4 to 6 months after one or two doses of vaccine [8–10] and the vaccines' immunogenicity and reactogenicity against SARS-CoV-2 in pregnancy seem to be similar to those observed in non-pregnant women [11]. A recent metanalysis reported a decreased risk of neonatal intensive care unit (NICU) admission and intrauterine fetal death and no increase in the risk of adverse peripartum outcomes among women who received at least one dose during pregnancy, compared with those who did not [12].

In Italy, from January 2021, the vaccination with mRNA vaccines was recommended from the second trimester of pregnancy in women at increased risk of SARS-CoV-2 infection and/or severe disease [13]. In September 2021, the recommendation was extended to all pregnant women, regardless of risk factors [14]. Since September 2022, primary vaccination and booster doses are recommended at any time in gestation.

Since the beginning of the pandemic, the Italian Obstetric Surveillance System (ItOSS) of the *Istituto Superiore di Sanità* (Italian National Institute of Health) launched a national study to monitor the effect of SARS-CoV-2 in pregnancy [15]. To date, few studies have yet been conducted on the effects of the Omicron variant on vaccinated and unvaccinated pregnant women [16,17].

The present study aimed to compare maternal and perinatal outcomes of women infected with SARS-CoV-2 during the Omicron wave in Italy, according to their vaccine protection.

## Methods

### Study design, participants, and data collection

The present national prospective cohort study enrolled pregnant women with a positive SARS-CoV-2 nasopharyngeal swab within 7 days from hospital admission in any Italian maternity unit, between 1 January and 31 May, 2022. The Ethics Committee of the Italian National Institute of Health approved the study (Prot. 0010482 CE 01.00, Rome 24/03/2020).

Trained reference clinicians in each Italian maternity unit ([Appendix 1](#)) collected the women's informed consent and entered through an online form the information of interest. Women were also asked if they received vaccination against SARS-CoV-2 and the number and timing (before and/or during pregnancy) of the doses received. Data was transmitted through a secure server.

The present analysis includes the cases notified within 15 September 2022. Weekly e-mail reminders and phone contacts were used to reduce incomplete reporting. Maternal deaths were crosschecked with the ItOSS surveillance data [18].

### Outcomes

The main outcome measure was the COVID-19 severity, defined as mild (absence of COVID-19 pneumonia), moderate (confirmed pneumonia requiring at most oxygen therapy), and severe (confirmed pneumonia requiring mechanical ventilatory support and/or intensive care unit [ICU] admission). The two highest severity levels, characterised by the presence of pneumonia, were aggregated for the statistical analysis in the category 'moderate or

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severe COVID-19' (MSCD). Secondary outcomes included (1) pre-term birth, (2) mode of delivery, (3) stillbirth, (4) NICU admission, and (5) early neonatal mortality before hospital discharge.

### Covariates

Protection against MSCD was considered the exposure variable. During the study period, vaccination against SARS-CoV-2 was recommended from the second trimester of pregnancy [13]. Its protection was assumed to last from 4 to 6 months following one or two doses [8–10]. Women who received at least one dose during pregnancy and those who completed the vaccine cycle with the first booster were considered protected against MSCD; unvaccinated women and those who received one or two doses before pregnancy and were SARS-CoV-2 positive  $\geq 22$  weeks of gestation were considered unprotected. Women with missing information about vaccination and those who received one or two doses before pregnancy and were SARS-CoV-2 positive  $<22$  weeks of gestation were considered 'unknown with regard to protection status'.

Maternal age, educational level, citizenship (Italian, not Italian), area of birth, at least one previous comorbidity (asthma requiring medical treatment, cardiovascular diseases, diabetes, HIV/AIDS, hypertension, lung diseases, other diseases such as thyroid and autoimmune pathologies), and obesity (body mass index,  $>30 \text{ kg/m}^2$ ) were analysed as potential risk factors for MSCD, as suggested by previous studies [2,15].

### Statistical analysis

Cases with missing information about the status of vaccine protection were excluded from the descriptive analysis. Frequency distributions by socio-demographic, obstetric and medical characteristics, and prevalence of infection outcomes were computed for protected and unprotected women. Missing data  $<5\%$  were excluded from frequency distributions.

The association between COVID-19 severity and women's protection status was assessed using a multivariable logistic regression model to estimate mutually adjusted ORs and 95% CIs. The likelihood ratio test was used to select variables included in the model

and to test plausible interactions. The model was performed including cases without information on women's protection. Assuming that the data were missing at random, the model was applied to multiple-imputed data. The imputation of 20 data sets was performed using chained equations [19]; Rubin's rules were used to combine model estimates across the data sets [20]. By using the following definitions of vaccine protection, a sensitivity analysis was carried out to evaluate the robustness of the model results: (1) the 'unprotected' women who received two doses before pregnancy were included among the 'protected', and the 'protected' women who received only one dose during pregnancy among the 'unprotected'; (2) all abovementioned women were included among 'unknown about vaccine protection status'.

Statistical analyses were carried out using STATA/MP version 14.2.

### Results

From 1 January to 31 May, 2022, 2774 women with a positive SARS-CoV-2 test within 7 days of hospital admission were notified. The information about protection status was available for 2147 women and no relevant socio-demographic and clinical differences were detected between these women and the whole cohort (Table S1). According to the study definition, 1069 of 2147 (49.8%) were considered protected against MSCD (Table 1). Of these, 74 received one vaccine dose during pregnancy, 596 two, of which at least one during pregnancy, and 327 the first booster. On the contrary, 1078 of 2147 women (50.2%) were considered unprotected, 989 because unvaccinated, and 89 because SARS-CoV-2 positive  $\geq 22$  weeks of gestational age after one or two doses administered before pregnancy. For the cases in which the information about the type of vaccine administered was available (66.8% of the 1207 women who received at least one dose), mRNA vaccines were used in all but 26 women who received traditional vaccines alone or in combination with mRNA.

Compared with protected women, the unprotected were more often younger, with a lower educational degree, of foreign citizenship, and symptomatic (Table 2).

The majority of women (2069/2147, 96.4%) were hospitalised to give birth or for obstetrical reasons, whereas 78 of 2147 (3.6%) were

**Table 1**

Women by vaccine protection status, timing of vaccination, and number of vaccine doses received ( $n = 2774$ )

Vaccination status	Timing and number of vaccine doses	Vaccine protection status		
		Protected	Unprotected	Unknown
Vaccinated ( $n = 1207$ )				
	Before pregnancy			
	One dose		18 <sup>a</sup>	2 <sup>b</sup>
	Two doses		71 <sup>a</sup>	12 <sup>b</sup>
	Booster	28		
	Unknown			24
	During pregnancy			
	One dose	74		
	Two doses	469		
	Booster	150		
	Unknown	32		
	Before and during pregnancy			
	Two doses	127		
	Booster	147		
	Unknown	40		
	Timing unknown			
	One dose			5
	Two doses			6
	Booster	2		
Unvaccinated ( $n = 989$ )			989	
Unknown vaccination status ( $n = 578$ )				578
Total ( $n = 2774$ )		1069	1078	627

<sup>a</sup> SARS-CoV-2 diagnosis  $\geq 22$  weeks of gestation.

<sup>b</sup> SARS-CoV-2 diagnosis  $<22$  weeks of gestation.

**Table 2**Women's characteristics by vaccine protection status (*n* = 2147)

Variable	Unprotected women <sup>a</sup> ( <i>n</i> = 1078)		Protected women <sup>b</sup> ( <i>n</i> = 1069)		Total ( <i>n</i> = 2147)		P
	n	%	n	%	N	%	
Age (y) (23 missing)							
<30	421	39.6	289	27.3	710	33.4	<0.001
30–34	314	29.5	366	34.5	680	32.0	
≥35	329	30.9	405	38.2	734	34.6	
Citizenship							
Not Italian	337	31.3	177	16.6	514	23.9	<0.001
Italian	741	68.7	892	83.4	1633	76.1	
Area of birth							
Italy, Western Europe	689	63.9	857	80.2	1546	72.0	<0.001
East Europe	182	16.9	66	6.2	248	11.6	
Africa	123	11.4	57	5.3	180	8.4	
South and Central America	27	2.5	39	3.6	66	3.1	
Asia	57	5.3	50	4.7	107	5.0	
Level of education <sup>c</sup>							
Low	342	31.7	163	15.2	505	23.5	<0.001
Medium	404	37.5	418	39.1	822	38.3	
High	136	12.6	296	27.7	432	20.1	
Missing	196	18.2	192	18.0	388	18.1	
Previous comorbidities							
No	910	84.4	877	82.0	1787	83.2	0.126
Yes	75	7.0	100	9.4	175	8.2	
Missing	93	8.6	92	8.6	185	8.6	
BMI >30 kg/m <sup>2</sup>							
No	886	82.2	894	83.6	1780	82.9	0.458
Yes	113	10.5	95	8.9	208	9.7	
Missing	79	7.3	80	7.5	159	7.4	
Symptoms (46 missing)							
No	614	58.7	691	65.5	1305	62.1	0.001
Yes	432	41.3	364	34.5	796	37.9	
COVID-19 severity							
Mild	1049	97.3	1057	98.9	2106	98.1	0.008
MSCD	29	2.7	12	1.1	41	1.9	

BMI, body mass index; MSCD, moderate or severe COVID-19.

<sup>a</sup> Low: primary school or lower; medium: high school; high: bachelor's degree or higher.<sup>a</sup> Unvaccinated women and those who received one or two doses before pregnancy and were SARS-CoV-2 positive ≥22 weeks of gestation.<sup>b</sup> Women who received at least one dose of vaccine during pregnancy.**Table 3**Women's outcome by vaccine protection status (*n* = 2147)

Outcome	Unprotected women <sup>a</sup> ( <i>n</i> = 1078)		Protected women <sup>b</sup> ( <i>n</i> = 1069)		Total ( <i>n</i> = 2147)	
	n	%	n	%	n	%
Mild disease (absence of COVID-19 pneumonia)	1049	97.3	1057	98.9	2106	98.1
Moderate disease (COVID-19 pneumonia with at most oxygen therapy)	22	2.0	11	1.0	33	1.5
Severe disease (COVID-19 pneumonia with mechanical ventilatory support and/or ICU admission)	7	0.6	1	0.1	8	0.4
Noninvasive ventilatory support	7	0.6	1	0.1	8	0.4
Orotracheal intubation	3	0.3	1	0.1	4	0.2
ECMO	0	0.0	0	0.0	0	0.0
ICU admission	6	0.6	1	0.1	7	0.3
Death	1	0.1	0	0.0	1	0.0

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

<sup>a</sup> Unvaccinated women and those who received one or two doses before pregnancy and were SARS-CoV-2 positive ≥22 weeks of gestation.<sup>b</sup> Women who received at least one dose of vaccine during pregnancy.

because of COVID-19. Among the latter eight developed severe disease, 12 a moderate disease, and 58 a mild disease.

Overall, MSCD disease was rare (41/2147, 1.9%; 95% CI, 1.4–2.6) but more frequent among the unprotected (29/1078, 2.7%; 95% CI, 1.9–3.9) compared with protected women (12/1069, 1.1%; 95% CI, 0.6–2.0) (Table 2). Among the 41 cases of MSCD, 27 out of 29 unprotected women were unvaccinated, and two received two vaccine doses before pregnancy. Among the 12 protected women, three received the booster and nine two doses, the first before pregnancy and the second during pregnancy.

Seven out of eight severe cases and one maternal death occurred among unprotected women (Table 3). The woman who died had a

body mass index of 49.6 kg/m<sup>2</sup>, gestational diabetes, and hypertension. She developed Acute Respiratory Distress Syndrome with a SpO<sub>2</sub> of 80 mmHg, was intubated and was admitted to ICU. COVID-19 pneumonia was considered to be the cause of death, which occurred 2 weeks after birth. She delivered at 34 weeks through emergent CS, and the baby was admitted to NICU for 30 days with an Apgar of 5 after 5 minutes.

Table 4 shows the ORs of developing MSCD estimated on multiple-imputed data and mutually adjusted for women's protection status, age, area of birth, previous comorbidities, and obesity. Unprotected women presented a higher occurrence of MSCD compared with protected (OR, 2.78; 95% CI, 1.39–5.57) as

**Table 4**

Mutually adjusted odds ratios of moderate/severe COVID-19 for the selected variables - logistic regression model on imputed data

Variable	OR	95% CI	
Vaccine protection status			
Protected	1		
Unprotected	2.78	1.39	5.57
Age (y)			
<30	1		
30–34	1.30	0.59	2.86
≥35	1.68	0.80	3.54
Area of birth			
Italy, Western Europe, America	1		
East Europe	0.85	0.29	2.46
Africa	1.73	0.73	4.08
Asia	3.05	1.23	7.56
Previous comorbidities			
No	1		
Yes	2.86	1.34	6.12
BMI >30 kg/m <sup>2</sup>			
No	1		
Yes	1.95	0.90	4.24

BMI, body mass index.

<sup>a</sup>Moderate: COVID-19 pneumonia with at most oxygen therapy; severe: COVID-19 pneumonia requiring mechanical ventilatory support and/or admission to the intensive care unit.

well as women born in Asian countries (OR, 3.05; 95% CI, 1.23–7.56) and those with previous comorbidities (OR, 2.86; 95% CI, 1.34–6.12).

The results of the model performed using only complete cases did not change noticeably (Table S2).

The sensitivity analysis described in the Methods confirmed significantly higher MSCD odds among unprotected compared with protected women (Table S3).

Considering only the women who gave birth, the proportion of preterm births was 8.7% (169/1942), mostly late preterm (Table S4), without significant differences between protected and unprotected women (8.2% [79/967] versus 9.2% [90/975], p = 0.407), whereas caesarean section (CS) occurred in 29.3% (283/967) and 34.4% (336/977) respectively (p = 0.015). The percentage of preterm birth was higher among women with MSCD compared with milder cases (32.0% (8/25) versus 8.4% (161/1917), p < 0.001) as well as the percentage of CS (52.0% [13/25] versus 31.6% [606/1919], p = 0.029) (Table S4). Five out of 619 cases of CS were urgent/emergent because of COVID-19, all among women with MSCD (whose four were unprotected).

Overall, 5.6% of the live births (110/1968) were admitted to the NICU (Table S5), 5.2% (51/982) and 6.0% (59/986) among protected and unprotected women, respectively. Among neonates delivered by mothers with MSCD, 33.3% (9/27) were admitted to NICU (Table S5). Ten stillbirths (10/1978, 0.5%) and one neonatal death (0.1%, 1/1968) were recorded.

## Discussion

### Key results

This prospective national study, conducted when the Omicron SARS-CoV-2 represented the most widespread variant in Italy [21,22], detected a low prevalence of MSCD (1.9%) in pregnant women. Unprotected women (50.2%), mostly younger, with a lower educational degree and foreigners, presented a higher occurrence of MSCD than those protected by at least one dose of vaccine against SARS-CoV-2 administered during pregnancy (OR, 2.78; 95% CI, 1.39–5.57). Moreover, higher percentages in preterm birth and CS were recorded in the case of MSCD. One maternal death

occurred, and stillbirth and neonatal death were in line with national figures.

### Strengths and limitations

The present study evaluated maternal and perinatal outcomes among the largest prospective Italian cohort of protected and unprotected SARS-CoV-2 pregnant women during the Omicron wave. The diagnosis within 7 days of hospital admission ensured a homogeneous population in terms of the timing of infection. Moreover, the number of administered doses, their timing and the interval between the onset of pregnancy and gestational age at infection have been carefully considered to ensure an accurate definition of the women's protection status. The continuous monitoring by e-mail and telephone of contact clinicians and the crosscheck of maternal deaths through the ItOSS surveillance system [18] ensured robust data collection.

The study also has limitations. The Italian national surveillance of SARS-CoV-2 infections among the general population registered a threefold increase in the number of cases from January to May 2022, compared with February 2020 and June 2021, whereas ItOSS did not detect a similar increase [15] configuring a possible underreporting of cases during the Omicron wave. Moreover, about 23% of the notified cases were excluded from data analysis due to unknown women's protection status. Nevertheless, no differences in socio-demographic and clinical characteristics have been detected between the analysed group of women with known vaccination status and the whole cohort.

Due to the small number of severe cases, we grouped them with moderate cases, although they presented different clinical characteristics. However, these two categories were comparable because characterised by the presence of COVID-19 pneumonia.

The information about vaccination was collected by asking women and could be biased by social desirability [23]. Therefore, an overestimation of the vaccine uptake cannot be excluded. Moreover, the date of vaccination was unavailable, we only knew if women were vaccinated before and/or during pregnancy. This aspect prevented us to estimate the length of vaccine protection and the time interval between vaccination and the SARS-CoV-2 positivity.

### Interpretation

This study detected a lower prevalence of MSCD during the Omicron wave in Italy compared with previous variants [15]. Similarly, Omicron was the strain associated with low rates of severe maternal morbidities in a cohort of American pregnant women [24].

In addition to known risk factors for severe COVID-19 among pregnant women (aged ≥35 years, not Italian citizenship, and previous comorbidities) [15], this study detected a higher occurrence of severe outcomes among women without vaccine protection. Three recent systematic reviews described the effectiveness of vaccination against the original SARS-CoV-2 strain and the alpha and delta variants [6,11,12]. Our data confirmed that the lack of vaccine protection during pregnancy resulted in worse outcomes even during the Omicron circulation; the majority of women developing MSCD were unprotected and associated with the highest proportion of urgent/emergent CS and preterm birth. The rate of NICU admissions was higher among newborns of mothers with MSCD, probably consequent to their higher rate of preterm birth.

Although the literature unanimously agreed in considering mRNA vaccines safe and effective during pregnancy [6,11], vaccination hesitancy and resistance are still high among pregnant

women [25]. A systematic review reported a 53.5% worldwide vaccination acceptance rate against SARS-CoV-2 in pregnancy [26]. Among the 2196 women of the ItOSS cohort whose vaccination data were available, 1207 (55.0%) received at least one vaccine dose, slightly higher than the proportion recorded in Scotland in October 2021 (42.8%) [7] but lower than in the general population [26]. Transplacental transfer of maternal antibodies [27] following SARS-CoV-2 vaccination during pregnancy can protect the mother and neonate throughout the first 6 months of life [28–30]. It is essential to disseminate this information to encourage vaccination compliance during pregnancy.

Overall, we reported a low incidence of severe COVID-19 in pregnant women and good protection provided by the vaccine. Our study is one of the few focusing on the role of vaccination in pregnancy on the effects of the Omicron variant, which seems to produce milder maternal and perinatal outcomes than the previous variants. These data can be the groundwork to inform hesitant pregnant women about the vaccine's effectiveness and entangle them towards the importance of vaccination and the opportunity to protect their newborns.

## Author contributions

SD conceptualized the study. MAS and SD designed the methodology. ECD, MAS, and SD performed software analysis. MAS and DM conducted formal analysis. IA, FC, AC, FD, FDS, LD, FD, GE, DF, DM, RP, Roberta Picinno, FP, MR, SS, Serena Simeone, MT, CT, MV, and AV conducted investigation for the study. Project administration was done by SD. Conduct of this study was supervised by SD, PC, IC, MPF, LL, ML, LLS, ML CM, GP, FM, AM, ADM, LM, EP, LR, SCAS, DS, MS, FT, and VT. ECD and SD wrote the original draft. ECD, MAS, DM, LS, and SD review and edited the manuscript. All authors had full access to the data, reviewed the manuscript, approved the final version, and accepted responsibility for submitting it for publication.

## Transparency declaration

The authors declare that they have no conflicts of interest. This work was supported by a call for independent research of the Italian National Institute of Health (project code ISS20-32f66b0087 d, number BB45). The study's funder had no role in study design, data collection, analysis, interpretation, or report writing.

## Access to data

The data presented in this study are available on request from the corresponding author.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2023.01.013>.

## Appendix 1

### *The ItOSS national network of maternity units*

#### *Piedmont region*

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Livio Leo *Ospedale Umberto Parini Aosta*.

#### *Liguria region*

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