Bivalent prefusion F vaccination in pregnancy and respiratory syncytial virus hospitalisation in infants in the UK: results of a multicentre, test-negative, case-control study

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Summary

Background Respiratory syncytial virus (RSV) is the leading cause of acute lower respiratory infections (ALRI) in infants younger than 6 months globally. A maternal bivalent RSV prefusion F (RSVpreF) vaccine was introduced to the UK in late summer in 2024 (August 12 in Scotland and September 1 in England), with all pregnant women at 28 weeks or more of gestation eligible for vaccination. We aimed to understand RSVpreF vaccine effectiveness in a real-world setting.

Methods We conducted a multicentre, test-negative, case-control study to analyse the vaccine effectiveness of maternal RSVpreF vaccination against the primary outcome of hospitalisation (ie, admission to hospital) for RSV-associated ALRI in infants. Patient and public involvement from a group of parents informed the study protocol design. Included patients were infants with ALRI born after Aug 12, 2024 (Scotland), and Sept 1, 2024 (England), and therefore had mothers eligible for maternal vaccination, who were admitted to 30 hospital sites across the UK from Sept 30, 2024, to Jan 20, 2025, and tested for RSV. Infants were followed up until hospital discharge or death as an inpatient. Primary vaccine effectiveness of maternal RSVpreF vaccination against RSV-associated hospitalisation was calculated with the use of a conditional logistic regression adjusted by site, calendar month of hospital attendance for the infant, age, preterm birth, and sex.

Findings We included 537 mother–infant pairs, in whom there were 391 RSV-positive infant cases (median age 1·63 months [IQR 0·94–2·26]) and 146 RSV-negative infant controls (1·41 months [0·77–2·03]). Of 537 recruited infants, 297 (55%) were male and 240 (45%) were female. Ethnicity data were available for 533 mothers, of whom 434 (81%) self-identified as White. The mothers of 73 (19%) RSV-positive cases and 60 (41%) RSV-negative controls had received RSVpreF vaccine before delivery. The adjusted effectiveness of maternal RSVpreF vaccination for preventing infant hospitalisation was 58% (95% CI 28–75) for infants whose mothers were vaccinated at any time before delivery and 72% (48–85) for infants whose mothers were vaccinated more than 14 days before delivery (39 [11%] of 357 RSV-positive cases *vs* 43 [33%] of 129 RSV-negative controls).

Interpretation In the real-world setting of the first season of vaccine implementation in England and Scotland, maternal RSVpreF vaccination was effective and equivalent to trial settings in reducing the risk of hospitalisation in infants with RSV-associated ALRI.

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Introduction

Respiratory syncytial virus (RSV) is the most common cause of hospitalisation (ie, admission to hospital) for respiratory disease in infants globally. Every year in infants aged 0–6 months old there are an estimated 1·4 million hospital admissions due to RSV-associated acute lower respiratory infection (ALRI) and 45 700 RSV-attributable deaths,[1] with most of the morbidity and mortality concentrated in low-income and middle-income countries (LMICs). Direct vaccination against RSV has faced historical and more recent challenges.[2] However, since 2023, two treatment options have been available for the prevention of RSV in term-born infants. The first option is nirsevimab, a long-acting monoclonal antibody, which has shown efficacy in randomised controlled trials (RCTs)[3,4] and equivalent effectiveness in several real-world settings.[5,6] The other option is the maternal bivalent RSV prefusion F protein (RSVpreF)–based vaccine, which showed efficacy of 68% (99·17% CI 16–90) in preventing hospitalisation in the first 90 days after birth, and 57% (10–81) within 180 days after birth, in an RCT.[7] At present, the higher costs of a

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See Online for appendix

Research in context

Evidence before this study

After the publication of evidence for the efficacy of maternal respiratory syncytial virus (RSV) bivalent prefusion (RSVpreF) vaccination in preventing RSV disease in infants, RSVpreF vaccination has been recommended for pregnant individuals in several northern and southern hemisphere countries. RSVpreF maternal vaccination was introduced in the UK in the late summer of 2024, with all pregnant individuals at a gestation of 28 weeks or more eligible for vaccination. We searched PubMed using the terms (RSV AND maternal AND vaccin*) on March 13, 2025, with no date or language restrictions. We identified three randomised controlled trials (RCTs) of different RSV fusion protein-based vaccines in pregnant women. One RCT (Prepare) did not meet the prespecified success criterion for efficacy, and another (RSV MAT-009) halted enrolment due to an imbalance of preterm births in the vaccine group compared with that in the placebo group. A final phase 3 clinical trial (MATISSE) assessed the efficacy of maternal RSV vaccination in preventing RSV-related hospitalisation (ie, admission to hospital) at 90 days and 180 days after birth. The study reported a vaccine efficacy of 68% (99·17% CI 16–90) and 57% (10–81) at days 90 and 180, respectively. Four papers have reported efficacy from the MATISSE trial: results from a prespecified interim analysis (aforementioned results), a substudy for outcomes in Japan, a full report of outcomes at the study conclusion, and a report examining preterm birth frequency and associated outcomes. No studies were identified that reported the real-world effectiveness of maternal RSVpreF vaccination in preventing infant hospitalisation.

Added value of this study

We conducted this multicentre test-negative study, based on a published study-specific protocol, which included a prespecified analysis plan, to evaluate maternal RSVpreF vaccine effectiveness in a high-income setting. We assessed the effectiveness of maternal vaccination for the prevention of RSV-associated hospitalisation for acute lower respiratory infection (ALRI). The adjusted effectiveness of maternal RSVpreF vaccination for preventing infant hospitalisation was 72% (95% CI 48–85) for infants whose mothers were vaccinated more than 14 days before delivery, and 58% (28–75) for infants whose mothers were vaccinated at any time before delivery.

Implications of all the available evidence

This early assessment of vaccine effectiveness using a test-negative design shows that, in the context of an RSVpreF vaccine roll-out, maternal vaccination was effective in reducing the risk of hospitalisation in infants with RSV-associated ALRI. The results support those from MATISSE and should be helpful for the many countries considering the adoption of universal maternal vaccination for RSV. Our findings highlight that maternal RSV vaccination campaigns should begin before the start of the RSV season, to maximise uptake, and so that mothers receive the vaccine in time for the generation and transplacental transfer of protective anti-RSV antibodies before birth.

long-acting monoclonal antibody are likely to limit its introduction to LMICs.[8] However, a lower cost, effective maternal RSV vaccination, which could be incorporated into routine maternal vaccination schedules, has great promise for reducing the burden of RSV disease in infants globally.

In the late summer of 2024 the UK, following the USA and Argentina,[8] introduced year-round maternal RSV vaccination into its routine immunisation schedule, with vaccination recommended as soon as possible after 28 weeks of gestation.[9] At the start of the programme, the vaccine was offered to all pregnant individuals at a gestation of 28 weeks or more, with eligibility for vaccination until delivery.[10] In the UK in a typical year, RSV cases in infants start to increase in September or October, peak in December or January, and then decrease;[11] RSV seasonality is similar in England[12] and Scotland.[13] During the time of vaccination roll-out, the post-licensure real-world effectiveness of maternal RSV vaccination in the prevention of RSV-associated ALRI remained unclear.

Our aim was to assess the real-world effectiveness of the newly introduced maternal RSVpreF vaccine in preventing RSV ALRI hospitalisation in infants by leveraging a pre-established UK-wide clinical research programme (BronchStart[14,15], renamed BronchStop for this vaccine effectiveness substudy). As secondary objectives, we aimed to understand vaccine effectiveness in infants born more than 14 days after maternal vaccination, and to compare in-hospital outcomes in maternally vaccinated and unvaccinated RSV-positive infants.

Methods

Study design

We conducted a national multicentre prospective, test-negative case-control study nested in a previously established national multicentre cohort study to assess the effectiveness of maternal RSVpreF vaccination against hospitalisation for RSV-associated ALRI among infants born to vaccine-eligible pregnant mothers. A test-negative design was chosen because this reduces the chance of bias, including collider bias[16] due to differential health care-seeking behaviours.[17]

The BronchStart-Stop clinical research programme is delivered by the Paediatric Emergency Research in the UK and Ireland (PERUKI) Network. The study-specific protocol, which included a prespecified analysis plan, has been previously published.[18] Patient and public

involvement was sought from parents in the development of this nested study protocol, specifically to inform data collection and consent procedures. The study was submitted for Integrated Research Application System (IRAS) approval with University Hospitals of Leicester NHS Trust as the study sponsor (IRAS ID 297802), and received ethics approval from The London City & East Research Ethics Committee (REC reference 21/HRA/1844) on Aug 8, 2024. Informed consent was obtained from each infant participant's mother, either in person or over the telephone.

UK maternal vaccination programme

For the 2024–25 RSV season, the governments of the four countries within the UK recommended year-round, free-of-charge administration of the RSVpreF vaccination to pregnant women at a gestation of 28 weeks or later, from Aug 12 in Scotland[19] and Sept 1 in England[20] (gestational age was determined based on an ultrasound scan conducted at 10–14 weeks of pregnancy).[21] After what was effectively a catch-up campaign for the first months of the programme, when all pregnant women were eligible for vaccination up until the time of delivery,[10] pregnant women were subsequently offered the RSVpreF vaccination at as close as possible to 28 weeks of gestation as part of the routine, year-round maternal immunisation schedule. Nirsevimab was not available in the UK during the study period.

Study participants

In this test-negative study, we recruited infants (and their mothers) born after Aug 12, 2024 (Scotland) or Sept 1, 2024 (England; (the same dates as the commencement of RSV maternal vaccination in the two countries) admitted to 30 hospital sites across the UK from Sept 30, 2024, onwards. Eligible infants could therefore be aged between 0 and 5 months, depending on geographical location and birth date. Eligible infants were those with a clinician-assigned diagnosis of bronchiolitis (defined as cough, tachypnoea, or chest recession, and wheeze or crackles on chest auscultation), lower respiratory tract infection (clinician diagnosis), or first episode of wheeze.[18] All participating sites had the capacity to undertake overnight paediatric admissions. At all participating centres, all infants admitted with one of these diagnoses received testing for RSV as per their usual hospital admission protocol and UK-wide Royal College of Paediatrics and Child Health guidance,[22] in all cases using real-time reverse transcription polymerase chain reaction or equivalent testing (full details on testing by site are in the appendix [p 3]). Test-positive infants were defined as those admitted with a positive RSV test. Test-negative infants were defined as those admitted who tested negative for RSV. Infants who had previously received palivizumab as part of routine clinical care, or the long-acting monoclonal antibodies nirsevimab or clesrovimab as part of a clinical trial, were excluded from the study.

Procedures

We collected data on infant demographic characteristics including sex (as reported in the infant's medical records), Index of Multiple Deprivation (a marker of socioeconomic status) using home postcode, gestation at birth, and other comorbidities known to be risk factors for severe RSV disease (ie, chronic lung disease of prematurity, congenital heart disease, and neuromuscular disease), length of hospital admission, highest level of care received, and respiratory support administered. Preterm birth was defined as birth at less than 37 weeks of gestation as per the WHO definition.[23] Paediatric intensive care, including access to invasive mechanical ventilation, is available free-of-charge to all children in the UK, either in-hospital (if this has a paediatric critical care unit) or via a paediatric critical care transfer team. Infants recruited were followed up until discharge from hospital or death, if this occurred as an inpatient. Data on self-reported maternal ethnicity, breast-feeding status, and maternal immunisation status were collected. Additionally, consent was sought to access maternal medical records to ascertain RSVpreF and pertussis immunisation status (pertussis vaccination is offered at 20 weeks of gestation[24]), and for RSVpreF date of vaccination. In order to ascertain this exposure, maternal medical records were accessed either locally by research staff, or centrally when they were unable to do so. However, difficulties in discriminating between cases where the vaccine had not been given, and it might have been given but not documented, meant that formal documentation of vaccination status could not be determined for a proportion of participating mothers; these cases were disregarded for the vaccine effectiveness analysis. Data were entered using the validated online data entry software REDCap (Research Electronic Data Capture tools[25]) using the clinical report forms provided in the study protocol.[18] REDCap is hosted on the University Hospitals Bristol and Weston NHS Foundation Trust secure server, which is accessible on the Health and Social Care Network that is managed by NHS England.

Outcome and exposure measures

The primary outcome was infant hospitalisation with RSV-associated ALRI. The treatment exposure was maternal RSVpreF receipt status before birth among both cases and controls. Additionally, in keeping with the analyses conducted in the MATISSE RCT[7] we performed a prespecified vaccine effectiveness analysis for the subgroup of infants whose mothers had received RSVpreF more than 14 days before birth; this time period is considered to allow for the maternal generation of anti RSV pre-F IgG, and transplacental transfer of this IgG[26] (although a longer time period may be more beneficial).[27] We also performed prespecified subgroup analyses comparing hospitalised vaccinated and unvaccinated RSV-positive cases according to highest

level of care afforded (high-dependency unit or paediatric intensive care unit), and respiratory support administered (low-flow oxygen, high-flow oxygen, continuous positive airway pressure, or invasive mechanical ventilation).

Statistical analysis

Effectiveness of the RSVpreF maternal vaccine against RSV-associated hospitalisation was assessed using a test-negative design, comparing odds of vaccination among infants who were RSV positive (cases) with those who were RSV negative (controls). To determine if the study was feasible, initial sample size calculations were based on the precision of the vaccine effectiveness estimated by the test-negative design, as recommended by WHO and implemented using their vaccine effectiveness calculator.[28] At the time of sample size calculations, the most up-to-date estimate of maternal vaccine coverage of the combined inactivated tetanus, diphtheria, and acellular pertussis vaccine (also known as Tdap) was just less than 60% in England[29] due to anticipated logistical challenges in the first months of immunisation roll-out, and we assumed maternal RSV vaccine coverage could be as low as 30% in the first season. Assuming the true vaccine effectiveness for RSV-associated hospitalisation among infants was 70%, this method predicted the study would need to recruit 145 RSV-associated hospitalisations, with 1:1 case:control matching to reach a precision width of 40% (±20%) for the vaccine effectiveness.

However, recognising that effectiveness might not match efficacy, and that vaccine coverage was likely to be highly dynamic due to the vaccine roll-out, we used an alternative method (epiR::epi.sscc[30]) to draw up contingency tables for different levels of vaccine uptake and effectiveness (appendix p 4). To then determine the number of our sites we would require for recruitment of participants in this new study, we used data from the previous BronchSTART season (2023–24) to simulate likely recruitment cohorts for a range of number of sites, vaccine coverage, and vaccine effectiveness. This approach ensured we would have enough sites such that we would reach the targeted recruitment before the end of the RSV season and that our analysis methods would have power to account for any adjustment variables. Weekly analysis of the dataset was undertaken with calculation of vaccine effectiveness using recruitment to that date; recruitment was completed when the estimate of vaccine effectiveness had stabilized over 2 consecutive weeks.[31]

For more on the **recruitment data** see https://bronchstop.netlify.app/

The primary effectiveness of maternal RSVpreF vaccination against RSV-associated hospitalisation in infants was estimated using conditional logistic regression. Vaccine effectiveness was calculated using the following equation:

$$\textit{Vaccine effectiveness} = 100\% \times (1 - \textit{adjusted odds ratio})$$

Identification of potential confounders was based on the use of a directed acyclic graph[16] (appendix p 5). This analysis was adjusted by site, calendar month of attendance, age of younger than 3 months, preterm birth, and sex. Adjustment by site and calendar month of hospital attendance for the infant was used to allow for geographical and temporal differences in maternal vaccine uptake.

To look for evidence of confounding or other unmeasured sources of bias due to our analysis method, we also calculated the effectiveness of maternal pertussis vaccination against admission with RSV bronchiolitis adjusting for the same factors. Demographic variables for cases and controls were compared using a Wilcoxon rank sum test, a Pearson's χ^2 test or a Fisher's exact test. Clinical outcomes in maternally vaccinated versus unvaccinated RSV-positive cases were compared using a Wilcoxon rank sum test, Pearson's χ^2 test or a Fisher's exact test as an exploratory analysis. The prespecified subgroup analysis looking at vaccine effectiveness in those infants whose mothers had received RSVpreF more than 14 days before delivery was conducted in the same manner as the main analysis but excluding (on the basis of maternal vaccination date and infant date of birth) recruits whose mothers were vaccinated less than 14 days before birth. For prespecified subgroup analyses examining vaccine effectiveness for preventing RSV-associated illness requiring different levels of respiratory support and high-dependency unit or paediatric intensive care unit admission, estimates were made using the screening method to calculate the vaccine effectiveness.[32]

All statistical tests were two-sided, and $p<0{\cdot}05$ was considered to indicate statistical significance; p values were not adjusted for multiplicity. CIs were calculated as 95% unless otherwise stated. The widths of the CIs have not been adjusted for multiplicity and should not be used in place of hypothesis testing. Statistical analyses were carried out with the use of R software version 4.4.1.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Throughout the recruitment period, due to the sharp increase in RSV positivity from October to December, 2024, RSV-positive cases consistently outnumbered RSV-negative controls, as seen on our live recruitment dashboard. Recruitment commenced Sept 30, 2024, and was completed on Jan 20, 2025. By this point, RSV activity in English hospitals had decreased to baseline level according to the UK Health Security Agency weekly respiratory virus surveillance report.[33] During the study period, 655 infants were recruited to the study across the 30 study sites (appendix p 3). Of these, one infant was excluded because palivizumab had been previously

received, 84 infants were excluded because maternal vaccination status was not available from medical records, 27 infants were excluded because RSV testing results were not available, and six infants were excluded because complete clinical information was not available (figure). 391 RSV-positive infants and 146 RSV-negative infants were included in the analysis. None of the infants recruited died while being an inpatient.

The characteristics of the cases and controls are shown in table 1. Of 537 recruited infants, 297 (55%) were male and 240 (45%) were female. Sex ratios were similar in cases and controls (p=0·81) and the median age at hospitalisation was similar for both groups: 1·63 months (IQR 0·94–2·26) for the RSV-positive cases and 1·41 months (0·77–2·03) for the RSV-negative controls (p=0·073). Congenital heart disease was more common in controls (six [4%] of 146) than cases (four [1%] of 391; p=0·028). Disease was more severe in cases than controls: they were more likely to receive supplemental oxygen (287 [73%] of 391 cases *vs* 62 [42%] of 146 controls; p<0·0001) and to be admitted to paediatric intensive care (37 [10%] of 391 cases versus six [4%] of 146 controls; p=0·042). Of the 533 mothers for whom data were available, 434 (81%) self-identified as White: 317 (82%) of 387 mothers of cases, and 117 (80%) of 146 mothers of controls (p=0·64).

The mothers of 73 (19%) RSV-positive cases and 60 (41%) RSV-negative controls had received RSVpreF vaccine before delivery. Once adjusted for site and month, sex, aged younger than 3 months, and preterm birth, the estimated adjusted effectiveness of maternal RSVpreF vaccination was 58% (95% CI 28–75). Pertussis vaccination was used as a negative control to identify potential residual confounding. We found that pertussis vaccination did not protect against RSV hospitalisation and the adjusted vaccine effectiveness was 25% (95% CI –20 to 53).

We conducted a prespecified subgroup analysis to look at vaccine effectiveness in infants born to mothers more than 14 days after receipt of RSVpreF. In this cohort, a maternal RSVpreF vaccine had been received more than 14 days before delivery in 39 (11%) of 357 RSV-positive cases and 43 (33%) of 129 RSV-negative controls. The adjusted vaccine effectiveness (adjusted for site, month, sex, aged younger than 3 months, and preterm birth) of maternal RSVpreF vaccination for this cohort was 72% (95% CI 48–85). In a predefined exploratory analysis, clinical outcomes amongst RSV-positive infants whose mothers were RSV vaccination recipients more than 14 days before delivery were compared with outcomes for those with unvaccinated mothers (table 2). RSVpreF vaccination more than 14 days before delivery was not associated with a significantly different length of stay (p=0·87), risk of receiving high-flow nasal cannulae respiratory support (p=0·43), risk of invasive mechanical ventilation (p=0·41), or risk of admission to paediatric intensive care unit (p=0·38).

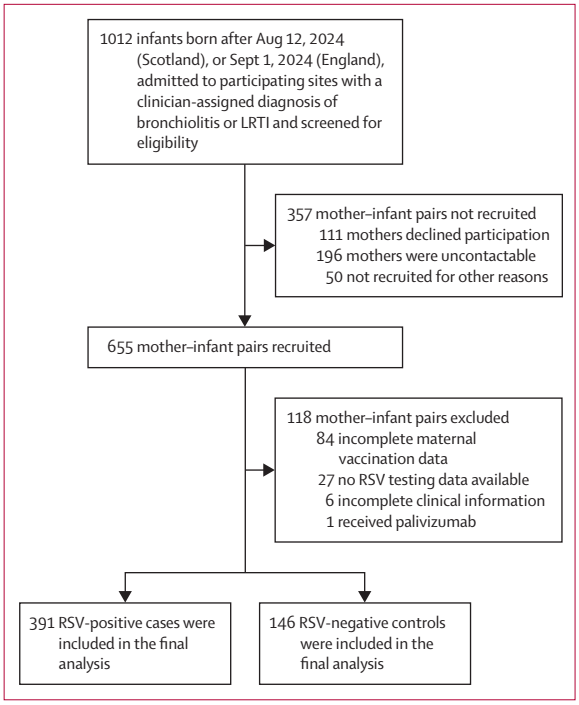

Figure: **Study population**
RSV test-positive case patients were infants born after Aug 12, 2024 (Scotland), or Sept 1, 2024 (England), who were hospitalised with a clinician-assigned diagnosis of bronchiolitis or LRTI between Sept 30, 2024, and Jan 20, 2025, at the BronchStop recruiting sites. RSV test-negative control patients were infants with the same diagnoses presenting to the same recruiting sites. LRTI=lower respiratory tract infection. RSV=respiratory syncytial virus.

Vaccine effectiveness estimates were performed comparing clinical outcomes for RSV-positive infants whose mothers were vaccinated more than 14 days before delivery with unvaccinated infants, using the screening method. The unadjusted vaccine effectiveness of maternal RSVpreF vaccination in preventing RSV-associated ALRI requiring high-flow nasal cannulae support was 71% (95% CI 47–85; 18 [13%] of 144 cases *vs* 43 [33%] of 129 controls), and the unadjusted vaccine effectiveness of maternal vaccination in preventing RSV-associated paediatric intensive care admission was 64% (1–87; five [15%] of 33 cases *vs* 43 [33%] of 129 controls), although this analysis was limited by the small number of patients.

Discussion

In this study, we estimated the post-licensure effectiveness of the RSVpreF maternal vaccine against hospitalisation for RSV-associated ALRI and found an overall effectiveness of 58% (95% CI 28–75), which increased to 72% (48–85) when limiting the analysis to infants who had been born more than 14 days after maternal receipt of RSVpreF. Our results are in a real-world setting and show similar effectiveness when measured at 14 days after vaccination to those seen in the MATISSE trial,[7] which found vaccine efficacy to

	RSV-positive cases (n=391)	RSV-negative controls (n=146)	p value*
Demographic and clinical characteristics			
Age at admission, months	1·63 (0·94–2·26)	1·41 (0·77–2·03)	0·073
Sex	..	..	0·81
Male	215/391 (55%)	82/146 (56%)	..
Female	176/391 (45%)	64/146 (44%)	..
Gestation at birth	..	..	0·17
Born at term	349/391 (89%)	124/146 (85%)	..
Born preterm (<37 weeks of gestation)	42/391 (11%)	22/146 (15%)	..
Risk factor for severe bronchiolitis			
Chronic lung disease of prematurity	0/391	0/146	..
Congenital heart disease	4/391 (1%)	6/146 (4%)	0·028
Neuromuscular disease	0/391	1/146 (1%)	0·27
Maternal age, years	31·5 (27·7–34·6)	31·8 (28·5–35·3)	0·44
Unknown maternal age	52	23	..
Maternal ethnicity	..	..	0·64
White	317/387(82%)	117/146 (80%)	..
Non-White	70/387 (18%)	29/146 (20%)	..
Unknown	4	0	..
Maternal breastfeeding	..	..	0·15
Yes	157/389 (40%)	69/146 (47%)	..
No	232/389 (60%)	77/146 (53%)	..
Unknown	2	0	..
Maternal SES quintile	..	..	0·19
1	118/372 (32%)	30/138 (22%)	..
2	71/372 (19%)	25/138 (18%)	..
3	51/372 (14%)	21/138 (15%)	..
4	76/372 (20%)	34/138 (25%)	..
5	56/372 (15%)	28/138 (20%)	..
Unknown	19	8	..
Maternal pertussis vaccination			
Yes	260/368 (71%)	107/139 (77%)	0·16
No	108/368 (29%)	32/139 (23%)	..
Unknown	23	7	..
Clinical findings			
Supplemental oxygen use	287/391 (73%)	62/146 (42%)	<0·0001
Respiratory support			
High flow nasal cannulae	157/391 (40%)	25/146 (17%)	<0·0001
Continuous positive airway pressure	43/391 (11%)	3/146 (2%)	0·0010
Invasive ventilation	20/391 (5%)	5/146 (3%)	0·41
Level of care			
High-dependency unit admission	54/391 (14%)	8/146 (6%)	0·0072
Paediatric intensive care unit admission	37/391 (10%)	6/146 (4%)	0·042

Data are median (IQR), n, or n/N (%). Denominators differed based on patients with available data. SES=Socioeconomic Status (quintile 1 is the most socioeconomically deprived group, quintile 5 the least socioeconomically deprived group). *Generated using Wilcoxon rank sum test, Pearson's χ^2 test, or Fisher's exact test.

Table 1: **Characteristics of the included case patients and control patients**

	Mother unvaccinated (n=318)	Mother vaccinated >14 days before delivery (n=39)	p value*
Length of admission, days	3 (2–5)	4 (1–6)	0·87
Nasogastric feeds	206 (65%)	24 (62%)	0·69
Intravenous fluids	81 (25%)	15 (38%)	0·084
Low-flow oxygen	200 (63%)	21 (54%)	0·27
High-flow nasal cannulae	126 (40%)	18 (46%)	0·43
Continuous positive airway pressure	35 (11%)	7 (18%)	0·20
Invasive mechanical ventilation	14 (4%)	3 (8%)	0·41
High-dependency unit admission	43 (14%)	7 (18%)	0·45
Paediatric intensive care unit admission	28 (9%)	5 (13%)	0·38

Data are n (%) or median (IQR). RSV=respiratory syncytial virus. *Generated using Wilcoxon rank sum test, Pearson's χ^2 test, or Fisher's exact test.

Table 2: **Comparison of clinical outcomes for RSV-positive infants with unvaccinated mothers compared with RSV-positive infants with mothers vaccinated more than 14 days before delivery**

be 68% (99·17% CI 16–90) with respect to RSV-associated hospitalisation within 90 days after birth, and 57% (10–81) within 180 days after birth.

The most likely reason for the discrepancy between the results of the main analysis and the subgroup analysis is the initial catch-up nature of the vaccination campaign in England and Scotland, with a proportion of mothers receiving the vaccine too close to the time to delivery for optimal generation and transfer of IgG mediated immunity. A survey from England and Scotland conducted as part of the BronchStop vaccine effectiveness sub-study found that a large proportion of mothers (35%) who had not received the vaccine disagreed or strongly disagreed with the statement "the RSV vaccine was easy for me to get", highlighting the challenges of introducing a routine immunisation programme at the same time as a catch-up campaign.[34] A previous study suggested that a longer period of up to 5 weeks from RSVpreF administration to birth could provide better protection for infants.[27] Ensuring that pregnant individuals can access RSVpreF vaccination as soon as possible within the regulatory-approved timeframe (from 28 weeks gestation in the UK) and well before their estimated due date should be a priority for policy makers.

Once hospitalised, outcomes for the infants of vaccinated mothers who had received RSVpreF more than 14 days before delivery were similar to those for infants whose mothers had not been vaccinated. Effectiveness data for nirsevimab showed a significant reduction in both need for low-flow oxygen supplementation and length of stay for RSV-positive infants who had received nirsevimab, compared with those who had not.[35] Effectiveness data examining in-hospital outcomes after palivizumab prophylaxis in preterm infants and those with congenital heart disease showed heterogenous results: palivizumab prophylaxis showed variable associations with oxygen requirement, length of stay, or invasive mechanical ventilation.[36] Given the current paucity of evidence on in-hospital outcomes

for RSV-positive infants after RSVpreF maternal vaccination, our results provide useful information for clinicians counselling the carers of infants with vaccinated mothers who are admitted to hospital with RSV disease. Once hospitalised, vaccination does not appear to offer protection against more severe disease. However, further studies with larger sample sizes will be required to understand in more detail in-hospital outcomes for infants whose mothers received RSVpreF vaccination.

Our study has strengths and weaknesses. The large number of recruiting sites (n=30) means that we have probably captured a population that is representative of England and Scotland as a whole, with a high proportion of mothers recruited self-identifying as not being of White ethnicity (18% of cases and 20% of controls). We were able to recruit maternal participants from all five socioeconomic quintiles, which provides reassurance that the study population is representative of that of England and Scotland as a whole. Consistent testing of infants hospitalised with RSV as part of hospital protocols reduced the risk of collider and other biases in affecting the association between the exposure and the outcome; this conclusion is supported by our demonstration of an absence of vaccine effectiveness for the pertussis vaccine against hospitalisation for RSV ALRI. We were able to collect detailed information on in-hospital outcomes for recruits and demonstrate equivalent in-hospital outcomes for maternally vaccinated and unvaccinated infants once admitted: this observation has implications for clinicians and carers, and the cost-effectiveness of future vaccination campaigns.

Our study has some limitations. First, the study was not designed to assess safety and so cannot independently inform the observed safety signal between RSV maternal vaccination and preterm birth.[37] Second, the test-negative observational study design does not allow for causal conclusions to be drawn; therefore, further studies in other settings will be needed to support our findings. Third, because the effectiveness of maternal vaccination was assessed very soon after the introduction of a national programme, this limits the applicability of our findings to all settings; results from this study might not be reflective of the experience of RSV maternal vaccination as this becomes more embedded in national programmes and a greater proportion of infants are born more than 14 days after maternal vaccination. Fourth, the timescale of our observations limits the reporting of vaccine effectiveness to infants younger than 6 months, and data continue to be required for older children. However, this youngest population of infants are those most susceptible to severe RSV disease. Finally, the study was powered to analyse the effectiveness of RSVpreF maternal vaccination against RSV-associated hospitalisation with ALRI for all recruited infants; as such, subgroup analyses should be considered exploratory.

This study evaluating the effectiveness of RSVpreF maternal vaccination within the first 5 months of national implementation indicated that vaccination was effective against RSV-associated ALRI leading to hospitalisation. When analysis was restricted to infants born to mothers who had received RSVpreF more than 14 days before delivery, vaccine effectiveness was comparable to that seen in the randomised controlled trial for RSVpreF.[7]

Contributors

SC, SBD, DI, HEG, MDL, RM, SO'H, DR, TW, and TCW conceived the study. SC, SBD, DI, HEG, XL, MDL, RM, SO'H, DR, TW, and TCW made substantial contributions to the design of the work. CDM and SH contributed towards acquisition of data for the work. RM and TCW performed the analysis and interpretation of the data. SC, SBD, RM, DR, and TCW drafted the manuscript. RM, TW, and ML accessed and verified the data. All the authors had access to data reported in the study, all authors revised the manuscript critically for important intellectual content and all authors approved the final manuscript before submission. The authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

Declaration of interests

We declare no competing interests.

Data sharing

The R code used to make the calculations for this paper is available on GitLab (https://git.ecdf.ed.ac.uk/twillia2/bronchstop/-/tree/main/maternal_vaccine effectiveness_study); the BronchStop dataset will be held for a minimum of 3 years and is available to be shared on reasonable request to the authors.

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References

1 Li Y, Wang X, Blau DM, et al, and the Respiratory Virus Global Epidemiology Network, and the RESCEU investigators. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. *Lancet* 2022; **399:** 2047–64.

2 Cohen J. 'Safety signal' in Moderna's RSV vaccine studies halts trials of other vaccines for childhood killer. 2024. https://www.science.org/content/article/safety-signal-moderna-s-rsv-vaccine-studies-halts-trials-other-vaccines-childhood (accessed April 30, 2025).

3 Drysdale SB, Cathie K, Flamein F, et al, and the HARMONIE Study Group. Nirsevimab for prevention of hospitalizations due to RSV in infants. *N Engl J Med* 2023; **389:** 2425–35.

4 Hammitt LL, Dagan R, Yuan Y, et al, and the MELODY Study Group. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. *N Engl J Med* 2022; **386:** 837–46.

5 Ares-Gómez S, Mallah N, Santiago-Pérez M-I, et al, and the NIRSE-GAL study group. Effectiveness and impact of universal prophylaxis with nirsevimab in infants against hospitalisation for respiratory syncytial virus in Galicia, Spain: initial results of a population-based longitudinal study. *Lancet Infect Dis* 2024; **24:** 817–28.

6 Assad Z, Romain A-S, Aupiais C, et al. Nirsevimab and hospitalization for RSV bronchiolitis. *N Engl J Med* 2024; **391:** 144–54.

7 Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. *N Engl J Med* 2023; 2023; **388:** 1451–64.

8 Pecenka C, Sparrow E, Feikin DR, et al. Respiratory syncytial virus vaccination and immunoprophylaxis: realising the potential for protection of young children. *Lancet* 2024; **404:** 1157–70.

9 UK Health Security Agency. Respiratory syncytial virus: the green book, chapter 27a. The green book. 2025. https://www.gov.uk/government/publications/respiratory-syncytial-virus-the-green-book-chapter-27a (accessed April 30, 2025).

10 UK Health Security Agency. RSV vaccination of pregnant women for infant protection: information for healthcare practitioners. UKHSA Guidance. 2025. https://www.gov.uk/government/publications/respiratory-syncytial-virus-rsv-programme-information-for-healthcare-professionals/rsv-vaccination-of-pregnant-women-for-infant-protection-information-for-healthcare-practitioners (accessed April 17, 2025).

11 Joint Committee on Vaccination and Immunisation. Respiratory syncytial virus (RSV) immunisation programme for infants and older adults: JCVI full statement, 11 September. 2023. https://www.gov.uk/government/publications/rsv-immunisation-programme-jcvi-advice-7-june-2023/respiratory-syncytial-virus-rsv-immunisation-programme-for-infants-and-older-adults-jcvi-full-statement-11-september-2023 (accessed Sept 27, 2023).

12 UK Health Security Agency. National flu and COVID-19 surveillance report: 17 April 2025 (week 16). 2025. https://www.gov.uk/government/statistics/national-flu-and-covid-19-surveillance-reports-2024-to-2025-season/national-flu-and-covid-19-surveillance-report-17-april-2025-week-16 (accessed April 17, 2025).

13 Public Health Scotland. Viral respiratory diseases (including influenza and COVID-19) in Scotland surveillance report. 2025. https://www.publichealthscotland.scot/publications/viral-respiratory-diseases-including-influenza-and-covid-19-in-scotland-surveillance-report/viral-respiratory-diseases-including-influenza-and-covid-19-in-scotland-surveillance-report-10-april-2025/ (accessed April 17, 2025).

14 Williams TC, Cunningham S, Drysdale SB, et al, and the Paediatric Emergency Research in the UK and Ireland (PERUKI). Update to: Study Pre-protocol for "BronchStart - The Impact of the COVID-19 Pandemic on the Timing, Age and Severity of Respiratory Syncytial Virus (RSV) Emergency Presentations; a Multi-Centre Prospective Observational Cohort Study". *Wellcome Open Res* 2024; **6:** 120.

15 Williams TC, Marlow R, Hardelid P, et al, and the PERUKI. Clinical impact of serious respiratory disease in children under the age of 2 years during the 2021–2022 bronchiolitis season in England, Scotland, and Ireland. *J Infect Dis* 2024; **230:** e111–20.

16 Williams TC, Bach CC, Matthiesen NB, Henriksen TB, Gagliardi L. Directed acyclic graphs: a tool for causal studies in paediatrics. *Pediatr Res* 2018; **84:** 487–93.

17 Dean N, Amin AB. Test-negative study designs for evaluating vaccine effectiveness. *JAMA* 2024; **332:** 163–64.

18 Williams TC, Cunningham S, Drysdale SB, et al, and the Paediatric Emergency Research in the UK and Ireland (PERUKI). Update to: study pre-protocol for "BronchStart - the impact of the COVID-19 pandemic on the timing, age and severity of respiratory syncytial virus (RSV) emergency presentations; a multi-centre prospective observational cohort study". *Wellcome Open Res* 2024; **6:** 120.

19 Scottish Government. RSV vaccination: CMO letter to Health Boards. 2024. https://www.gov.scot/publications/rsv-vaccination-cmo-letter-to-health-boards/ (accessed Sept 25, 2024).

20 UK Health Security Agency. Introduction of new NHS vaccination programmes against respiratory syncytial virus (RSV). 2024. https://www.gov.uk/government/publications/respiratory-syncytial-virus-rsv-vaccination-programmes-letter/introduction-of-new-nhs-vaccination-programmes-against-respiratory-syncytial-virus-rsv (accessed July 4, 2024).

21 National Health Service. 12-week scan. 2025. https://www.nhs.uk/pregnancy/your-pregnancy-care/12-week-scan/ (accessed April 17, 2025).

22 Royal College of Paediatrics and Child Health. National guidance for the management of children in hospital with viral respiratory tract infections (2023). 2024. https://www.rcpch.ac.uk/resources/guidance-management-children-viral-respiratory-tract-infections (accessed April 18, 2025).

23 Ohuma EO, Moller AB, Bradley E, et al. National, regional, and global estimates of preterm birth in 2020, with trends from 2010: a systematic analysis. *Lancet* 2023; **402:** 1261–71.

24 UK Health Security Agency. Whooping cough vaccination in pregnancy guide. 2024. https://www.gov.uk/government/publications/resources-to-support-whooping-cough-vaccination/whooping-cough-vaccination-in-pregnancy-guide (accessed April 17, 2025).

25 Harris PA, Taylor R, Minor BL, et al, and the REDCap Consortium. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform* 2019; **95:** 103208.

26 Simões EAF, Pahud BA, Madhi SA, et al, and the MATISSE (Maternal Immunization Study for Safety and Efficacy) Clinical Trial Group. Efficacy, safety, and immunogenicity of the MATISSE (Maternal Immunization Study for Safety and Efficacy) maternal respiratory syncytial virus prefusion F protein vaccine trial. *Obstet Gynecol* 2025; **145:** 157–67.

27 Jasset OJ, Lopez Zapana PA, Bahadir Z, et al. Enhanced placental antibody transfer efficiency with longer interval between maternal respiratory syncytial virus vaccination and birth. *Am J Obstet Gynecol* 2025; **232:** 554.

28 World Health Organization. Evaluation of COVID-19 vaccine effectiveness. 2021. https://www.who.int/en/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021·1 (accessed July 25, 2024).

29 UK Health Security Agency. Prenatal pertussis vaccination coverage in England from October to December 2023. 2024. https://www.gov.uk/government/publications/pertussis-immunisation-in-pregnancy-vaccine-coverage-estimates-in-england-october-2013-to-march-2014/prenatal-pertussis-vaccination-coverage-in-england-from-october-to-december-2023 (accessed July 25, 2024).

30 Dupont WD. Power calculations for matched case-control studies. *Biometrics* 1988; **44:** 1157–68.

31 Walker AM. Conditional power as an aid in making interim decisions in observational studies. *Eur J Epidemiol* 2018; **33:** 777–84.

32 Flannery B, Andrews N, Feikin D, Patel MK. Commentary: estimation of vaccine effectiveness using the screening method. *Int J Epidemiol* 2023; **52:** 19–21.

33 UK Health Security Agency. National flu and COVID-19 surveillance report: 16 January (week 3). 2025. https://www.gov.uk/government/statistics/national-flu-and-covid-19-surveillance-reports-2024-to-2025-season/national-flu-and-covid-19-surveillance-report-16-january-week-3 (accessed Jan 21, 2025).

34 Williams TC, Marlow R, Cunningham S, et al, and the PERUKI & BronchStart Collaboration. Maternal views on RSV vaccination during the first season of implementation in England and Scotland. *Lancet Infect Dis* 2025; **25:** e135–36.

35 Jeziorski E, Ouziel A, Cotillon M, et al. Impact of nirsevimab on respiratory syncytial virus bronchiolitis in hospitalized infants: a real-world study. *Pediatr Infect Dis J* 2025; **44:** e124–26.

36 Gonzales T, Bergamasco A, Cristarella T, et al. Effectiveness and safety of palivizumab for the prevention of serious lower respiratory tract infection caused by respiratory syncytial virus: a systematic review. *Am J Perinatol* 2024; **41:** e1107–15.

37 Boytchev H. FDA advisers back Pfizer's maternal RSV vaccine after voicing safety concerns. *BMJ* 2023; **381:** 1187.