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Vaccine effectiveness against mild and severe covid-19 in pregnant individuals and their infants in England: test negative case-control study

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ABSTRACT

OBJECTIVE To estimate real world vaccine effectiveness against symptomatic disease and hospital admission with the delta and omicron variants of the SARS-CoV-2 virus in pregnant individuals, and to estimate the protection conferred by previous infection and maternal vaccination in their infants.

DESIGN Test negative case-control study.

SETTING Community and hospital testing for covid-19, in England, 26 April 2021 to 9 January 2022 (delta variant period) and 29 November 2021 to 31 March 2022 (omicron variant period). Testing data were linked to Hospital Episode Statistics and Maternal Services Data Set (for data on pregnant individuals and infants), National Immunisation Management System (for covid-19 vaccinations), and Secondary Uses Service (for hospital admissions).

PARTICIPANTS 35 206 negative and 16 693 positive eligible test results in the delta variant period from pregnant individuals with symptoms of infection, aged 16-55 years, whose pregnancy ended in 2021, and 5974 negative and 4715 positive eligible test results in the omicron variant period. For infants born in 2021, 23 053 negative and 2924 positive eligible test results in the delta variant period and 13 908 negative and 5669 positive test results from infants in the omicron period.

MAIN OUTCOME MEASURES Vaccine effectiveness against symptomatic disease and hospital admission with the delta and omicron variants of the SARS-CoV-2 virus in pregnant women. Also, effectiveness of maternal vaccination and the protection conferred by previous infection in mothers in preventing symptomatic disease and hospital admission in their infants in the first six months of life. Symptomatic SARS-CoV-2 infection was confirmed by a positive polymerase chain reaction test result.

RESULTS Vaccine effectiveness against symptomatic disease (delta and omicron infection) and against hospital admission (delta infection only) in pregnant individuals was high, as seen in the general population. A booster dose of vaccine gave sustained protection, with no evidence of waning up to 15 weeks after vaccination. Vaccine effectiveness against symptomatic disease peaked at 98.4% (95% confidence interval (CI) 88.4% to 99.8%) and 80.1% (73.8% to 84.9%) against the delta and omicron variants, respectively, after the booster dose of vaccine. Vaccine effectiveness after a two dose primary schedule against hospital admission with delta infection peaked at 92.7% (95% CI 79.9% to 97.4%) in pregnant individuals. Maternal vaccination during and after pregnancy also provided sustained protection from symptomatic disease and hospital admission after delta and omicron infection in infants aged up to six months, with the highest protection seen when maternal vaccination occurred during later pregnancy. The effectiveness of two maternal doses when the last dose was given in the third trimester was 86.5% (95% CI 81.9% to 90.0%) and 56.6% (46.7% to 64.6%) against symptomatic disease with delta and omicron infection, respectively, in infants, and effectiveness against hospital admission was 94.7% (78.2% to 98.7%)

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Since December 2021, vaccine policy in the UK includes pregnancy in the priority list for a covid-19 vaccine, with seasonal boosters offered to those at clinical risk (including pregnant individuals)
⇒ Studies have shown moderate vaccine effectiveness after a second dose of mRNA covid-19 vaccines in pregnant individuals against symptomatic omicron disease, with evidence that booster doses confer higher protection against serious omicron disease
⇒ Real world evidence from test negative case-control studies has shown that protection in infants after maternal vaccination is highest after vaccination in the third trimester and wanes with increasing infant age

WHAT THIS STUDY ADDS

⇒ In pregnant individuals, vaccine effectiveness against symptomatic delta and omicron infection, and against hospital admission with delta infection, was high after maternal vaccination, with limited waning
⇒ Previous infection and maternal vaccination protected infants after birth against symptomatic disease and hospital admission with delta and omicron infection
⇒ Vaccine effectiveness was highest when maternal vaccination occurred in the later stages of pregnancy

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ The findings of the study support the benefits of maternal vaccination in preventing disease in pregnant individuals and in their infants in the first months of life
⇒ Policy questions remain as to whether pregnant women should continue to be offered the vaccine as part of seasonal booster campaigns or during the later stages of pregnancy throughout the year
⇒ The findings provide valuable data for countries currently considering whether booster doses of vaccine should be given later in pregnancy to optimise protection for the infant

and 78.7% (58.2% to 89.1%), respectively. Previous infection with wild-type, alpha, and delta variants of the SARS-CoV-2 virus in pregnant individuals was more protective against mild and severe delta infection than omicron infection in their infants.
CONCLUSIONS The results of this study indicated that maternal vaccination prevented mild and severe disease in pregnant individuals and their infants for up to six months after birth. The findings support the promotion of both primary and booster vaccination for pregnant individuals to protect themselves and their infants.

Introduction

Pregnant individuals are at increased risk of adverse outcomes from infection with the SARS-CoV-2 virus, such as venous thromboembolism and admission to critical care, compared with non-infected pregnant individuals, as well as having an increased risk of preterm birth.[1–5] In the US, higher rates of respiratory support, admission to the intensive care unit, and death were reported in women giving birth with a diagnosis of covid-19 disease recorded in the same admission than in other pregnant women.[6] An increased risk of stillbirth and neonatal mortality has also been reported in babies born to women with SARS-CoV-2 infection in later pregnancy, with increased odds of neonatal admission to intensive care.[3] In the US, covid-19 was ranked as the seventh leading cause of death in infants aged <1 year, accounting for 0.7% of all deaths in this age group.[7]

As part of the UK covid-19 vaccination programme, from December 2020, all adults in England were offered a primary vaccination course (consisting of two doses), followed by a booster dose from December 2021. Initially, the Joint Committee on Vaccination and Immunisation advised that pregnant individuals should be offered vaccines at the same time as people of the same age or risk group.[8] As data accumulated on the severity of infection with emergent SARS-CoV-2 variants in pregnant individuals together with data on vaccine safety, the Joint Committee on Vaccination and Immunisation updated their recommendation in December 2021 to include pregnant individuals in the UK's priority covid-19 vaccine list.[9]

A covid-19 vaccine in pregnancy has been reported to directly reduce the risk of serious disease in pregnant women; booster doses of vaccine gave increased protection against hospital admission in pregnant women compared with a primary course only.[10–12] Also, studies have consistently found no association between covid-19 vaccination in pregnancy and adverse outcomes in pregnant women, pregnancy, or the neonate.[1 2 13–17] Maternal vaccination protects infants in utero against the consequences of serious disease in the mother, including preterm birth and stillbirth.[15] Also, transplacental transfer of maternal antibodies can provide passive protection in the infant from birth in their first months of life,[2 18] and others have reported real world evidence from test negative case-control studies that maternal vaccination with two and three doses also protected infants.[19–22] Protecting mothers by vaccination might also reduce their risk of SARS-CoV-2 infection after birth and consequently reduce the risk of infecting infants postnatally.

Currently, covid-19 vaccination for pregnant persons in the UK is aligned with seasonal programme recommendations for high risk groups, but policy questions remain as to whether vaccination should instead be recommended during the later stages of pregnancy throughout the year to maximise protection for mothers and their infants. The primary aim of this study was to use the test negative case-control study design to assess whether covid-19 vaccination under the recommended policy schedule in the UK was effective in preventing symptomatic disease and hospital admission with the delta and omicron variants of the SARS-CoV-2 virus in pregnant women who delivered in 2021 in England. Furthermore, we aimed to investigate whether previous infection and maternal vaccination was effective in preventing symptomatic disease and hospital admission with the delta and omicron variants in their infants in the first six months of life.

Methods

Study design and data sources

We used a test negative case-control study design to estimate the effectiveness of the covid-19 vaccines in preventing disease in pregnant individuals, and to estimate the effectiveness of maternal vaccination and previous maternal infection in preventing disease in infants. Pregnant individuals who had a positive test result for the SARS-CoV-2 virus were defined as cases and those testing negative as controls. The variable of interest was either vaccination or previous infection.

Testing for the SARS-CoV-2 virus by polymerase chain reaction (PCR) in England is undertaken by hospital and public health laboratories (pillar 1), as well as by community testing (pillar 2) (online supplemental table 1). Pillar 2 testing data include symptom status (self-reported at the time the test was requested). To estimate vaccine effectiveness against symptomatic disease in pregnant individuals, the odds of vaccination in cases (community test results from individuals who reported symptoms) were compared with the odds of vaccination in comparable PCR negative controls, as previously described.[23–25]

To estimate the protective effect of maternal vaccination and previous infection against symptomatic disease in infants, cases and controls comprised pillar 2 PCR test results with reported symptoms as well as

pillar 1 (hospital based) PCR test results in patients admitted to hospital with a respiratory infection in the primary diagnosis field. For the infant analysis of vaccine effectiveness against symptomatic disease, we included pillar 1 and pillar 2 test results because there were many more pillar 1 test results from infants. We believe that this greater number of pillar 1 test results in infants was likely because testing was done in hospital after birth or because parents went to a hospital when their infant was unwell. The variables of interest were maternal vaccination status and maternal past infection status.

To estimate vaccine effectiveness against hospital admission in pregnant individuals and their infants, the odds of vaccination (or maternal vaccination) in patients admitted to hospital (SARS-CoV-2 pillar 1 positive test results which could be linked to a respiratory hospital admission with a minimum two day inpatient stay) were compared with the odds of vaccination (or maternal vaccination) in negative controls (negative SARS-CoV-2 pillar 1 PCR test results were linked by NHS number and date of birth to the national hospital admission data to identify respiratory hospital admissions with a minimum two day inpatient stay; online supplemental table 2), as previously described.[24 26 27] Online supplemental appendix has full details of the data sources.

Hospital Episode Statistics

Data on all individuals with a delivery episode recorded in 2021 (regardless of the outcome), aged 16-55 years, in England, were extracted from the Hospital Episode Statistics (an administrative database with details about admissions, outpatient appointments, and previous attendances at the accident and emergency department at NHS hospitals in England; online supplemental table 1) in November 2022. Data were available for those with a valid NHS number who delivered in an NHS hospital after 24-42 weeks of pregnancy. Miscarriages and pregnancy terminations before 24 weeks were not included in the analysis. Pregnant individuals who delivered in 2021 were identified by ICD-10 (international classification of diseases, 10th revision) codes for all deliveries (including stillbirths, live births, and births when the outcome was not known), and therefore this study of vaccine effectiveness in pregnancy was for pregnancies that ended in 2021.

Maternity Services Data Set

Pregnant individuals were linked to the Maternal Services Data Set (online supplemental table 1) by NHS number and delivery date to extract the date of the last menstrual period. Data on infants born in 2021 and linked to pregnant individuals were extracted from the Maternal Services Data Set in November 2022 (online supplemental table 1). The start date of pregnancy was calculated as the earliest possible start date where the gestational age of the infant was known. If gestational age was not known, the date of the last menstrual period was used. If gestational age and date of the last menstrual period were not known, the earliest possible pregnancy start date was estimated based on the delivery date and whether the infant was term or preterm. If information on the infant's birth was not know (ie, if an infant was born term or preterm), the pregnancy start date was estimated assuming that the infant was born at term. Trimesters were defined as before pregnancy, trimester 1 (week 0 (+0 days) to 11 (+6 days)), trimester 2 (week 12 (+0 days) to 26 (+6 days)), and trimester 3 (week 27 (+0 days) to 15 days before birth (infant only)).

Testing data

Individuals whose pregnancy ended in 2021 (regardless of the pregnancy outcome) and their infants born in 2021 were linked to pillar 1 (hospital PCR test results) and pillar 2 (community PCR and lateral flow test results) testing data by NHS number. Pillar 1 or 2 SARS-CoV-2 testing was recorded for 58% of pregnant individuals that had been linked to the National Immunisation Management System, where the date of the test was within 90 days before the start date of pregnancy or up to 90 days after the delivery date. Only PCR test results from after the pregnancy start date up to 90 days after the delivery date were included in the final analysis. Pillar 1 or 2 testing data were recorded for 40% of infants that had been linked to the National Immunisation Management System. Data were also extracted on the date of the most recent past infection (with a 90 day interval), confirmed by a positive lateral flow test result or a PCR test result from either pillar 1 or 2.

National Immunisation Management System

Testing data were linked to the National Immunisation Management System by using combinations of the unique individual NHS number, date of birth, surname, first name, and postcode, with deterministic linkage (online supplemental table 1). National Immunisation Management System was accessed for dates of vaccination and manufacturer, as well as personal characteristics and clinical risk status.

When assessing effectiveness in infants, maternal vaccination status was defined according to doses received >14 days before birth and doses received after this date but >14 days before the onset date in the infant. When assessing effectiveness in pregnant individuals, vaccination status was defined by the number of doses at onset or sample date and the interval in weeks since the previous dose (0-1, 2-4, 5-9, 10-14, 15-19, 20-24, and ≥25 weeks), regardless of whether the doses were given in pregnancy. Analyses were done irrespective of the manufacturers of the vaccines.

Identification of variant status

Analyses were grouped by delta or omicron variant. The delta predominant period comprised test results

from pregnant individuals between 26 April 2021 and 9 January 2022, and tests from infants between 2 May 2021 and 9 January 2022. Test results from infants were excluded if the week of birth was before 2 May 2021 because maternal vaccination was minimal before this date, and only pregnant individuals at high risk of infection or severe disease received a vaccine before mid-April 2021. The omicron predominant period comprised test results between 29 November 2021 and 31 March 2022 for both pregnant persons and infants.

Variants were defined based on whole genome sequencing, genotyping, S gene target failure status, or period, with sequencing taking priority, followed by genotyping, S gene target failure status, and then period. If subsequent positive test results within 14 days included information on sequencing, genotyping, or S gene target failure, this information was used to classify the variant. During the period 26 April 2021 to 27 June 2021, when the alpha and delta variants co-circulated, and from 29 November 2021 to 9 January 2022, when the delta and omicron variants co-circulated, only positive test results with available sequencing information, genotyping, or S gene target status were included as cases. Controls in the overlapping period were included in both analyses.

In the analysis of vaccine effectiveness in infants, past infection in the mother was defined as an infection at least 14 days before birth and was assigned to a variant based on the date of the last positive test result (in the period until 14 days before birth). The wild-type variant dominant period was up until 6 December 2020, the alpha variant dominant period was 7 December 2020 to 9 May 2021, the delta variant dominant period was 10 May 2021 to 12 December 2021, and the omicron variant dominant period was 13 December 2021 onwards.[28]

Covariates and adjustment

Variables of interest and likely confounding variables were prespecified. Variables were vaccine status and most recent past infection in the child bearer (in the infant analysis, past infection was defined as an infection at least 14 days before birth). Confounding variables were week of symptom onset, age (of infant and pregnant individuals in five year categories), risk group status of pregnant individuals, region, index of multiple deprivation group (a measure of deprivation derived from the individual's postcode, with five domains), and ethnic group. In the infant analysis, additional confounding variables were pillar of testing (and its interaction with age because there were many more pillar 1 test results from the youngest infants, likely reflecting testing done in hospital after birth), prematurity, and sex. Index of multiple deprivation group, region, and ethnic group were assessed for confounding effects of ≥5% and only included if they changed effectiveness by at least this amount for at least one of the variants.

Statistical methods

We used multivariable logistic regression with the test result as the outcome, vaccination status and past infection in the pregnant individual as the primary variables of interest, and with confounder adjustment as described. Vaccine effectiveness or protective effect of past infection was calculated as 1−odds ratio and recorded as a percentage. Estimates are not shown if the 95% confidence interval (CI) lower bound was <−50% and the top bound was >80%, because the precision for these estimates was too low to be clinically meaningful. The main comparator group was pregnant individuals who were not vaccinated or those who were never vaccinated (including after birth). To compare estimates of vaccine effectiveness, significance was concluded when 95% confidence intervals did not overlap.

The primary analysis of vaccine effectiveness during pregnancy included test results from the start date of pregnancy up to three months post partum because insufficient data were available to estimate vaccine effectiveness against the omicron variant if the data were restricted to test results only during pregnancy. Sensitivity analyses were performed to assess vaccine effectiveness within the pregnancy (trimesters 1-3) for the delta variant period. Sensitivity analyses were also done to assess the effect of removing the adjustment for past infection in pregnant individuals (during the delta and omicron variant study periods) and removing test results during overlapping periods when the variants co-circulated. An additional analysis was conducted to estimate vaccine effectiveness against symptomatic disease in all women aged 20-44 years (the age of most pregnant individuals) who were not pregnant, tested in pillar 2 during the omicron variant period.

In infants, the primary analysis included all infants aged 0-5 months. Grouping was by trimester of vaccination and by infant age at 0-2 months and 3-5 months. For the omicron variant, stratification for infants aged 6-8 months was also possible.

Patient and public involvement

Members of the public were not directly involved in this unfunded study, which involved analysis of national surveillance data. The study was, however, conducted in consultation with the UK Joint Committee on Vaccination and Immunisation, which includes lay membership to represent the perspective of patients or NHS service users. This study will be publicly available via open access so all members of the general public can read it.

Results

Vaccine effectiveness against symptomatic disease

Between 26 April 2021 and 9 January 2022 (the delta variant period), 35 206 negative and 16 693 positive eligible test results were available from pregnant individuals with symptoms of infection, aged

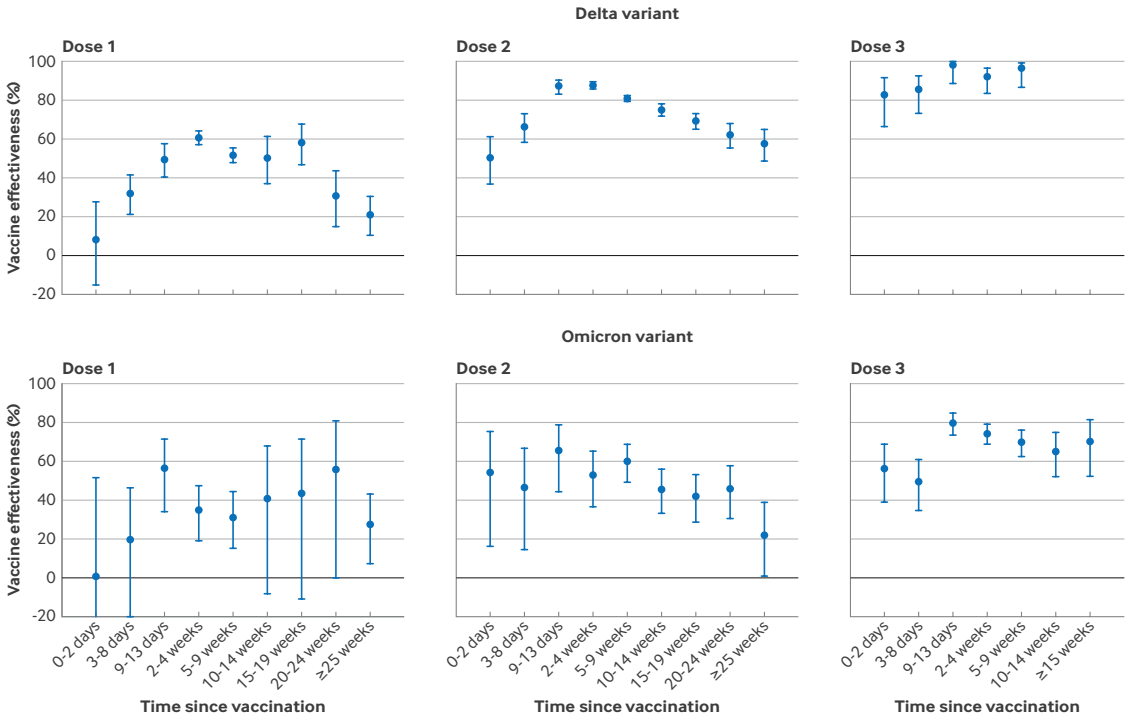

Figure 1 | Vaccine effectiveness against symptomatic disease with the delta and omicron variants of the SARS-CoV-2 virus in pregnant women who were vaccinated with one, two, or three doses of vaccine. Online supplemental table 4 has the full data

16-55 years, who had given birth in 2021. Between 29 November 2021 and 31 March 2022 (the omicron variant period), 5974 negative and 4715 positive eligible test results were available. Online supplemental table 3 has a description of individuals with eligible tests.

After vaccination with one dose, vaccine effectiveness against symptomatic disease during pregnancy was 50-60% for the delta variant and 30-40% for the omicron variant, within 20 weeks of the first dose being given (figure 1 and online supplemental table 4). After a second dose, protection against the delta variant peaked at >85% and then waned to about 60% after 25 weeks compared with a peak of 65% against the omicron variant which waned to just below 30% for the same period. Booster vaccination increased vaccine effectiveness against symptomatic disease with the delta variant to >90% (although numbers were small) and with the omicron variant to about 75% in the relatively short term (most data <15 weeks) (figure 1 and online supplemental table 4).

Sensitivity analyses showed little difference in estimates of vaccine effectiveness when we restricted the analysis to the pregnancy period (and excluded the three month postpartum period) for the delta variant (online supplemental table 5). Sensitivity analyses for the delta and omicron variants without adjustment for past infection (online supplemental table 5) and for excluding the overlapping periods when the variants co-circulated (online supplemental table 5) also gave similar results. An additional analysis of vaccine effectiveness in non-pregnant women aged 20-44 years showed that vaccine effectiveness against symptomatic disease peaked at a similar level but waned more rapidly than vaccine effectiveness during pregnancy (online supplemental table 5).

Vaccine effectiveness against hospital admission

In the delta variant period, 86 negative and 1249 positive eligible test results were available from pregnant women tested in hospital settings (pillar 1) that could be linked to a respiratory coded hospital admission with a length of stay of at least two days (online supplemental table 6). Vaccine effectiveness against hospital admission with omicron infection could not be estimated because of insufficient data (only 11 eligible test results linked to a respiratory coded hospital admission). Vaccine effectiveness against hospital admission with delta infection was >90% in the 5-19 week period after a first or second vaccine dose (table 1). Vaccine effectiveness after a booster dose for either variant could not be estimated because of insufficient data.

Effectiveness of maternal vaccination and previous infection against symptomatic disease in infants

Between 2 May 2021 and 9 January 2022 (the delta variant period), 23 053 negative and 2924 positive eligible test results were available from infants born in 2021, and between 29 November 2021 and 31 March 2022 (the omicron variant period), 13 908 negative and 5669 positive eligible test results were available. Online supplemental table 7 has a description of infants with eligible tests.

Table 1 | Vaccine effectiveness against hospital admission with infection with the delta variant of the SARS-CoV-2 virus in pregnancy (from the start of pregnancy up to three months post partum), in England, in pregnant individuals with a positive test result for the SARS-CoV-2 virus (cases) and in those who tested negative (controls)

Vaccination status	Interval (weeks)	Controls	Cases	Odds ratio (95% CI)†	Vaccine effectiveness (%, 95% CI)†
Not vaccinated		55	1109	Baseline	Baseline
Dose 1*	0-4	4	32	0.31 (0.09-1.04)	69.2 (-4.1 to 90.9)
	5-19	8	26	0.06 (0.02-0.19)	94.1 (81.2 to 98.1)
	20+	2	30	NA‡	NA‡
Dose 2*	0-4	4	4	0.03 (0.0-0.18)	97.3 (82.1 to 99.6)
	5-19	12	34	0.07 (0.03-0.2)	92.7 (79.9 to 97.4)
	≥20	1	14	NA‡	NA‡

*Primary course mRNA vaccines were Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273), or adenovirus vector vaccine Oxford-AstraZeneca (ChAdOx1 nCoV-19).

†Confounding variables were week of test, age (in five year categories), risk group status, region, index of multiple deprivation group, ethnic group, and likely variant of most recent past infection.

‡Insufficient data.

CI, confidence interval; NA, not available.

Clear protective effects of maternal vaccination against symptomatic disease for both the delta and omicron variants were seen in infants aged 0-5 months (figures 2 and 3, and online supplemental table 8). The general pattern showed that doses given later in pregnancy provided higher protection, with increasing protection after the second and third dose compared with the first dose. Additional doses given to pregnant individuals after birth also added to the protection. Vaccine effectiveness was also higher against symptomatic infection with the delta than the omicron variant. The highest estimate against the delta variant was seen when the second dose was given in the third trimester, with vaccine effectiveness at 86.5% (95% CI 81.9% to 90.0%). Vaccine effectiveness after a third dose in the third trimester for the delta variant could not be estimated because of insufficient data, but for the omicron variant, vaccine effectiveness was 84.0% (95% CI 72.7% to 90.6%) after a maternal booster dose in the third trimester.

When grouped by infant age, we found no evidence of waning of protection conferred by maternal vaccination against symptomatic disease with the delta or omicron variant in infants aged 3-5 months compared with infants aged 0-2 months. Follow-up after 6 months of age was unavailable for infants during the delta period but maternal vaccination also had sustained protection against the omicron variant in infants aged 6-8 months, with some suggestion of waning by this age, although the 95% confidence intervals overlapped (figures 2 and 3, and online supplemental table 8). We found a protective effect in the infant when individuals were not vaccinated during pregnancy but received a vaccine after birth; vaccine effectiveness of two doses given after delivery was about 50% and 25% against symptomatic disease with the delta and omicron variants, respectively (figures 2 and 3, and online supplemental table 8).

Previous infection with the SARS-CoV-2 virus in the child bearer also had a protective effect for the infant against developing symptomatic disease. Past maternal infection with the wild-type, alpha, or delta variant of the SARS-CoV-2 virus was about 70%, 83%, and 88% protective, respectively, against symptomatic disease with the delta variant in infants aged 0-5 months (table 2). Maternal infection was less protective against symptomatic disease with the omicron than the delta variant. The protective effect of past infection with wild-type, alpha, and delta variants was about 24%, 37%, and 41%, respectively, against the omicron variant in infants aged 0-5 months (table 2).

Effectiveness of maternal vaccination and previous infection against infant hospital admission

Between 2 May 2021 and 9 January 2022 (the delta variant period for infants), 4588 negative and 436 positive eligible test results were available in infants born in 2021, who were tested in hospital settings and linked to a respiratory coded hospital admission with a length of stay of at least two days.[26] Between 29 November 2021 and 26 June 2022 (the omicron variant period), 1413 negative and 457 positive eligible test results were available (online supplemental table 9).

Maternal vaccination during pregnancy and previous infection (during or before pregnancy) both protected infants from hospital admission with the delta and omicron variants, with higher vaccine effectiveness against hospital admission than against symptomatic disease (figure 4, table 3, and online supplemental table 10). Protection conferred by maternal vaccination during the second trimester was about 70-85%, depending on the number of vaccine doses, for both the delta and omicron variants. Infants had the highest protection when maternal vaccination took place during the third trimester; maternal vaccination with a second dose in the third trimester was about >90% and >75% protective against hospital admission with the delta and omicron variants, respectively. Vaccine effectiveness of maternal booster doses of vaccine against severe disease in infants infected with the delta variant

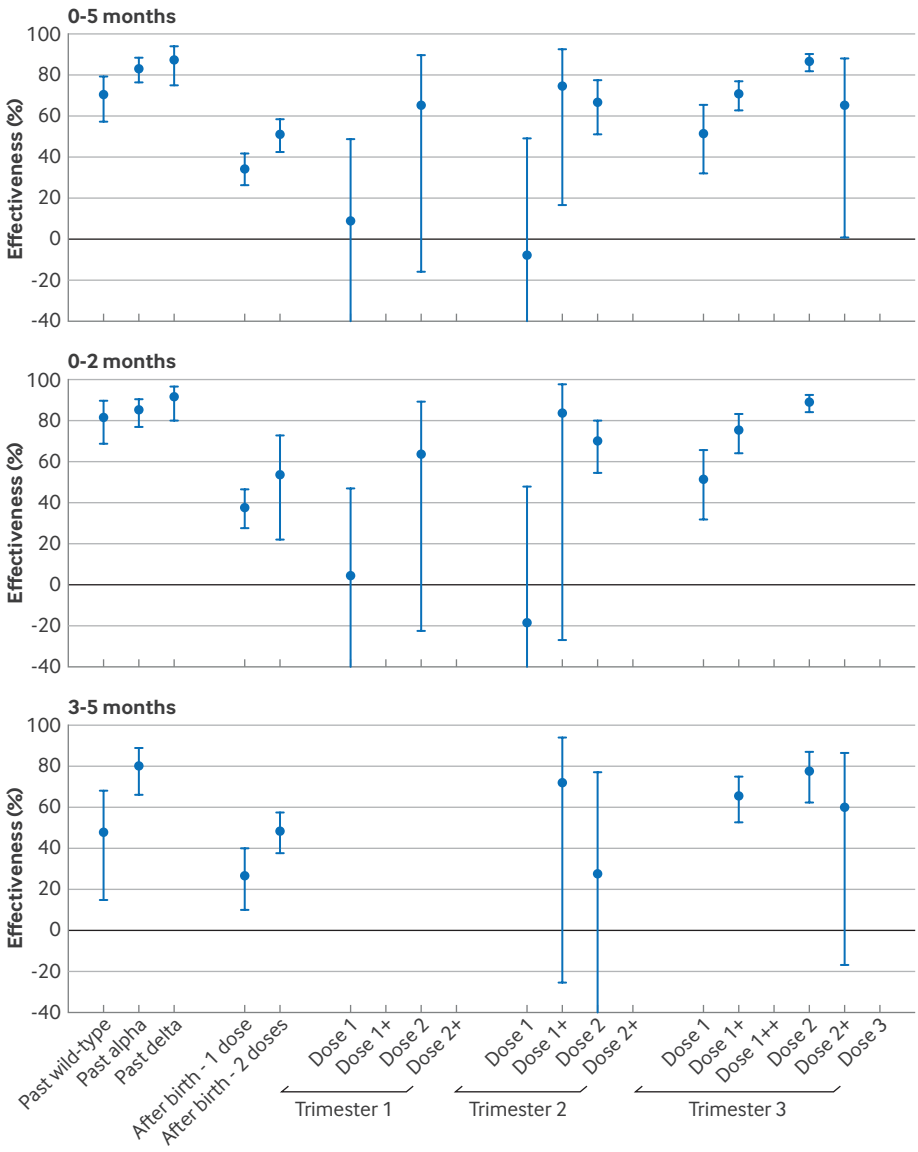

Figure 2 | Protection of previous infection in the mother with the wild-type, alpha, or delta variant of the SARS-CoV-2 virus, and effectiveness of maternal vaccination against symptomatic disease with the delta variant in infants in England. After birth, one or two doses of vaccine refer to doses given after birth to women who had not received a vaccine previously. Doses given during each trimester are noted as doses 1, 2, and 3. Plus signs (+, ++) indicate when maternal vaccination occurred during pregnancy and an additional one dose (+) or two doses (++) of maternal vaccines were given after birth. Online supplemental tables 7 and 8 show the full data

could not be estimated because of insufficient data, but a maternal booster dose in the third trimester provided about 90% protection against hospital admission with the omicron variant in infants aged 0-6 months (figure 4 and online supplemental table 10).

Previous maternal infection with any variant of the SARS-CoV-2 virus also protected infants from severe disease with the delta variant (table 3). The protective effect of previous maternal infection with the wild-type, alpha, or delta variant of the SARS-CoV-2 virus against hospital admission of infants with a delta variant infection was 93.4% (95% CI 52.0% to 99.1%), 63.3% (33.9 to 79.7%), and 85.1% (38.0% to 96.4%), respectively. The protection conferred by previous maternal infection against hospital admission of infants with an omicron variant infection was less evident, with 95% confidence intervals crossing 0% for infection with any previous variant (table 3).

Discussion

Principal findings

In this study, the evidence indicated that covid-19 vaccines gave protection during pregnancy, and that both previous infection in the child bearer and maternal vaccination (during and after pregnancy) provided sustained protection against symptomatic disease and hospital admission in the infant. We found the highest protection when maternal vaccination occurred during the later stages of pregnancy.

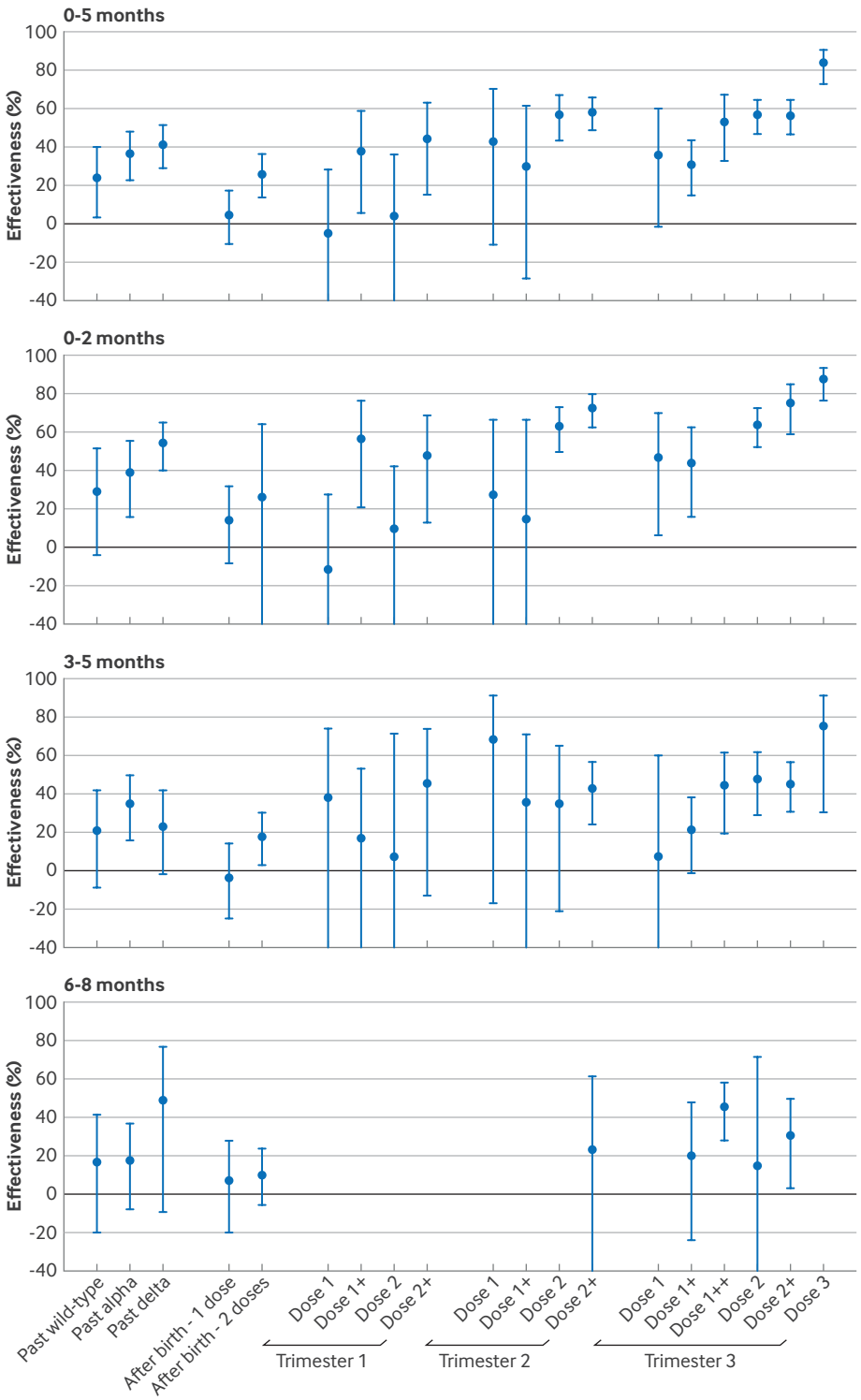

Figure 3 | Protection of previous infection in the mother with the wild-type, alpha, or delta variant of the SARS-CoV-2 virus, and effectiveness of maternal vaccination against symptomatic disease with the omicron variant in infants in England. After birth, one or two doses of vaccine refer to doses given after birth to women who had not received a vaccine previously. Doses given during each trimester are noted as doses 1, 2, and 3. Plus signs (+, ++) indicate when maternal vaccination occurred during pregnancy and an additional one dose (+) or two doses (++) of maternal vaccines were given after birth. Online supplemental tables 7 and 8 show the full data

Protection against symptomatic covid-19 and severe disease from previous infection or vaccination was substantially higher with the delta compared with the omicron variant.

Our estimates for vaccine effectiveness after the first and second doses of vaccine against mild and severe disease with the delta variant in pregnant individuals were similar to earlier test negative

Table 2 | Protection of maternal past infection with the wild-type, alpha, or delta variant of the SARS-CoV-2 virus against symptomatic disease with delta and omicron variants in infants, in England. Pregnant individuals had a positive test result for the SARS-CoV-2 virus (cases) or tested negative (controls)

		Delta variant			Omicron variant		
Infant age (months)	Maternal previous infection	Cases	Controls	Protection against delta (%, 95% CI)	Cases	Controls	Protection against omicron (%, 95% CI)
0-5	None	2684	18 483	Baseline	3269	8010	Baseline
	Wild-type	34	699	70.3 (57.4 to 79.2)	118	339	23.7 (3.1 to 39.9)
	Alpha	35	1333	83.3 (76.4 to 88.1)	162	569	36.5 (22.4 to 47.9)
	Delta	8	607	87.7 (75.0 to 93.9)	172	640	41.1 (28.7 to 51.3)
0-2	None	1723	12 208	Baseline	1234	3532	Baseline
	Wild-type	14	468	81.8 (68.5 to 89.5)	45	151	28.6 (−4.7 to 51.3)
	Alpha	21	903	85.1 (76.8 to 90.4)	61	263	38.6 (15.5 to 55.4)
	delta	5	532	91.8 (80.1 to 96.7)	84	436	54.1 (40.1 to 64.9)
3-5	None	961	6275	Baseline	2035	4478	Baseline
	Wild-type	20	231	47.7 (14.6 to 68.0)	73	188	20.3 (−8.8 to 41.5)
	Alpha	14	430	80.3 (65.8 to 88.6)	101	306	34.8 (15.6 to 49.6)
	Delta	3	75	NA*	88	204	23.0 (−1.8 to 41.8)
6-8	None	—	—	—	1795	3941	Baseline
	Wild-type	—	—	—	51	131	16.1 (−20.1 to 41.4)
	Alpha	—	—	—	92	243	17.2 (−8.2 to 36.6)
	Delta	—	—	—	10	32	49.1 (−9.6 to 76.3)

*Insufficient data.
CI, confidence interval; NA, not available.

case-control vaccine effectiveness studies in the general population.[12 23 29] Since the emergence of the more immune evasive omicron variant of the SARS-CoV-2 virus in late December 2021, we have had limited data on vaccine effectiveness after a third (booster) dose of vaccine against the delta variant. Vaccine effectiveness against hospital admission with infection with the delta variant was high, as we and others have seen previously in non-pregnant populations.[10 26 29]

In pregnant individuals, vaccine effectiveness after a second dose against symptomatic disease with the omicron variant was also similar to earlier studies in non-pregnant populations.[12 23] Vaccine effectiveness after the third dose, however, remained high, even at ≥15 weeks after vaccination, with limited waning observed. This finding contrasts with our earlier studies in non-pregnant populations that found substantial waning after a booster dose of vaccine against symptomatic disease with the omicron variant. We further investigated this effect by estimating vaccine effectiveness in all individuals of childbearing age who did not contribute a test result as part of the vaccine effectiveness analysis of pregnant individuals. In these non-pregnant individuals, we found that vaccine effectiveness waned at ≥15 weeks after the booster vaccine, as we have previously reported for the general population.[30] Although the reason why vaccine effectiveness against mild disease with the omicron variant after a third dose seemed to be higher in pregnant than in non-pregnant women is unclear, vaccine effectiveness was not lower during pregnancy, and these differences might be because of confounding.

As well as protection against mild and severe disease in pregnant individuals, maternal vaccination during pregnancy also conferred protection in the infant. In the US, a test negative case-control study reported 52% (95% CI 33% to 65%) vaccine effectiveness after two maternal doses against hospital admission for covid-19 overall and 38% (8% to 58%) during the omicron period, increasing to 58% when the second dose was given after 20 weeks' gestation.[19] In a Canadian study, maternal vaccine effectiveness after three doses was 73% (95% CI 61% to 80%) against omicron infection in infants and 80% (64% to 89%) against hospital admission for infants with omicron infection.[20] Similar to the US study, we also found higher protection in infants when vaccination occurred later in pregnancy, with the highest protection after vaccination in the third trimester. Longer term follow-up of infants infected during the delta period could not be carried out because of insufficient data and the emergence of the omicron variant, but follow-up of infants during the omicron period indicated that waning of protection occurred in the infant; protection after maternal vaccination in the third trimester was lower in infants aged 6-8 months than those aged 0-5 months.

It is difficult to separate direct and indirect protection in infants from maternal vaccination. Data on vaccination, grouped by doses given before and after birth, explain some of this effect, given that maternal doses after birth still protected the infant

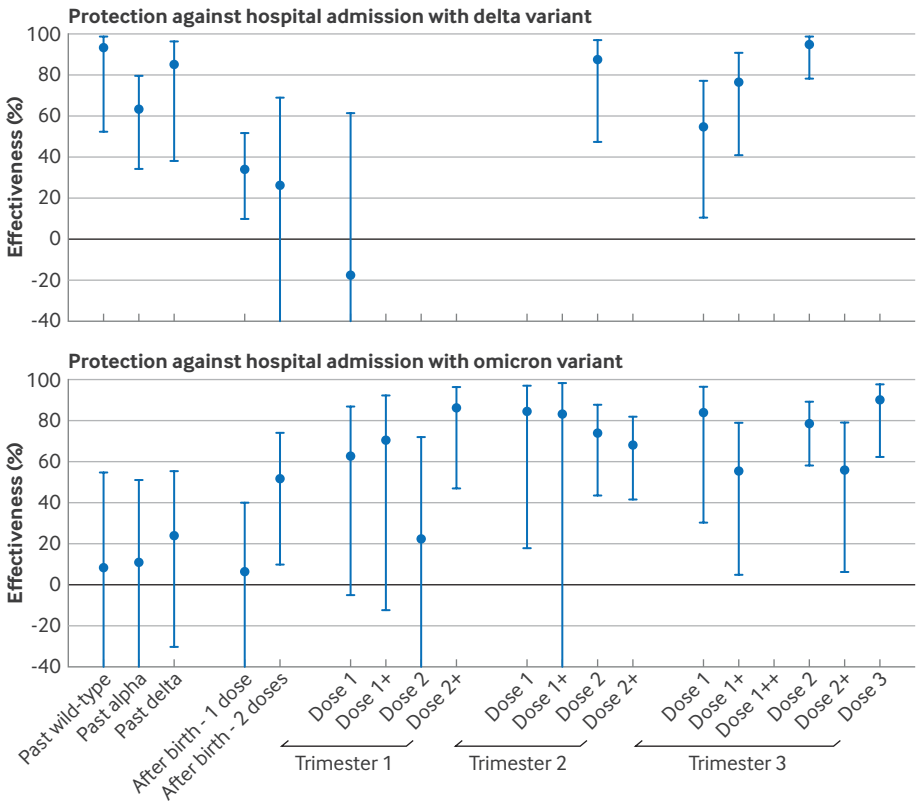

Figure 4 | Protection of previous infection in the mother with the wild-type, alpha, or delta variant of the SARS-CoV-2 virus, and maternal vaccine effectiveness against hospital admission with the delta and omicron variants in infants in England. After birth, one or two doses of vaccine refer to doses given after birth to women who had not received a vaccine previously. Doses given during each trimester are noted as doses 1, 2, and 3. Plus signs (+, ++) indicate when maternal vaccination occurred during pregnancy and an additional one dose (+) or two doses (++) of maternal vaccines were given after birth. Online supplemental table 10 shows the full data

but generally to a lesser extent than vaccine doses during pregnancy. We postulate that the protection from doses given after delivery is most likely because of the indirect effect of the mother not becoming infected herself, although protection from transfer of passive antibodies through breast milk could also be possible.[31 32]

Previous infection with any variant of the SARS-CoV-2 virus in the child bearer was also protective against mild and severe disease with the delta and omicron variants in the infant, although protection differed by variant; the highest protection was achieved after delta infection in the mother against a subsequent delta infection in the infant (this finding likely reflects both antigen similarity and a shorter interval between maternal and infant infection). Many wild-type and alpha infections, however, would not have been confirmed because community testing was not widely available early in the pandemic, and confirmed infections might have been more severe. A protective effect was seen even if the most recent infection was with a wild-type or alpha variant against a subsequent delta infection in the infant, despite these infections occurring in the child bearer many months before pregnancy. Neutralising antibodies can be detected for at least 12 months

Table 3 | Protection of maternal past infection with the wild-type, alpha, or delta variant of the SARS-CoV-2 virus against hospital admission with delta and omicron variants in infants aged 0-6 months, in England. Pregnant individuals had a positive test result for the SARS-CoV-2 virus (cases) or tested negative (controls)

	Delta variant			Omicron variant		
Maternal previous infection	Cases	Controls	Protection against delta (%, 95% CI)	Cases	Controls	Protection against omicron (%, 95% CI)
None	420	4021	Baseline	390	1173	Baseline
Wild-type	1	141	93.4 (52.0 to 99.1)	15	52	8.4 (-85.5 to 54.8)
Alpha	13	299	63.3 (33.9 to 79.7)	24	87	11.2 (-61.9 to 51.3)
Delta	2	127	85.1 (38.0 to 96.4)	28	100	24.0 (-30.1 to 55.6)

CI, confidence interval.

after infection,[33] and we have previously shown that antibodies after wild-type or alpha infection remain protective against the delta variant.[28] Protection from past infection in the mother might therefore have been from antibody transfer but is also likely to be an indirect consequence of the mother being protected herself.

The long lasting duration of protection from previous infection is consistent with other studies[28] but we have shown that it extends to infants after birth. Infection with all variants before the omicron variant offered substantially less protection against subsequent mild or severe omicron infection in the infant, which is known to be more immune evasive than previous variants.[28 34] The protection conferred by omicron infection in the child bearer against subsequent omicron disease in the infant could not be investigated because of insufficient data. Nonetheless, given the high rates of past infection in the population, that many newborn infants (even those born to mothers who were not vaccinated) likely have some level of immunity to covid-19 is useful to know. Maternal vaccination achieved greater protection against omicron disease in the infant than previous infection, however, highlighting the importance of maternal vaccination in the omicron period.

Strengths and weaknesses of this study

Our large study investigated the effectiveness of maternal covid-19 vaccines on both maternal and infant health. The test negative case-control design has been well validated and used for evaluation of covid-19 vaccines. One of the key strengths of our study is that this approach helps in dealing with unmeasured confounders related to differences in health seeking behaviours and infectious disease exposure between individuals who are vaccinated and those who are not vaccinated.

The study had several limitations. We found some apparent protection in the early period after vaccination before a true effect would be expected, as in our previous test negative case-control studies.[35 36] We suspect that this effect is likely related to a combination of deferral of vaccination in individuals who knew they were infected with the SARS-CoV-2 virus because of a positive test result from a lateral flow test at home and a healthy vaccinee effect (ie, those with early symptoms of covid-19 were more unwell than controls and consequently less likely to be vaccinated). Our estimates of vaccine effectiveness were only for those pregnancies that resulted in a delivery (a live birth or stillbirth), and pregnancies resulting in miscarriage or termination at <24 weeks' gestation were not included. Our estimates were similar to other estimates of vaccine effectiveness in non-pregnant individuals and hence should also be generalisable to all pregnancies.

Coding errors in the electronic database of the Hospital Episode Statistics could result in misclassification of covariates and outcomes. Similarly, given the observational nature of the study, unmeasured confounders might exist that we could not adjust for. Despite our large study, given that the outcomes were rare, substantial uncertainty in some of our outcomes still existed (eg, subanalysis by trimester of vaccination or infant age in months). Throughout the study, to compare estimates of vaccine effectiveness, statistical significance was concluded when 95% confidence intervals did not overlap. We consider that this method is conservative, but because many comparisons of the data presented are possible, care is needed when formal comparison between multiple groups is the focus. Furthermore, because of the small numbers of individuals in some categories, we found wide confidence intervals for some estimates of vaccine effectiveness. We chose not to show estimates when the lower bound was <−50% and the top bound was >80% because these estimates are not clinically meaningful. Even with these limits, however, we presented some estimates with wide confidence intervals around the estimate; these estimates should be interpreted appropriately as not meaningful.

Policy implications

With increasing population immunity against the SARS-CoV-2 virus from previous infection and vaccination, many countries are now restricting booster doses of vaccines to high risk groups, such as older adults and those with specific underlying conditions. Consequently, healthy women of childbearing age might no longer be eligible for future booster campaigns. Currently, many countries, including the UK, continue to recommend covid-19 vaccination in pregnancy, aligned with the recommendations for high risk groups. A key question remains as to whether pregnant persons should continue to be offered a covid-19 vaccine as part of the seasonal booster campaign for at risk populations to ensure they are vaccinated against the most recent variants, or whether pregnant individuals should be vaccinated during the later stages of pregnancy throughout the year to maximise protection for themselves and their infants. Another important finding in our study was the protection post partum against infection, indicating that postpartum vaccination in those who were not vaccinated during pregnancy might be valuable. Offering vaccination during and after pregnancy will, however, have to be balanced against the low risk of severe disease outcomes, including in women of childbearing age. Also, this risk is likely to continue to decline because of ongoing circulation of the SARS-CoV-2 virus, which will boost population immunity against the virus, reducing the risk of infection and severe disease in both the pregnant individual and their infant.

Conclusions

Together with increasing evidence on the safety of covid-19 vaccination during pregnancy,[1 2 13–16]

our study adds to a consistent and growing body of evidence of the benefits of maternal vaccination in preventing both mild and severe disease in pregnant individuals and their infants during the first six months of life.

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Contributors FCMK and HJC wrote the manuscript. JLB, NA, FCMK, SL and MR conceptualised the study. AAM, FCMK and JS curated the data. FCMK and NA conducted the formal analysis. FCMK, NA, AAM and JS accessed and verified the data. All co-authors reviewed the manuscript and were responsible for the decision to submit the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. JLB and HJC are joint last authors. FCMK is responsible for the overall content as the guarantor. Transparency: The lead author (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: funding from UK Health Security Agency for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. The Immunisation Department provides vaccine manufacturers (including Pfizer) with post-marketing surveillance reports about pneumococcal and meningococcal disease which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports.

Ethics 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 sections 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.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. This work was done under regulation 3 of the Health Service (Control of Patient Information; Secretary of State for Health, 2002) and used patient identification information without individual patient consent as part of the UK Health Security Agency legal requirement for public health surveillance and monitoring of vaccines. As a result, we cannot make the underlying dataset publicly available for ethical and legal reasons. All the data used for this analysis, however, are included as aggregated data in the article and appendix. Requests for access to relevant anonymised data should be submitted to the UK Health Security Agency Office for Data Release.

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