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COVID-19 reinfection in pregnancy: Assessment of severity and pregnancy outcomes in England

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SUMMARY

Background: Disease severity and pregnancy outcomes following SARS-CoV-2 reinfections in pregnancy are not well understood.
Methods: We linked women aged 18 to 50 years testing positive in the community for COVID-19 between April 2021 and March 2022 to hospital, vaccine and maternal services databases. We compared hospital and intensive care unit (ICU) admission rates following infection and reinfection in pregnant and non-pregnant women, and low birthweight, prematurity and stillbirth in women infected and reinfected during pregnancy.
Results: We identified 68,842 pregnant and 3,915,069 infected non-pregnant women. Hospital admission after SARS-CoV-2 reinfection was more common in pregnancy, especially during the third trimester (aOR= 18.56; 95% CI: 9.46 - 36.42) and was similar following reinfection or primary infection in pregnancy (aOR= 0.82; 95% CI: 0.50 - 1.33). All ICU admissions (n=49) in pregnancy occurred after primary infection with delta. There was no notable difference in adverse pregnancy outcomes after primary infection or reinfection with SARS-CoV-2 during pregnancy.
Conclusion: Pregnant women remain at higher risk of more severe disease during reinfection compared to non-pregnant women yet; hospitalisation and ICU admissions risk were low during the omicron period. The virulence of circulating variants needs to be assessed to guide maternal COVID-19 vaccination programmes against.

Introduction

The pregnant state is associated with an increased susceptibility to infectious diseases which can lead to severe complications and poor outcomes for both the mother and the infant, including miscarriage, stillbirth and preterm birth.[1] Severe complications and poor outcomes have also been reported in pregnant individuals infected with SARS-CoV-2 during the COVID-19 pandemic.[2] Early in the pandemic where COVID-19 vaccines were not available, infection in the late second or third trimester, older age, overweight or obesity, pre-existing co-morbidities and being in an ethnic minority group were associated with a higher risk of severe SARS-CoV-2 disease in pregnancy.[3] In the UK, 10% of 427 pregnant women admitted to hospital with severe COVID-19 during March-April 2020 needed respiratory support, and five (1%) died.[2] Importantly, too, pregnant individuals had a higher risk of severe disease and intensive care admission than non-pregnant women of similar age, leading many countries to prioritise COVID-19 vaccination in pregnancy during the rollout of their national COVID-19 vaccination programme.[2,4] As the pandemic progressed, the emergence of new SARS-CoV-2 variants and the development of effective vaccines, which were modified to include new variants over time, both had a significant impact on disease severity across the population, including in pregnant individuals.

The emergence of the Omicron variant since November 2021 was associated with less severe infections across the population compared to previous SARS-CoV-2 variants. Pregnant individuals, too, were significantly less likely to be hospitalised, require ICU admission or give birth before term when infected during the omicron compared to the delta period.[5]

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In England, by the end of September 2021, 62.5% of the female population had received at least two COVID-19 vaccine doses and 32.1% of individuals giving birth during September 2021 had received at least one vaccine dose.[6,7] The emergence of the Omicron variant during winter 2021 was associated with a large increase in SARS-CoV-2 infection irrespective of vaccination status or previous infection, with an increase of individuals testing positive for SARS-CoV-2 more than once with an interval of at least 90 days between positive results.[6]

SARS-CoV-2 reinfections are generally associated with less severe disease because of immune protection conferred by previous infection in addition to COVID-19 vaccination.[8,9] There are, however, limited data on SARS-CoV-2 infections in pregnancy after a previous infection, restricted mainly to a few case reports.[10,11] Consequently, little is known about the risk of severe disease or pregnancy outcomes associated with reinfection in pregnant individuals. The aim of this study is to use national surveillance data to assess the risk, severity and pregnancy outcomes of SARS-CoV-2 infection and reinfection with the delta and early emergent omicron variant in unvaccinated and vaccinated pregnant individuals over an 11-month period when these variants were circulating in England. We also assessed outcomes according to the timing of SARS-CoV-2 infection during pregnancy.

To our knowledge, this study is the first to report population-level data of SARS-CoV-2 reinfection in pregnant individuals. We assess COVID-19 disease severity (hospital and ICU admission after a positive COVID-19 test) and pregnancy outcomes (preterm birth, low birthweight and stillbirth) after a SARS-CoV-2 reinfection in pregnancy compared to a first infection. The effects of SARS-CoV-2 variants delta and omicron and timing of infection using gestational trimester of positive testing for COVID-19 are also considered.

Methods

We compared COVID-19 severity between pregnant and non-pregnant women of similar age (18 to 50 years old) testing positive for SARS-CoV-2 infection as first recorded (primary infection) and those with a second positive test (reinfection). We also compared pregnancy outcomes in women with a primary infection and reinfection by SARS-CoV-2 in pregnancy.

Study population

The data was extracted in November 2022 covering a study period from 16 April 2021 until 31 March 2022. From 16 April 2021, pregnant individuals were eligible to receive COVID-19 vaccine as part of the national immunisation programme while individuals with a risk of COVID-19 complication were eligible earlier. On 1 April 2022, free community COVID-19 testing ended in the UK, rendering the detection of COVID-19 infections more susceptible to biases arising from behavioural and economic disparities in the community. The study population had different inclusion criteria depending on the outcome of interest.

To investigate COVID-19 severity, we included all women aged between 18 and 50 years old who tested positive for SARS-CoV-2 infection in England, between April 2021 and March 2022. The extract was then linked to the pregnancy cohort to identify pregnant women.

When looking at pregnancy outcomes after SARS-CoV-2 infection: the eligible population included all pregnancies from individuals aged between 18 to 50 years at the time of pregnancy start with a delivery date between 16 April 2021 and 31 March 2022. Pregnancies that reached a minimum gestational age of 24 weeks and a maximum of 44 weeks were included in the study.

The eligible populations required a valid NHS number to enable linkages with multiple datasets.

Data sources and linkages

We used the Maternity Services Data Set (MSDS) antenatal booking records which includes data from NHS-funded maternity services to identify pregnant individuals.[12] Missing pregnancy outcomes were completed through linkage with the Hospital Episode Statistic (HES) containing records of all admissions, outpatient appointments and accident and emergency (A&E) attendances for patients admitted to NHS hospitals in England.[13] We used the Secondary Uses Service (SUS) to classify hospital and intensive care unit (ICU) admission following a positive COVID-19 testing.[14] COVID-19 vaccination history was ascertained using the National Immunisation Management System (NIMS) which contains COVID-19 immunisation records for all patients accessing the NHS in England.[15] The NIMS demographics database was used to collect information on ethnicity, NHS region, Index of multiple deprivation (IMD) Quintiles, and vaccine delivery priority groups: healthcare worker, CEV, severely immunosuppressed and “at risk” status on all patients including those not vaccinated. We identified SARS-CoV-2 infections from the national laboratory reporting system which captures routine laboratory test results on infectious diseases from community and healthcare settings. The data extracted covered the study period plus an additional postpartum period of 6 weeks for the mothers which was used when comparing hospitalisation rates in those infected and reinfected. Positive SARS-CoV-2 test were identified through linkage to the Second Generation Surveillance System (SGSS).[16]

Outcomes

We measured the severity of COVID-19 disease as hospital admission within 14 days of a positive SARS-CoV-2 community test, either by retro transcriptase-polymerase chain reaction (RT-PCR) or lateral flow devices (LFD). Eligible hospital admissions had to have an acute respiratory code (Table S1) in their primary diagnosis and a minimum length of stay of two days. For those hospitalised, we identified individuals who were referred to ICU during that episode (Main specialty and/or Treatment code=192). Pregnancy outcomes examined included live births preterm delivery between 24 and 37 gestational weeks, stillbirth, and low birthweight (under 2.5 kg) in infants born at term. Because of the strong correlation between low birthweight and gestational age, only pregnancies reaching 37 weeks were included for this outcome analysis.

Reinfection definition

SARS-CoV-2 infections were identified as positive PCR or LFD test results from community and healthcare services testing. A primary SARS-CoV-2 infection was the first positive test recorded for an individual while a reinfection was a sequential positive PCR or LFD SARS-CoV-2 tests at least 90 days after a previous positive test. Individuals were not allowed to test SARS-CoV-2 positive during the 90-day interval to exclude possible persistent infections.

We categorised individuals infected in pregnancy according to the timing of test results: either during their first trimester, second, third or during postpartum (within 42 days of giving birth). A few individuals had their first and second SARS-CoV-2 infection during pregnancy and/or the post-partum period. When stratifying for gestational trimester of infection, we used the corresponding test, e.g.: one individual can be a control in one analysis (first infection in trimester 1) and a case in another one (reinfection in 3rd trimester or postpartum).

For the analysis on preterm birth, low birth weight and still birth, we only included pregnancies that reached at least 24 weeks as healthcare settings in England have to notify/ record live births from 20 weeks and 24 weeks for still births.

Table 1
Demographic characteristics of pregnant and non-pregnant women who tested positive for COVID-19 between 16 April 2021 and 31st March 2022 in England.

	Non-pregnant women		Pregnant women	
Risk factors	Primary infection	Reinfection	Primary infection	Reinfection
Age groups in Years	***3,553,544***	***361,525***	***64,105***	***4737***
18 to 24	686,545 (19.32)	86,330 (23.88)	10,050 (15.68)	836 (17.65)
25 to 29	556,045 (15.65)	62,409 (17.26)	17,661 (27.55)	1442 (30.44)
30 to 34	584,427 (16.45)	58,362 (16.14)	21,232 (33.12)	1516 (32.00)
35 to39	582,870 (16.40)	55,072 (15.23)	12,074 (18.83)	762 (16.09)
40 to 44	566,709 (15.95)	51,738 (14.31)	2937 (4.58)	169 (3.57)
45 to 50	576,948 (16.24)	47,614 (13.17)	151 (0.24)	12 (0.25)
Ethnicity	***3,289,390***	***326,624***	***51,032***	***3375***
White	2,462,697 (74.87)	246,773 (75.55)	37,979 (74.42)	2531 (74.99)
Mixed Multiple Ethnic groups	82,521 (2.51)	9467 (2.90)	1251 (2.45)	74 (2.19)
Black/Black British	107,745 (3.28)	12,605 (3.86)	1658 (3.25)	115 (3.41)
Asian/Asian British	228,703 (6.95)	23,636 (7.24)	4036 (7.91)	334 (9.90)
Any other ethnic groups	407,724 (12.40)	34,143 (10.45)	6108 (11.97)	321 (9.51)
At risk of COVID-19 complications	***3,436,700***	***350,906***	***64,046***	***4733***
No	2,749,087 (79.99)	278,122 (79.26)	50,791 (79.30)	3713 (78.45)
Yes	687,613 (20.01)	72,784 (20.74)	13,255 (20.70)	1020 (21.55)
Vaccination status	***3,337,196***	***349,530***	***49,342***	***4076***
Unvaccinated	462,219 (13.85)	54,455 (15.58)	21,149 (42.86)	1674 (41.07)
1 dose	280,238 (8.40)	17,459 (4.99)	7655 (15.51)	447 (10.97)
2 or more doses	2,594,739 (77.75)	277,616 (79.43)	20,538 (41.62)	1955 (47.96)
Index of Multiple Deprivation	***3,550,567***	***361,456***	***64,102***	***4737***
1 Most Deprived	708,122 (19.94)	89,821 (24.85)	16,921 (26.40)	1446 (30.53)
2	750,815 (21.15)	81,944 (22.67)	14,341 (22.37)	1126 (23.77)
3	723,438 (20.38)	71,050 (19.66)	12,421 (19.38)	853 (18.01)
4	693,232 (19.52)	63,292 (17.51)	10,997 (17.16)	739 (15.60)
5 Least Deprived	674,960 (19.01)	55,349 (15.31)	9422 (14.70)	573 (12.10)
Region	***3,550,567***	***361,456***	***64,102***	***4737***
East Midlands	299,520 (8.44)	31,407 (8.69)	5624 (8.77)	425 (8.97)
East of England	387,762 (10.92)	34,563 (9.56)	6583 (10.27)	446 (9.42)
London	604,649 (17.03)	58,413 (16.16)	10,339 (16.13)	786 (16.59)
North East	175,513 (4.94)	22,089 (6.11)	3626 (5.66)	286 (6.04)
North West	464,692 (13.09)	59,093 (16.35)	9319 (14.54)	821 (17.33)
South East	574,497 (16.18)	49,438 (13.68)	9075 (14.16)	554 (11.70)
South West	359,178 (10.12)	29,564 (8.18)	5736 (8.95)	292 (6.16)
West Midlands	346,071 (9.75)	37,655 (10.42)	7055 (11.01)	597 (12.60)
Yorkshire and Humber	338,685 (9.54)	39,234 (10.85)	6745 (10.52)	530 (11.19)
Pillar	***3,553,544***	***361,525***	***64,105***	***4737***
Testing in hospital	178,468 (5.02)	23,534 (6.51)	13,211 (20.61)	1414 (29.85)
Community testing	3,375,076 (94.98)	337,991 (93.49)	50,894 (79.39)	3323 (70.15)
Variant	***3,011,952***	***292,321***	***56,629***	***3776***
Alpha	11,482 (0.38)	415 (0.14)	576 (1.02)	24 (0.64)
Delta	1272,602 (42.25)	27,468 (9.40)	38,216 (67.48)	1009 (26.72)
Omicron	1727,868 (57.37)	264,438 (90.46)	17,837 (31.50)	2743 (72.64)

Covariates

We obtained additional information on participants' age at the start of the pregnancy, index of multiple deprivation (IMD) quintiles, region of test, the timing of COVID-19 test, ethnicity, comorbidities, risk of COVID-19 complications, COVID-19 test setting (community or healthcare), and infective variant (Delta or Omicron) from vaccine registry and testing datasets.

Whole genome sequencing, genotyping, S-gene target failure (SGTF) status or period of test, were used to identify Delta and Omicron (BA.1 and BA.2). If the variant information was missing and a subsequent positive test within 14 days included identification of the infective variant, we used this information. The period of test to identify Delta was restricted from 26 April 2021 to 9 January 2022 and from 29 November 2021 onwards for Omicron. Sequencing took priority, followed by genotyping, SGTF status and period when categorising infective variant.

The unvaccinated cohort had not received a vaccine at the time of infection or had received only one dose less than 21 days prior to testing positive, the partially vaccinated cohort received one dose more than 21 days prior to testing positive and the fully vaccinated two or three doses more than 14 days prior to testing positive.

Gestational length was calculated using in order of priority: gestational age at birth or last menstrual period and delivery date. We defined pregnancy trimesters as up to day 83 for the first trimester, from day 84 until day 188 for the second and from day 189 up until 308 for the third as the maximum recorded gestational age in HES is 44 weeks.

Statistical methods

We described all covariates distribution in the different populations: infected and reinfected non pregnant women and infected and reinfected pregnant women.

We compared hospital and ICU admission between SARS-CoV2 primary infection and reinfections in pregnant and non-pregnant women; and pregnancy outcomes in those infected for the first time and reinfected by SARS-CoV-2. We compared outcomes by infective strains Delta or Omicron (BA.1 or BA.2) and pregnancy trimester of COVID-19 positive test. In the analyses restricted to one infective variant, those with primary infections or reinfections were infected by the same variant (although the first infection in those re-infected could be different). We used multivariable logistic regression to assess the odds of each outcome in the different cohorts. Models were adjusted for the following predefined covariates: age as a continuous variable, ethnicity, vaccination status as the time of infection, IMD-5, comorbidities, at risk of complication from COVID-19 disease and quarter of the year of positive test. Other covariates were added if

Table 2
Adjusted[a] odds ratios from logistic regression comparing hospital admission in primary infection versus reinfection with SARS-CoV-2 and in both reinfections episode in pregnant and non-pregnant women.

	COVID-19 in pregnancy			Non-pregnant	Pregnant	
outcomes	Primary infection	Reinfection	OR (95% CI)	Reinfection	Reinfection	OR (95% CI)
Hospital admission	***50,894***	***3323***		***25,683***	***3323***	
No	49,770 (97.79)	3296 (99.19)		337,897 (99.97)	3296 (99.19)	
Yes	1124 (2.21)	27 (0.81)	0.82 (0.50 - 1.33)	94 (0.03)	27 (0.81)	6.79 (3.98 - 11.59)
for delta	***32,269***	***798***		***25,683***	***798***	
No	31,263 (96.88)	781 (97.87)		25,654 (99.89)	781 (97.87)	
Yes	1006 (3.12)	17 (2.13)	0.81 (0.45 - 1.45)	29 (0.11)	17 (2.13)	14.55 (6.53 - 32.44)
for omicron	***12,592***	***1898***		***249,782***	***1898***	
No	12,543 (99.61)	1892 (99.68)		249,724 (99.98)	1892 (99.68)	
Yes	49 (0.39)	6 (0.32)	0.86 (0.36 - 2.02)	58 (0.02)	6 (0.32)	3.90 (1.73 - 8.79)
ICU admission	***50,894***	***3323***		***337,991***	***3323***	
No	50,845 (99.90)	3323 (100.00)		337,982 (100.00)	3323 (100.00)	
Yes	49 (0.10)	0 (0.00)	0 (0 - 1.20)[b]	9 (0.00)	0 (0.00)	0 (0 - 43.42)[b]
for delta	***32,269***	***798***		***337,991***	***798***	
No	32,220 (99.85)	798 (100.00)		25,681 (99.99)	798 (100.00)	
Yes	49 (0.15)	0 (0.00)	0 (0 - 3.17)[b]	2 (0.01)	0 (0.00)	0 (0 - 61.90)[b]
for omicron	***17,837***	***2743***		***249,782***	***2743***	
No	12,592 (100.00)	1898 (100.00)		249,776 (100.00)	1898 (100.00)	
Yes	0 (0.00)	0 (0.00)	-	6 (0.00)	0 (0.00)	0 (0 - 84.29)[b]

[a] Analyses are adjusted by age at the start of pregnancy, vaccine status, ethnicity, risk of COVID-19 complications, year and monthly quarter of infection, region and variant (for overall estimates only).
[b] Unadjusted estimates due to low numbers.

they had a P-value < 0.05 using a likelihood ratio test. Odds ratios with 95% confidence intervals (CI) are reported for each model.

We used Microsoft SQL Server Management Studio 18 for data curation and linkages across datasets and STATA 17 for statistical analyses.

Results

COVID-19 severity

We identified 68,842 pregnant women with confirmed SARS-CoV-2 infections between 16 April 2021 and 31st March 2022 in England - 6.1% of those reinfections - and a total of 3,915,069 infected non-pregnant women, 9.1% of those reinfections (Table 1).

There were 4205 non-pregnant and 1151 pregnant women admitted to hospital with an acute respiratory code in their first diagnostic code for a minimum stay of two days within 14 days of testing positive for SARS-CoV-2 in the community. In pregnancy, 66% of hospital admissions occurred during the third trimester (Tables 2–4). Hospitalisation rates in pregnant women after an infection with delta were 3.1% (1023/33,067) and 0.4% (55/14,490) after an infection with omicron, and 0.3% (3379/1246,869) after delta and 0.03% (568/1894,592) after omicron infection in non-pregnant women.

When COVID-19 reinfection occurs in pregnancy, the risk of being admitted to hospital was similar to the risk after a primary infection in pregnancy (aOR= 0.82; 95% CI: 0.50 - 1.33). This was true for infections with both delta (aOR= 0.81; 95% CI: 0.45 - 1.45) and omicron variants (aOR= 0.86; 95% CI: 0.36 - 2.02) (Table 2). On the other hand, the risk of hospital admission was lower after a reinfection than a primary infection in non-pregnant women of similar age (aOR= 0. 62; 95% CI: 0.49 – 0.77) (Table 4).

Pregnant women were more likely be admitted to hospital after SARS-CoV-2 first infection than non-pregnant women (aOR= 5. 76; 95% CI: 5.24 – 6.33) and to require intensive care treatment (aOR= 2.38; 95% CI: 1.25 - 4.54). A SARS-CoV-2 infection during the third trimester of pregnancy showed the most elevated risk of hospital (aOR= 15. 13; 95% CI: 13.43 – 17.03) and ICU admission (aOR= 6.28; 95% CI: 2.69 - 14.69) (Table 5**a**). During a reinfection episode, pregnant women were also at higher risk of hospital admission compared to non-pregnant women (aOR= 6.79; 95% CI: 3.98 - 11.59) with the highest risk occurring in the second (aOR= 21.29; 95% CI: 9.07 - 49.96) and third trimester of pregnancy (aOR= 18.56; 95% CI: 9.46 - 36.42) (Table 5**b**).

Intensive care unit (ICU) admissions, a proxy for severe disease, were low with a total of 49 admissions following COVID-19 positive testing in pregnancy, amounting to 0.09% of all confirmed infections in pregnancy and 4% of hospitalised cases. All the ICU admissions occurred in primary infection with delta and, the majority, 65% (32/49) were during the third trimester of pregnancy. Notably, there were no ICU admissions after primary infection with omicron or after reinfection with either variant (Table 3).

Pregnancy outcomes

We identified 76,252 COVID-19 infections in pregnancy, 3794 (4.9%) of those were reinfections. Most primary infections (54.7% - 32,974/60,265) in this period were due to the delta variant and most reinfections were due to the omicron variant (67.5% - 2683/3764). Reinfection in pregnancy was proportionally higher in those with comorbidities and in the lower most deprive IMD quintiles compared to those with primary infections only (Table 6).

In those infected in pregnancy, 8.7% (6342/73,292) had a premature delivery, 2.3% (1578/67,890) of babies born at term were low birth weight and 4.4‰ (327/73,700) were still born (Table 7).

We found that women reinfected with COVID-19 in pregnancy compared to being first infected were less likely to give birth to a low birthweight infant (aOR= 0.65; 95% CI: 0.44 - 0.97) especially when infected by the omicron variant (aOR= 0.56; 95% CI: 0.34 - 0.93) P-Value = 0.035 and in their third trimester (aOR= 0.57; 95% CI: 0.34 - 0.96) P-Value = 0.034. However, this wasn't the case for those reinfected with the delta variant (aOR= 0.75; 95% CI: 0.38 - 1.50) (Table 7).

Analysis of pregnancy outcomes did not identify any differences in the risk of premature birth or stillbirth after primary infection or reinfection with either the delta or the omicron variants, during pregnancy overall or during any of the three trimesters, with the exception of stillbirth reinfection with omicron during the third trimester which showed a higher risk in reinfection compared to primary infection (aOR= 3.25; 95% CI: 1.19 - 8.89) P-Value = 0.021, but with only seven events in the reinfected cohort (Table 7).

Table 3
Adjusted[a] odd ratios from logistic regression comparing hospital admission in primary infection versus reinfection with SARS-CoV-2 by gestational trimester of infection.

	COVID-19 in 1st trimester			COVID-19 in 2nd trimester			COVID-19 in 3rd trimester			COVID-19 postpartum		
outcomes	Primary infection	Reinfection	OR (95% CI)	Primary infection	Reinfection	OR (95% CI)	Primary infection	Reinfection	OR (95% CI)	Primary infection	Reinfection	OR (95% CI)
Hospital admission	***3314***	***121***		***13,942***	***546***		***25,106***	***2053***		***8532***	***603***	
No	3298 (99.52)	121 (100.00)		13,601 (97.55)	537 (98.35)		24,363 (97.04)	2036 (99.17)		8508 (99.72)	602 (99.83)	
Yes	16 (0.48)	0 (0.00)	0 (0 - 6.61)[b]	341 (2.45)	9 (1.65)	0.99 (0.45 - 2.18)	743 (2.96)	17 (0.83)	0.74 (0.40 - 1.39)	24 (0.28)	1 (0.17)	0.59 (0.01 - 3.62)[b]
for delta	***2982***	***76***		***12,097***	***334***		***13,288***	***321***		***3902***	***67***	
No	2967 (99.50)	76 (100.00)		11,773 (97.32)	328 (98.20)		12,642 (95.14)	311 (96.88)		3881 (99.46)	66 (98.51)	
Yes	15 (0.50)	0 (0.00)	0 (0 - 10.13)[b]	324 (2.68)	6 (1.80)	0.81 (0.32 - 2.03)	646 (4.86)	10 (3.12)	0.82 (0.37 - 1.79)	21 (0.54)	1 (1.49)	2.80 (0.07 - 17.94)[b]
for omicron	***118***	***37***		***963***	***133***		***8094***	***1282***		***3417***	***446***	
No	118 (100.00)	37 (100.00)		958 (99.48)	131 (98.50)		8051 (99.47)	1278 (99.69)		3416 (99.97)	446 (100.00)	
Yes	0 (0.00)	0 (0.00)	-	5 (0.52)	2 (1.50)	1.97 (0.32 - 12.09)	43 (0.53)	4 (0.31)	0.66 (0.23 - 1.87)	1 (0.03)	0 (0.00)	-
ICU admission	***3314***	***121***		***13,942***	***546***		***25,106***	***2053***		***8532***	***603***	
No	3313 (99.97)	121 (100.00)		13,926 (99.89)	546 (100.00)		25,074 (99.87)	2053 (100.00)		8532 (100.00)	603 (100.00)	
Yes	1 (0.03)	0 (0.00)	-	16 (0.11)	0 (0.00)	0 (0 - 6.13)[b]	32 (0.13)	0 (0.00)	0 (0 - 1.47)[b]	0 (0.00)	0 (0.00)	-
for delta	***2982***	***76***		***12,097***	***334***		***13,288***	***321***		***3902***	***67***	
No	2981 (99.97)	76 (100.00)		12,081 (99.87)	334 (100.00)		13,256 (99.76)	321 (100.00)		3902 (100.00)	67 (100.00)	
Yes	1 (0.03)	0 (0.00)	-	16 (0.13)	0 (0.00)	0 (0 - 8.70)[b]	32 (0.24)	0 (0.00)	0 (0 - 4.96)[b]	0 (0.00)	0 (0.00)	-
for omicron	***118***	***37***		***963***	***133***		***8094***	***1282***		***3417***	***446***	
No	118 (100.00)	37 (100.00)		963 (100.00)	133 (100.00)		8094 (100.00)	1282 (100.00)		3417 (100.00)	446 (100.00)	
Yes	0 (0.00)	0 (0.00)	-	0 (0.00)	0(0.00)	-	0 (0.00)	0 (0.00)	-	0 (0.00)	0 (0.00)	-

[a] Analyses are adjusted by age at the start of pregnancy, vaccine status, ethnicity, risk of COVID-19 complications, year and monthly quarter of infection, region and variant (for overall estimates only).
[b] Unadjusted estimates due to low numbers.

Table 4
Adjusted[a] odd ratios from logistic regression comparing hospital admission in primary infection versus reinfection with SARS-CoV-2 in non-pregnant women of childbearing age (18–50 years old).

	COVID-19 in non-pregnant women of childbearing age (18–50)		
outcomes	Primary infection	Reinfection	OR (95% CI)
Hospital admission	***3,375,076***	***337,991***	
No	3,370,965 (99.88)	337,897 (99.97)	
Yes	4111 (0.12)	94 (0.03)	0.62 (0.49 - 0.77)
for delta	***1,221,186***	***25,683***	
No	1,217,836 (99.73)	25,654 (99.89)	
Yes	3350 (0.27)	29 (0.11)	0.50 (0.33 - 0.75)
for omicron	***1,644,810***	***249,782***	
No	1,644,300 (99.97)	249,724 (99.98)	
Yes	510 (0.03)	58 (0.02)	0.73 (0.55 - 0.96)
ICU admission	***3,375,076***	***337,991***	
No	3,374,901 (99.99)	337,982 (100.00)	
Yes	175 (0.01)	9 (0.00)	0.75 (0.34 - 1.63)
for delta	***3,375,076***	***337,991***	
No	1,221,070 (99.99)	25,681 (99.99)	
Yes	116 (0.01)	2 (0.01)	1.34 (0.33 - 5.47)
for omicron	***1,644,810***	***249,782***	
No	1,644,758 (100.00)	249,776 (100.00)	
Yes	52 (0.00)	6 (0.00)	0.75 (0.30 - 1.87)

[a] Analyses are adjusted by age at the start of pregnancy, vaccine status, ethnicity, risk of COVID-19 complications, year and monthly quarter of infection, region and variant.

Table 5
a and 5b: Adjusted[a] odd ratios from logistic regression comparing hospital admissions in reinfection with SARS-CoV-2 between non pregnant and pregnant women by gestational trimester of infection.

	Pregnancy status at first infection	Hospital admission			ICU admission		
5a		*No*	*Yes*	OR (95% CI)	*No*	*Yes*	OR (95% CI)
	Non-pregnant	3,370,965 (99.88)	4111 (0.12)	1	337,897 (99.97)	94 (0.03)	1
	Pregnant	49,770 (97.79)	1124 (2.21)	5.76 (5.24 - 6.33)	50,845 (99.90)	49 (0.10)	2.38 (1.25 - 4.54)
	Infected in 1st trimester	3298 (99.52)	16 (0.48)	1.94 (1.07 - 3.53)	3313 (99.97)	1 (0.03)	5.82 (0.15 - 32.92)[b]
	Infected in 2nd trimester	13,601 (97.55)	341 (2.45)	8.66 (7.42 - 10.10)	13,926 (99.89)	16 (0.11)	5.48 (1.95 - 15.35)
	Infected in 3rd trimester	24,363 (97.04)	743 (2.96)	15.13 (13.43 - 17.03)	25,074 (99.87)	32 (0.13)	6.28 (2.69 - 14.69)
	Infected Postpartum	8508 (99.72)	24 (0.28)	2.00 (1.24 - 3.24)	8532 (100.00)	0 (0.00)	0 (0 - 1.08)[b]
	Pregnancy status at reinfection	Hospital admission			ICU admission		
5b		*No*	*Yes*	OR (95% CI)	*No*	*Yes*	OR (95% CI)
	Non-pregnant	337,897 (99.97)	94 (0.03)	1	337,982 (100.00)	9 (0.00)	1
	Pregnant	3296 (99.19)	27 (0.81)	6.79 (3.98 - 11.59)	3323 (100.00)	0 (0.00)	0(0 - 43)[b]
	Infected in 1st trimester	121 (100.00)	0 (0.00)	0 (0 - 114.23)[b]	121 (100.00)	0 (0.00)	0 (0 - 1200)[b]
	Infected in 2nd trimester	537 (98.35)	9 (1.65)	21.29 (9.07 - 49.96)	546 (100.00)	0 (0.00)	0 (0 - 265)[b]
	Infected in 3rd trimester	2036 (99.17)	17 (0.83)	18.56 (9.46 - 36.42)	2053 (100.00)	0 (0.00)	0(0 - 70)[b]
	Infected Postpartum	602 (99.83)	1 (0.17)	5.97 (0.15 - 34.20)[b]	603 (100.00)	0 (0.00)	0 (0 - 240)[b]

[a] Analyses are adjusted by age at the start of pregnancy, vaccine status, ethnicity, risk of COVID-19 complications, year and monthly quarter of infection, region and variant (for overall estimates only).
[b] Unadjusted estimates due to low numbers.

Discussion

Main findings

We assessed differences in disease severity of COVID-19 re-infection in pregnancy using hospitalisation and ICU admission as proxies. Pregnant women in this period remained at higher risk of COVID-19 hospitalisation during a reinfection when compared to non-pregnant women of the same age (aOR= 6.79; 95% CI: 3.98 - 11.59), especially when the infection occurred in later in pregnancy (aOR= 18.56; 95% CI: 9.46 - 36.42). The difference in hospitalisation rates after reinfection with either variant compared to primary infection was not statistically significant after adjusting for prior vaccination, underlying comorbidity and other risk factors when infection occurred in pregnancy (aOR= 0.82; 95% CI: 0.50 - 1.33), in contrast with reinfections in non-pregnant women (aOR= 0. 62; 95% CI: 0.49 – 0.77). The risk of hospitalisation during a reinfection was higher with delta than with omicron in both pregnant and non-pregnant women, and pregnant women had much higher risk of hospital admission compared to non-pregnant women following a reinfection with delta (aOR= 14.55; 95% CI: 6.53 - 32.4) than with omicron (aOR= 3.90; 95% CI: 1.73 - 8.79).

Overall, ICU admissions were rare and identified only after primary infection with the delta variant (n=49) predominantly in the third trimester of pregnancy (32/49). There were no ICU admissions after primary infection or reinfection with omicron.

When compared to stillbirth estimates in England from the Office for National Statistics (ONS), the 2021 general population estimates were comparable to those observed in our cohort of infected women 4.1‰ and 4.3‰ respectively, so were the rates of low birthweight infants born at term 2.6% vs 2.3%.[17,18] However, we observed a slightly higher proportion of premature births in our study population compared with the ONS population estimates for 2021: 8.8% vs 7.5%.[19] This could be a true observation, or due to differences in the way pregnancy length was calculated for ONS estimates vs in this study: as the highest proportion of preterm birth occurs during the 36th week of gestation, minor discrepancies on the start date of the pregnancy could affect the preterm status of some infants.

We found that infants born from reinfected mothers in their third trimester of pregnancy by the omicron variant were less likely to

Table 6
Demographic characteristics of pregnant women according to SARS-CoV-2 infection status in pregnancy between 16 April 2021 and 31st March 2022 in England.

	Covid-19 in pregnancy	
Risk factors	Primary infection	Reinfection
Age groups in Years	**72,458**	**3794**
18 to 24	12,254 (16.91)	757 (19.95)
25 to 29	21,441 (29.59)	1181 (31.13)
30 to 34	23,930 (33.03)	1187 (31.29)
35 to39	12,158 (16.78)	567 (14.94)
40 to 44	2521 (3.48)	92 (2.42)
45 to 50	154 (0.21)	10 (0.26)
Ethnicity	**71,042**	**3693**
White	55,634 (78.31)	2899 (78.50)
Mixed Multiple Ethnic groups	1047 (1.47)	62 (1.68)
Black/Black British	3229 (4.55)	154 (4.17)
Asian/Asian British	9000 (12.67)	489 (13.24)
Any other ethnic groups	2132 (3.00)	89 (2.41)
Parity	**72,617**	**3803**
Nulliparous	28,638 (39.44)	1694 (44.54)
Multiparous	43,979 (60.56)	2109 (55.46)
Multiple births pregnancy	**72,617**	**3803**
Single	71,366 (98.28)	3748 (98.55)
Multiple	1251 (1.72)	55 (1.45)
Comorbidities	**72,617**	**3803**
No	68,809 (94.76)	3571 (93.90)
Yes	3808 (5.24)	232 (6.10)
At risk of COVID-19 complications	***72,412***	***3790***
No	57,725 (79.72)	2996 (79.05)
Yes	14,687 (20.28)	794 (20.95)
Trimester of infection	***72,617***	***3803***
1st trimester	13,965 (19.23)	178 (4.68)
2nd trimester	24,713 (34.03)	641 (16.86)
3rd trimester	33,939 (46.74)	2984 (78.46)
Vaccination status	***49,950***	***2484***
Unvaccinated	26,742 (53.54)	557 (22.42)
1 dose	6571 (13.16)	349 (14.05)
2 or more doses	16,637 (33.31)	1578 (63.53)
Variant	***60,265***	***3008***
wild type	3435 (5.70)	2 (0.07)
Alpha	11,032 (18.31)	96 (3.19)
Delta	32,974 (54.72)	875 (29.09)
Omicron	12,824 (21.28)	2035 (67.65)
Hospital admission after positive test	***72,617***	***3803***
No	71,394 (98.32)	3777 (99.32)
yes	1223 (1.68)	26 (0.68)
Region	***71,278***	***3723***
East Midlands	6337 (8.89)	348 (9.35)
East of England	7968 (11.18)	376 (10.10)
London	11,283 (15.83)	575 (15.44)
North East	3880 (5.44)	235 (6.31)
North West	10,571 (14.83)	646 (17.35)
South East	10,062 (14.12)	426 (11.44)
South West	5627 (7.89)	222 (5.96)
West Midlands	8114 (11.38)	471 (12.65)
Yorkshire and Humber	7436 (10.43)	424 (11.39)
Index of Multiple Deprivation	***71,278***	***3723***
1 Most Deprived	18,579 (26.07)	1120 (30.08)
2	15,836 (22.22)	909 (24.42)
3	13,779 (19.33)	672 (18.05)
4	12,456 (17.48)	586 (15.74)
5 Least Deprived	10,628 (14.91)	436 (11.71)

have a low birthweight compared to those first infected (aOR= 0.57; 95% CI: 0.34 - 0.96). Additionally, we found that stillbirth during reinfection with omicron in the third trimester was higher than after primary infection (aOR= 3.25; 95% CI: 1.19 - 8.89), although stillbirth rates in the reinfection cohort were not exceeding the national average at 3.9‰ while those in the primary infection cohort were much lower than the expected national average at 2.3‰. We consider these results weak evidence because of the number of tests performed overall. We would consider a P-value < 0.001 as significant and with a P-values > 0.003 those results do not meet this standard.

Overall, in all our others analyses, we found that low birthweight, premature birth and stillbirth were similar after primary infection and reinfection with either the delta or omicron infection during all three trimesters of pregnancy.

Strengths and weaknesses

The strengths of this analysis include the use of national surveillance data in a large geographically defined population during a period of widespread testing for SARS-CoV-2 and availability of effective COVID-19 vaccines.

There are, however, important caveats in interpreting our results. Firstly, due to the small numbers of certain outcomes and the multiple testing aspect of our analysis we encourage caution in overanalysing the results. Secondly, those with asymptomatic or mild infection who didn't test themselves as well as those who didn't report their positive results might have been wrongly classified as never infected. This is important because it is also possible that some individuals reporting their first confirmed infection might already have been knowingly or unknowingly infected previously and should therefore have been considered as reinfections. At the same time, the immunity provided after primary infection may result in asymptomatic or mild reinfection, which may not be tested for SARS-CoV-2 and, therefore, only the more symptomatic/severe infection would be tested for and included in the surveillance dataset.

We anticipate that pregnant women with a positive SARS-CoV-2 test would seek medical care if they were unwell irrespective of whether they were vaccinated or unvaccinated, or whether they were experiencing a primary infection or reinfection. Additionally, the study period was chosen as a time that LFD testing was free of charge and test registration has been shown to be higher in those testing positive.[20]

Whilst we acknowledge that the delta variant is no longer in circulation, inclusion of cases affected by the delta variant in the analysis highlights the lower risk of hospitalisation with the omicron variant.

There were no identified ICU admissions during pregnancy with primary infection or reinfection with the omicron variant. This is particularly important because current infections are nearly all due to omicron subvariants in most parts of the world.

Our findings are consistent with other studies reporting a lower risk of severe disease with omicron compared to delta in the general population,[8,21–23] including pregnant individuals and is consistent with the observed decline in the proportion of pregnant individuals admitted to critical care with confirmed COVID-19 in England, Wales and Northern Ireland over time.[5,24,25]

We are only one of two studies who have shown that, in individuals testing positive for SARS-CoV-2, the outcomes of pregnancy (low birthweight in babies born at term, premature live births and stillbirths) were similar, irrespective of infecting variant, or prior infection or vaccination status.[26]

Furthermore, this study is the first to investigate the severity of COVID-19 reinfection in pregnancy using population-based datasets with high levels of record completion allowing us to include a large proportion of the eligible population demographically representative of England.

Another limitation of ours is that due to the timing of the study period, we could not assess term infants born with low birth weight and premature live birth for women infected during the first trimester of pregnancy with omicron. The limited study period also meant that further changes in COVID-19 disease severity as Omicron became established as the dominant variant could not be determined.

Hospital admission was used as a proxy for COVID-19 disease severity, and we sought to minimise the inclusion of hospitalisation

Table 7
Adjusted[a] odd ratios from logistic regression comparing pregnancy outcomes in primary infection versus reinfection with SARS-CoV-2 by gestational trimester at infection.

	COVID-19 in pregnancy			COVID-19 in 1st trimester			COVID-19 in 2nd trimester			COVID-19 in 3rd trimester		
outcomes	1st episode	2nd episode	OR (95% CI)	1st episode	2nd episode	OR (95% CI)	1st episode	2nd episode	OR (95% CI)	1st episode	2nd episode	OR (95% CI)
Low birthweight	***64,584***	***3306***		***12,132***	***109***		***21,158***	***429***		***31,294***	***2768***	
No	63,083 (97.68)	3229 (97.67)		11,857 (97.73)	107 (98.17)		20,673 (97.71)	419 (97.67)		30,553 (97.63)	2703 (97.65)	
Yes	1501 (2.32)	77 (2.33)	0.65 (0.44 - 0.97)	275 (2.27)	2 (1.83)	0.76 (0.10 - 5.84)	485 (2.29)	10 (2.33)	0.41 (0.10 - 1.74)	741 (2.37)	65 (2.35)	0.71 (0.47 - 1.08)
for delta	***29,040***	***770***		***2550***	***67***		***11,450***	***304***		***15,040***	***399***	
No	28,352 (97.63)	748 (97.14)		2468 (96.78)	65 (97.01)		11,180 (97.64)	298 (98.03)		14,704 (97.77)	385 (96.49)	
Yes	688 (2.37)	22 (2.86)	0.75 (0.38 - 1.50)	82 (3.22)	2 (2.99)	0.80 (0.10 - 6.20)	270 (2.36)	6 (1.97)	0.31 (0.04 - 2.27)	336 (2.23)	14 (3.51)	1.04 (0.46 - 2.31)
for omicron	***11,151***	***1747***		*N/A*	*N/A*		***307***	***27***		***10,844***	***1720***	
No	10,847 (97.27)	1715 (98.17)		*N/A*	*N/A*		291 (94.79)	25 (92.59)		10,556 (97.34)	1690 (98.26)	
Yes	304 (2.73)	32 (1.83)	0.56 (0.34 - 0.93)	*N/A*	*N/A*		16 (5.21)	2 (7.41)	1.13 (0.09 - 13.56)	288 (2.66)	30 (1.74)	0.57 (0.34 - 0.96)
Premature birth	***69,732***	***3560***		***13,228***	***124***		***23,175***	***506***		***33,329***	***2930***	
No	63,694 (91.34)	3256 (91.46)		11,992 (90.66)	108 (87.10)		20,912 (90.24)	426 (84.19)		30,790 (92.38)	2722 (92.90)	
Yes	6038 (8.66)	304 (8.54)	1.00 (0.84 - 1.20)	1236 (9.34)	16 (12.90)	1.44 (0.70 - 2.96)	2263 (9.76)	80 (15.81)	1.09 (0.73 - 1.63)	2539 (7.62)	208 (7.10)	1.00 (0.80 - 1.25)
for delta	***31,724***	***845***		***2807***	***75***		***12,606***	***342***		***16,311***	***428***	
No	28,665 (90.36)	764 (90.41)		2478 (88.28)	66 (88.00)		11,290 (89.56)	301 (88.01)		14,897 (91.33)	397 (92.76)	
Yes	3059 (9.64)	81 (9.59)	1.03 (0.76 - 1.41)	329 (11.72)	9 (12.00)	1.77 (0.76 - 4.12)	1316 (10.44)	41 (11.99)	1.30 (0.83 - 2.05)	1414 (8.67)	31 (7.24)	0.70 (0.42 - 1.14)
for omicron	***11,851***	***1856***		***110***	***37***		***500***	***50***		***11,351***	***1806***	
No	10,894 (91.92)	1710 (92.13)		*N/A*	*N/A*		300 (60.00)	27 (54.00)		10,594 (93.33)	1683 (93.19)	
Yes	957 (8.08)	146 (7.87)	1.01 (0.80 - 1.27)	110 (100)	37 (100)	-	200 (40.00)	23 (46.00)	0.73 (0.30 - 1.82)	757 (6.67)	123 (6.81)	1.09 (0.85 - 1.40)
Stillbirth	***70,120***	***3580***		***13,301***	***124***		***23,366***	***517***		***33,453***	***2939***	
No	69,808 (99.56)	3565 (99.58)		13,253 (99.64)	124 (100.00)		23,226 (99.40)	511 (98.84)		33,329 (99.63)	2930 (99.69)	
Yes	312 (0.44)	15 (0.42)	1.99 (0.98 - 4.05)	48 (0.36)	0 (0.00)	0 (0 - 8.57)[b]	140 (0.60)	6 (1.16)	1.40 (0.26 - 7.69)	124 (0.37)	9 (0.31)	2.31 (1.02 - 5.22)
for delta	***31,955***	***850***		***2469***	***76***		***12,721***	***345***		***16,393***	***430***	
No	31,761 (99.39)	846 (99.53)		2453 (99.35)	76 (100.00)		12,627 (99.26)	343 (99.42)		16,311 (99.50)	428 (99.53)	
Yes	194 (0.61)	4 (0.47)	1.24 (0.36 - 4.27)	16 (0.65)	0 (0.00)	0 (0 - 7.81)[b]	94 (0.74)	2 (0.58)	1.54 (0.17 - 13.84)	82 (0.50)	2 (0.47)	1.19 (0.22 - 6.31)
for omicron	***11,913***	***1871***		***2841***	***75***		***536***	***58***		***11,377***	***1813***	
No	11,871 (99.65)	1860 (99.41)		2823 (99.37)	75 (100.00)		520 (97.01)	54 (93.10)		11,351 (99.77)	1806 (99.61)	
Yes	42 (0.35)	11 (0.59)	2.43 (0.94 - 6.29)	18 (0.63)	0 (0.00)	0 (0 - 8.09)[b]	16 (2.99)	4 (6.90)	0.74 (0.01 - 106.21)	26 (0.23)	7 (0.39)	3.25 (1.19 - 8.89)

[a] Analyses are adjusted by age at the start of pregnancy, vaccine status, ethnicity, risk of COVID-19 complications, comorbidities, multiple birth, index of deprivation, testing method, hospital admission following infection, year and monthly quarter of infection, SARS-CoV-2 variant and gestational week at birth (except for analysis on prematurity).
[b] Unadjusted estimates due to low numbers.

with COVID-19 rather than due to COVID-19 disease by applying a set of rules for inclusion. It has been previously demonstrated that increasing the specificity and severity of hospitalisation definitions do have an impact on vaccine effectiveness and waning estimates.[27] However, it is still probable that some hospitalisations are coincidental with COVID-19 especially as pregnancy is a specific condition that warrants a lower threshold for hospital admission.

Implications

Our findings demonstrate that pregnant women remain at higher risk of severe COVID-19 disease after reinfection compared to non-pregnant women. And that reinfections in pregnancy are not less severe than primary infections in contrast with the non-pregnant population. However, at a time when most of the population will now have prior immunity through a combination of prior infection and vaccination, currently circulating SARS-CoV-2 strains belonging mainly to omicron subvariants, are associated with less severe disease compared to previous variants. Many countries continue to recommend COVID-19 vaccination during each pregnancy, while in the UK, new guidance does not recommend that pregnant individuals be included in the at-risk groups that remain eligible for seasonal COVID-19 vaccination.[28] Although the risk of severe disease is likely to be very low in the pregnant woman, we and others have shown that COVID-19 vaccination in pregnancy results in transplacental transfer of protective antibodies which reduces the risk of mild and severe disease in infants from birth up to 6 months of age.[29]

Vaccination in pregnancy would help protect their infants during their most vulnerable period. In a Canadian population-based retrospective cohort study, COVID-19 vaccination during pregnancy was associated with lower risks of neonatal death, and neonatal ICU admission.[30] Current data on vaccination in pregnancy shows that not only is vaccination effective at preventing severe disease in the vaccinee, but when administered in the last two trimesters of pregnancy it also offers protection to the infant in the first 8 months of life.[29]

Conclusion

Pregnant women remain at higher risk of severe disease even during a reinfection episode compared to non-pregnant women. Yet, we found a low risk of hospitalisation and no ICU admissions in pregnancy with confirmed omicron infection. Adverse pregnancy outcomes were similar after primary infection and reinfection.

Vaccination in pregnancy will provide additional protection during the third trimester, when the risk of severe disease and adverse pregnancy outcomes are most elevated, as well as protecting infants against COVID-19 during their first months of life. Nonetheless, it is important to consider the virulence of SARS-CoV-2 strain in circulation when assessing vaccine programmes as we found evidence of low hospitalisation rates during the early omicron period.

Our findings are important for policy makers who are currently considering the need for and timing of future COVID-19 vaccination for at-risk individuals, including pregnant individuals and their infants.

Ethics committee approval

Surveillance of COVID-19 testing and vaccination is undertaken under Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002 to collect confidential patient information (www.legislation.gov.uk/uksi/2002/1438/regulation/3/made) under Section 3(i) (a) to (c), 3(i)(d) (i) and (ii) and 3.[3] The study protocol was subject to an internal review by the UK Health Security Agency Research Ethics and Governance Group and was found to be fully compliant with all regulatory requirements. As no regulatory issues were identified, and ethical review is not a requirement for this type of work, it was decided that a full ethical review would not be necessary.

Authors' contributions

JLB, NA, HC, JS, AAM, SL,KV conceptualised the study. AAM curated the data. NA and AAM designed the analysis plan and AAM conducted the formal analysis assisted by NA. JS accessed and verified the data. AAM, JS,SL wrote the original draft of the manuscript. All co-authors reviewed the manuscript and were responsible for the decision to submit the manuscript.

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Data availability

This work is carried out under Regulation 3 of The Health Service (Control of Patient Information; Secretary of State for Health, 2002) using patient identification information without individual patient consent as part of the UKHSA legal requirement for public health surveillance and monitoring of vaccines. As such, authors cannot make the underlying dataset publicly available for ethical and legal reasons. However, all the data used for this analysis is included as aggregated data in the manuscript tables and appendix. Applications for relevant anonymised data should be submitted to the UKHSA Office for Data Release at https://www.gov.uk/government/publications/accessing-ukhsa-protected-data.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106392.

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