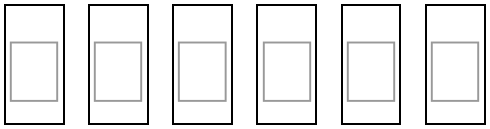

IMPORTANT

Real-world effectiveness of RSVpreF vaccination during pregnancy against RSV-associated lower respiratory tract disease leading to hospitalisation in infants during the 2024 RSV season in Argentina (BERNI study): a multicentre, retrospective, test-negative, case–control study

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Summary

Background In March, 2024, Argentina became the first country to implement a national maternal immunisation programme with bivalent respiratory syncytial virus (RSV) prefusion F vaccine (RSVpreF) as the primary strategy to prevent RSV disease among infants. We aimed to evaluate vaccine effectiveness against RSV-associated lower respiratory tract disease (LRTD) and severe LRTD leading to hospitalisation among infants during the first season after implementation.

Methods A multicentre, retrospective, test-negative, case-control study was done during the 2024 RSV season in 12 hospitals across Argentina (BERNI study). We included infants aged 6 months or younger who were hospitalised with LRTD between April 1 and Sept 30, 2024, and tested for RSV using PCR or indirect immunofluorescence; cases were infants with any positive RSV test and controls were PCR-confirmed negative for RSV. Infants were considered born to an RSVpreF-vaccinated pregnant woman if RSVpreF was received between $32^{+0/7}$ weeks and $36^{+6/7}$ weeks of gestation and 14 days or more before delivery. We estimated vaccine effectiveness against RSV-associated LRTD requiring hospitalisation (primary outcome) and RSV-associated severe LRTD requiring hospitalisation (key secondary outcome) by comparing the odds of RSVpreF vaccination during pregnancy among infant cases versus controls using multilevel logistic regression adjusted for potential confounders.

Findings Of 633 infants hospitalised for LRTD between April 1 and Sept 30, 2024, 505 (286 cases and 219 controls) met full eligibility criteria for inclusion in the primary vaccine effectiveness analysis; 51 (18%) cases and 109 (50%) controls were born to individuals who received RSVpreF during pregnancy. Vaccine effectiveness against RSV-associated LRTD leading to infant hospitalisation was 78·6% (95% CI 62·1–87·9) from birth to age 3 months and 71·3% (53·3–82·3) from birth to age 6 months. Effectiveness against RSV-associated severe LRTD leading to hospitalisation was 76·9% (45·0–90·3) from birth to age 6 months. Three RSV-associated in-hospital deaths occurred, all among infants whose mothers did not receive RSVpreF during pregnancy.

Interpretation These real-world estimates for the 2024 RSV season in Argentina show high RSVpreF effectiveness against RSV-associated LRTD and severe LRTD leading to hospitalisation from birth to age 3 months and sustained to age 6 months.

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For the Spanish translation of the abstract see **online** for appendix 1

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Introduction

Respiratory syncytial virus (RSV) is the leading cause of acute lower respiratory tract disease (LRTD) in children younger than 5 years, with severe illness and hospitalisation concentrated during the first 6 months of life.[1] Globally, RSV causes an estimated 6·6 million acute LRTD health-care episodes and 1·4 million LRTD hospitalisations annually among infants younger than 6 months. Beyond hospitalisation, RSV-LRTD is also associated with short-term and longer-term respiratory morbidity and higher health-care use.[2,3] Of an estimated 45 700 RSV-attributable deaths among infants younger than 6 months annually, more than 97% occur in low-income and middle-income countries.[1]

Before 2023, only palivizumab (a multi-dose monoclonal antibody [mAb]) was available for RSV prevention, but access was limited to the infants with the highest-risk, and use outside of high-resource settings

Research in context

Evidence before this study

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract disease (LRTD) in infants and children younger than 5 years globally and is responsible for considerable morbidity, mortality, and economic burden. A bivalent RSV prefusion F vaccine (RSVpreF) was first licensed in 2023 for prevention of LRTD and severe LRTD caused by RSV in infants from birth to age 6 months via active immunisation of pregnant individuals and is now approved and recommended in many countries worldwide. In the pivotal, phase 3, clinical trial of this vaccine (MATISSE trial), done in 18 countries, pregnant individuals at $24^{+0/7}$ to $36^{+0/7}$ weeks' gestation were randomly assigned to receive RSVpreF vaccine or placebo. Medically attended severe LRTD (primary endpoint) occurred within 90 days after birth in six of 3570 infants in the RSVpreF group and in 33 of 3558 infants in the placebo group, with a resulting vaccine efficacy of 81·8% (99·5% CI 40·6–96·3); efficacy against severe LRTD within 180 days after birth was 69·4% (97·58% CI 44·3–84·1). RSVpreF was also 57·1% (99·5% CI 14·7–79·8) efficacious in reducing incidence of medically attended RSV-associated LRTD (primary endpoint) within 90 days after birth and 51·3% (97·58% CI 29·4–66·8) efficacious to 180 days after birth. Post-licensure, real-world vaccine effectiveness studies in geographically and demographically diverse populations of pregnant individuals and their infants can further inform global vaccine policy and implementation; however, a PubMed search with no language restrictions on Feb 12, 2025, using the terms "RSV" AND "effectiveness" AND "RSVpreF" and "maternal" retrieved no publications. In Argentina, RSV is the predominant paediatric respiratory pathogen, and in September, 2023, the National Administration of Drugs, Food and Medical Devices in Argentina authorised RSVpreF for vaccination of pregnant individuals between $32^{+0/7}$ weeks and $36^{+6/7}$ weeks of gestation. As of March 1, 2024, Argentina became the first country globally to implement a national programme of RSVpreF vaccination during pregnancy as the primary strategy for prevention of RSV disease among infants. The vaccination strategy adopted nationwide is a seasonal programme, timed to align with local RSV seasonality.

Added value of this study

RSVpreF coverage during pregnancy reached 60% by the end of the first season, providing a unique opportunity to rapidly evaluate vaccine effectiveness in a diverse and representative real-world population of pregnant individuals and their infants. This study (BERNI) is an ongoing, 3-year, retrospective, observational, vaccine effectiveness and impact study being done across a network of 12 hospitals in seven different districts in Argentina. Following the first season of RSVpreF introduction, we evaluated vaccine effectiveness among infants hospitalised with LRTD from April 1 to Sept 30, 2024, using a test-negative, case–control design. We found high RSVpreF effectiveness against RSV-associated LRTD leading to hospitalisation among infants from birth to age 3 months and from birth to age 6 months. Vaccine effectiveness against RSV-associated severe LRTD requiring hospitalisation was 76·9% (45·0–90·3) from birth to age 6 months. As all infants in the BERNI study were hospitalised, which was not the case for the MATISSE pivotal, phase 3 trial, these results could help inform cost-effectiveness evaluations specific to hospitalisation for RSV-associated LRTD.

Implications of all the available evidence

These real-world findings from the 2024 RSV season in Argentina are consistent with efficacy results for the primary endpoints from the MATISSE clinical trial, despite differences between MATISSE and BERNI in study design, period, gestational age at vaccination, and setting. Together, these data suggest that RSVpreF vaccination in pregnancy is a successful strategy for the prevention of RSV-associated LRTD in infants during the first 6 months of life. The real-world data from the BERNI study could support public health decision making for implementation of national or district vaccination programmes in other settings. Additional study objectives to evaluate duration of protection, need for re-vaccination, and vaccine effectiveness among key subgroups and stratifications, crucial for informing implementation and maximising public health benefit (eg, among infants at high risk for RSV-associated LRTD), will be addressed after subsequent RSV seasons when the study size is larger.

was uncommon.[4] Recently, two new RSV prevention strategies have been developed, licensed, and implemented globally, including a single-dose, extended half-life mAb (nirsevimab) administered to infants and a bivalent RSV prefusion F vaccine (RSVpreF) administered to pregnant individuals.[5] In the phase 3 pivotal clinical trial (MATISSE), vaccination of pregnant individuals with RSVpreF was efficacious in preventing RSV-confirmed medically attended LRTD and severe LRTD in infants (both were primary endpoints).[6] However, post-licensure studies are needed to evaluate effectiveness in diverse and representative real-world populations of pregnant individuals and their infants, among key subgroups and stratifications crucial for understanding and maximising public health benefit,[7,8] and against outcomes not evaluated in MATISSE.

In Argentina, an average of 260 000 cases of bronchiolitis—with RSV as the leading cause[9]—are reported annually among children younger than 2 years (17 400 cases per 100 000),[10] causing a substantial burden to the health-care system each RSV season (typically, April–September).[5] In September, 2023, the National Administration of Drugs, Food and Medical Devices in Argentina authorised RSVpreF (Abrysvo; Pfizer, New York,

NY, USA) for vaccination of pregnant individuals from $32^{+0/7}$ to $36^{+6/7}$ weeks of gestation for prevention of RSV-associated LRTD and severe LRTD in infants from birth to age 6 months;[10] in November, 2023, the national immunisation technical advisory group recommended RSVpreF vaccination for all pregnant individuals.[5] Argentina's Ministry of Health introduced a nationwide seasonal vaccination programme on March 1, 2024, which provided RSVpreF free of charge as part of routine antenatal care (additional details on implementation of the RSVpreF vaccination programme in Argentina are available elsewhere).[5,11] By the end of the first seasonal campaign in August, 2024, more than 140 000 pregnant individuals had received RSVpreF vaccine, representing approximately 60% coverage of the pregnant population during that time.

The BERNI study is a 3-year study in Argentina to evaluate RSVpreF vaccine effectiveness over multiple RSV seasons. Here, we report vaccine effectiveness estimates for RSVpreF vaccination during pregnancy against RSV-associated LRTD leading to hospitalisation and RSV-associated severe LRTD leading to hospitalisation among infants from birth to age 6 months following the first season of the nationwide maternal RSVpreF vaccination programme.

Methods

Study design

We did a hospital-based, retrospective, test-negative, case-control study. Test-negative-design studies are frequently used to evaluate vaccine effectiveness against infectious respiratory diseases because of their efficiency and ability to reduce bias owing to differences in health-care-seeking behaviour between cases and controls.[12–14] A network of 12 hospitals (coordinated by iTRIALS) participated in the BERNI study in the 2024 season, including public, private, and social security hospitals located in four (South, Central, Northwest, and West) of the five health regions of Argentina, principally in major urban agglomerates (Buenos Aires, Rosario, Salta, Mendoza, Mar del Plata, Córdoba, La Plata, and Bariloche; appendix 2 p 2). In 2022, Argentina—with a population of approximately 46 million inhabitants—recorded 495 295 livebirths.[15]

The study was done in accordance with the Declaration of Helsinki and was approved by each hospital's ethics committee. The protocol was registered in the Heads of Medicines Agencies and the European Medicines Agency Catalogues of real-world data sources and studies (EUPAS1000000224) and on ClinicalTrials.gov (NCT06647654). The study is reported following STROBE guidelines.[16]

Participants

We included infants from birth to age 6 months (≤180 days) who were hospitalised from April 1 to Sept 30, 2024. In 2024, the circulation of RSV in Argentina began to rise in epidemiological week 16 (starting April 14), peaking in epidemiological week 26 (June 23), with the highest number of cases recorded between epidemiological weeks 23 (June 2) and 30 (July 21).[17] All infants had to be admitted to hospital for a minimum of 24 h and meet the definition for LRTD, which was cough or difficulty breathing, onset of symptoms within the preceding 10 days, and at least one of the following: fast breathing (respiratory rate ≥60 breaths per min for infants aged <2 months, respiratory rate ≥50 breaths per min for infants aged 2–6 months); oxygen saturation (SpO_2) less than 95%; or chest wall indrawing. Only those with a laboratory-confirmed RSV test result from a respiratory specimen collected within 10 days before to 3 days after hospitalisation (index date) were eligible (appendix 2 p 3), and only an infant's first LRTD hospitalisation was included. To ensure potential to have been born to an RSVpreF-vaccinated pregnant woman, infants must have been born to a pregnant woman who was expected to reach the indicated RSVpreF vaccination window ($32^{+0/7}$ to $36^{+6/7}$ weeks' gestation) on or after March 1, 2024, and must have been born on or after March 15, 2024. We excluded infants who received any other licensed or investigational RSV preventive product since birth, received any blood transfusion or other blood products containing antibody since birth, or required hospitalisation for reasons other than clinical criteria. Infants born to a pregnant woman whose RSVpreF vaccination status could not be confirmed were also excluded.

Procedures

Study data were collected by trained staff through review of electronic, paper, or laboratory medical records of participating hospitals. These data were supplemented with information from the respiratory virus sentinel units of the national health surveillance system (Sistema Nacional de Vigilancia de la Salud [SNVS 2.0]). Maternal RSVpreF vaccination status was ascertained from the national vaccine registry (Registro Federal de Vacunación Nominalizado) for all participants. Each site entered data into a case report form, which was subsequently compiled into a centralised study database at iTRIALS. A team of medical monitors verified 100% of the data related to the study outcomes; over 90% of the other study data uploaded into the case report form was also verified against source documents. Ongoing data quality checks were done to identify and address any discrepancies.

See Online for appendix 2

Data were collected on maternal and infant sociodemographic information, receipt of other routinely recommended vaccines during pregnancy (influenza, pertussis-containing, COVID-19), infant medical history, and infant feeding status at time of hospital admission. Additional clinical variables included dates of LRTD symptom onset, length of hospital stay, intensivw care unit (ICU) stay more than 4 h, mechanical ventilation or

high-flow oxygen therapy, discharge outcome, clinical features, respiratory diagnosis, and antibiotic use during hospitalisation. Details on study variables are provided in appendix 2 (p 5).

Outcomes

The primary outcome was RSV-associated LRTD leading to hospitalisation. Infants who met the LRTD definition and had any positive RSV test result (either PCR or indirect immunofluorescence) were considered cases, whereas control infants had to meet the LRTD definition and have a PCR-confirmed negative RSV test (appendix 2 p 4). The key secondary outcome—RSV-associated severe LRTD requiring hospitalisation—was a subset of the primary outcome, with severe LRTD additionally requiring the presence of at least one of the following: receipt of mechanical ventilation or high-flow oxygen therapy; SpO_2 less than 90%; intensive care unit (ICU) admission for more than 4 h; or failure to respond or loss of consciousness. Additional secondary and exploratory objectives will be addressed in future years when the study size is larger.

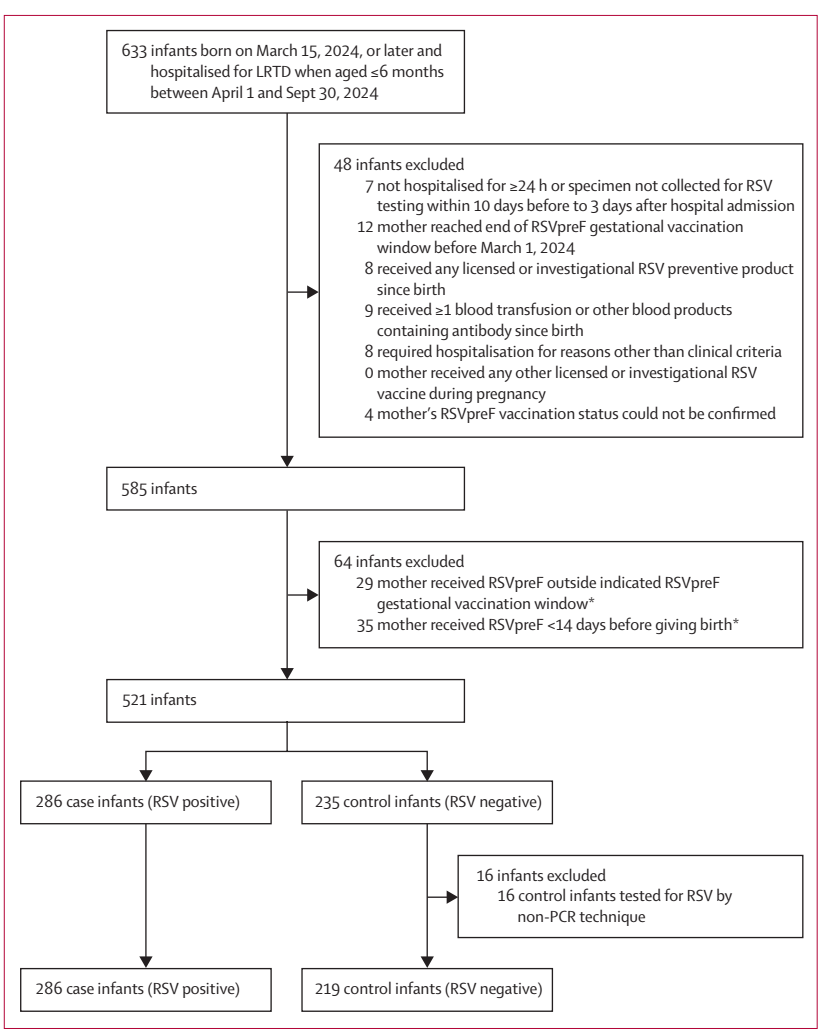

Figure: **Study flow diagram**
LRTD=lower respiratory tract disease. RSV=respiratory syncytial virus. RSVpreF=respiratory syncytial virus prefusion F vaccine. *Infants born to pregnant women who received RSVpreF at <32 weeks of gestation or at ≥37 weeks of gestation or to pregnant women vaccinated <14 days before giving birth were excluded from the main analyses but included in sensitivity analyses.

Statistical analysis

A-priori study size calculations, assuming vaccine effectiveness of 65% and RSVpreF coverage of 30% among the controls, indicated that 482 infants (241 cases and 241 controls) would be needed to achieve 90% power for the primary outcome analysis with a two-sided α level of 5%.

Infants were considered born to an RSVpreF-vaccinated pregnant woman if RSVpreF was received between $32^{+0/7}$ weeks and $36^{+6/7}$ weeks of gestation and at least 14 days before delivery. Infants whose mothers received RSVpreF at less than $32^{+0/7}$ weeks' gestation, more than $36^{+6/7}$ weeks' gestation, or less than 14 days before delivery were excluded from primary vaccine effectiveness analyses. We first estimated a crude odds ratio (OR) using a multilevel logistic regression model with infant case–control status as the dependent variable, maternal RSVpreF vaccination status as the independent variable, and hospital as a random intercept (assumed to be normally distributed) to account for correlation between infants admitted to the same hospital and possible hospital-level heterogeneity.

To estimate RSVpreF vaccine effectiveness against RSV-associated LRTD or severe LRTD leading to hospitalisation among infants up to age 6 months (the causal inference targets) we used a multilevel logistic regression model, with inverse probability-of-treatment weights (IPTWs) and multivariable adjustment to address confounding. We identified potential confounding variables a priori on the basis of previous knowledge and precedent from other maternal immunisation studies;[18–20] the variables selected meet criteria recommended for estimation of causal effects.[21] IPTW were derived from the propensity score representing the predicted probability of RSVpreF vaccination during pregnancy, conditional on the variables included in the model. We used logistic regression to calculate the propensity score among the test-negative control infants,[22,23] with maternal RSVpreF vaccination as the dependent variable and baseline variables measured before 32 weeks of gestation, which is the earliest gestational age recommended for RSVpreF vaccination, as independent variables (details in appendix 2 p 8).[23] In addition to IPTW, all adjusted models included fixed effects for date of hospitalisation[18] (to account for potential bias owing to temporal variation in the RSVpreF vaccination programme affecting opportunity to become vaccinated and for RSV seasonality affecting risk of the outcome) and infant age at time of hospitalisation;[19,20] both were modelled as natural cubic splines. We also considered two infant

variables (history of bronchiolitis and any infant comorbidity) if their inclusion changed the OR by more than 5%.[19] Any IPTW variables that remained unbalanced after weighting (absolute standardised mean difference >0·10) were included in the outcome model as covariates for doubly robust adjustment. The resulting adjusted OR (aOR) for RSVpreF vaccination was assumed to approximate the causal risk ratio and used to estimate vaccine effectiveness as $(1 - aOR) \times 100$.[12,22]

Prespecified sensitivity analyses for the primary outcome were exclusion of case infants tested for RSV with non-PCR techniques, inclusion of infants whose mothers received RSVpreF at less than $32^{+0/7}$ weeks or more than $36^{+6/7}$ weeks of gestation, inclusion of infants whose mothers received RSVpreF less than 14 days before delivery, and exclusion of infants tested for RSV more than 7 days after symptom onset to prevent misclassification of cases as controls. Prespecified sensitivity analyses for the key secondary outcome were inclusion of all control infants from the primary analysis and use of an alternative criterion for SpO_2 (<93%) to align with the definition for severe RSV-LRTD from the MATISSE trial.[6] We did post-hoc

	Infants hospitalised for LRTD aged ≤6 months and tested for RSV			Maternal RSVpreF vaccination status during pregnancy		
	Case infants (RSV positive)	Control infants (RSV negative)	Standardised mean difference	Received RSVpreF vaccine	Did not receive RSVpreF vaccine	Standardised mean difference
Number of infants or mothers	286	219	..	160	345	..
Infant characteristics						
Age at hospitalisation, days	73·6 (33·1)	76·7 (44·2)	0·08	68·5 (37·1)	77·9 (38·5)	0·25
Age at hospitalisation						
0 to ≤2 months (0 to ≤60 days)	115 (40%)	98 (45%)	0·09	75 (47%)	138 (40%)	0·14
>2 to ≤4 months (>60 to ≤120 days)	141 (49%)	81 (37%)	0·25	67 (42%)	155 (45%)	0·06
>4 to ≤6 months (>120 to ≤180 days)	30 (10%)	40 (18%)	0·22	18 (11%)	52 (15%)	0·11
Date of birth						
March 1–April 30, 2024	161 (56%)	65 (30%)	0·56	40 (25%)	186 (54%)	0·62
May 1–June 30, 2024	107 (37%)	92 (42%)	0·09	77 (48%)	122 (35%)	0·26
July 1–Sept 30, 2024	18 (6%)	62 (28%)	0·61	43 (27%)	37 (11%)	0·42
Date of hospitalisation						
April 1–May 31, 2024	11 (4%)	8 (4%)	0·01	2 (1%)	17 (5%)	0·21
June 1–July 31, 2024	203 (71%)	53 (24%)	1·06	58 (36%)	198 (57%)	0·43
Aug 1–Sept 30, 2024	72 (25%)	158 (72%)	1·06	100 (63%)	130 (38%)	0·51
Sex						
Male	155 (54%)	131 (60%)	0·11	98 (61%)	188 (54%)	0·14
Female	131 (46%)	88 (40%)	..	62 (39%)	157 (46%)	..
Gestational age at birth, weeks	38·2 (1·8)	38·3 (1·7)	0·04	38·5 (1·4)	38·1 (1·9)	0·24
Gestational age at birth						
<34 weeks	6 (2%)	4 (2%)	0·02	0	10 (3%)	0·24
34 to <37 weeks	36 (13%)	24 (11%)	0·05	15 (9%)	45 (13%)	0·12
≥37 weeks	244 (85%)	191 (87%)	0·06	145 (91%)	290 (84%)	0·20
Birthweight, g	3178·8 (560·1)	3122·2 (565·8)	0·10	3234·6 (523·9)	3115·9 (577·2)	0·22
Birthweight						
<2500 g	29 (10%)	25 (11%)	0·04	11 (7%)	43 (12%)	0·19
≥2500 g	241 (84%)	181 (83%)	0·04	143 (89%)	279 (81%)	0·24
Unknown	16 (6%)	13 (6%)	0·01	6 (4%)	23 (7%)	0·13
Any comorbidity*						
No	274 (96%)	213 (97%)	0·08	152 (95%)	335 (97%)	0·11
Yes	9 (3%)	6 (3%)	0·02	8 (5%)	7 (2%)	0·16
Unknown	3 (1%)	0	0·15	0	3 (1%)	0·13
Feeding status at time of hospitalisation						
Exclusive breastfeeding	150 (52%)	118 (54%)	0·03	93 (58%)	175 (51%)	0·15
Non-exclusive breastfeeding	129 (45%)	95 (43%)	0·03	63 (39%)	161 (47%)	0·15
Unknown	7 (2%)	6 (3%)	0·02	4 (3%)	9 (3%)	0·01

(Table 1 continues on next page)

	Infants hospitalised for LRTD aged ≤6 months and tested for RSV			Maternal RSVpreF vaccination status during pregnancy		
	Case infants (RSV positive)	Control infants (RSV negative)	Standardised mean difference	Received RSVpreF vaccine	Did not receive RSVpreF vaccine	Standardised mean difference
(Continued from previous page)						
Maternal characteristics						
Maternal age at delivery						
<20 years	23 (8%)	31 (14%)	0·20	19 (12%)	35 (10%)	0·06
20 to <25 years	71 (25%)	48 (22%)	0·07	34 (21%)	85 (25%)	0·08
25 to <30 years	80 (28%)	59 (27%)	0·02	44 (28%)	95 (28%)	<0·01
30 to <35 years	56 (20%)	42 (19%)	0·01	35 (22%)	63 (18%)	0·09
≥35 years	40 (14%)	21 (10%)	0·14	17 (11%)	44 (13%)	0·07
Unknown	16 (6%)	18 (8%)	0·10	11 (7%)	23 (7%)	0·01
Type of delivery						
Vaginal	131 (46%)	105 (48%)	0·04	75 (47%)	161 (47%)	<0.01
Caesarean	131 (46%)	93 (42%)	0·07	74 (46%)	150 (43%)	0·06
Unknown	24 (8%)	21 (10%)	0·04	11 (7%)	34 (10%)	0·11
Maternal health insurance†						
Social security or private	60 (21%)	41 (19%)	0·06	25 (16%)	76 (22%)	0·16
Public health	186 (65%)	161 (74%)	0·18	126 (79%)	221 (64%)	0·33
Unknown	40 (14%)	17 (8%)	0·20	9 (6%)	48 (14%)	0·28
Received any other routine vaccination during pregnancy‡						
No	56 (20%)	31 (14%)	0·15	7 (4%)	80 (23%)	0·57
Yes	229 (80%)	188 (86%)	0·15	153 (96%)	264 (77%)	0·57
Unknown	1 (<1%)	0	0·08	0	1 (<1%)	0·08
RSVpreF vaccination characteristics						
Received RSVpreF vaccine during pregnancy§	51 (18%)	109 (50%)	0·72	160 (100%)	..	..
Gestational age at RSVpreF vaccination, weeks	33·9 (1·4)	33·9 (1·2)	0·02	33·9 (1·3)	..	..
Gestational age at RSVpreF vaccination						
≥32 to <34 weeks	28/51 (55%)	54/109 (50%)	0·11	82/160 (51%)	..	..
≥34 to <37 weeks	23/51 (45%)	55/109 (50%)	..	78/160 (49%)	..	..
Time from RSVpreF vaccination to birth, days	30·2 (11·4)	31·8 (10·7)	0·15	31·3 (10·9)	..	..
Time from RSVpreF vaccination to birth						
≥14 to <42 days	41/51 (80%)	86/109 (79%)	0·037	127/160 (79%)	..	..
≥42 days	10/51 (20%)	23/109 (21%)	..	33/160 (21%)	..	..

Data are mean (SD) or n (%), unless otherwise stated. LRTD=lower respiratory tract disease. RSV=respiratory syncytial virus. RSVpreF=respiratory syncytial virus prefusion F vaccine. *History of a comorbidity mentioned in the infant's medical chart: bronchopulmonary dysplasia, cystic fibrosis, congenital heart disease, Trisomy 21, immunocompromised status, other (for details see appendix 2 p 6). †Maternal health insurance at index date: public, private (voluntary insurance entities), social security (coverage mainly through the employment of workers). ‡Other routinely recommended vaccines in pregnancy in Argentina: influenza, pertussis-containing (Tdap), and COVID-19. §RSVpreF was received during pregnancy between $32^{+0/7}$ and $36^{+6/7}$ weeks of gestation and ≥14 days before delivery.

Table 1: **Characteristics of the study population by infant case–control status and by maternal RSVpreF vaccination status during pregnancy**

analyses to further characterise RSVpreF effectiveness against the key secondary outcome from birth to age 3 months. All statistical analyses were performed using R software (version 4.4.1).

Role of the funding source

The funder of the study had a role in the study design, development of the data analysis plan, data interpretation, writing of the report, and the decision to submit for publication. The funder of the study had no role in data collection (managed by the iTRIALS team) or data analysis (conducted by the Universidad de San Martín team).

Results

Across the 12 hospitals, 633 infants aged up to 6 months were hospitalised for LRTD between April 1 and Sept 30, 2024 and were tested for RSV; 585 infants met eligibility criteria (figure). After excluding infants whose mothers received RSVpreF less than 14 days before delivery (n=35) or outside the indicated gestational age range (n=29), and 16 control infants tested for RSV by use of

non-PCR techniques, 505 infants were included in the main vaccine effectiveness analyses; the number of infants per hospital ranged from nine to 114 (appendix 2 p 2).

Of the 505 infants, 286 (57%) tested positive for RSV and comprised the cases, whereas 219 (43%) had a PCR-confirmed negative RSV test result and comprised the controls (table 1). Mean days of age at time of LRTD hospitalisation among cases and controls was 74 (SD 33) and 77 (SD 44), respectively; 256 case infants (90%) and 179 controls (82%) were aged 4 months or younger (≤120 days) at hospital admission (table 1). Case infants were more likely to be admitted early (April 1–July 31, 2024) in the study period compared with controls (table 1 and appendix 2 p 12). Among case infants, 142 (50%) progressed to severe LRTD, 69 (24%) were admitted to the ICU for more than 4 h, and there were three RSV-associated LRTD in-hospital deaths. Among control infants, 65 (30%) progressed to severe LRTD, 29 (13%) had an ICU stay of more than 4 h, and there were no deaths (table 2).

Overall, 160 (32%) of 505 infants were born to an RSVpreF-vaccinated pregnant woman —51 (18%) of 286 case infants and 109 (50%) of 219 controls. The distributions of gestational age at maternal RSVpreF vaccination and number of days from RSVpreF vaccination to birth were generally similar among case and control groups (table 1). Infants born to RSVpreF-vaccinated pregnant women were more likely to be admitted later in the study period (Aug 1–Sept 30, 2024) compared with infants born to pregnant women not vaccinated with RSVpreF (table 1 and appendix 2 p 12). 153 (96%) of 160 pregnant women who received RSVpreF also received at least one other recommended vaccine during pregnancy, compared with 264 (77%) of 345 pregnant women not vaccinated with RSVpreF. Among infants whose mothers did not receive RSVpreF, 154 (45%) progressed to severe LRTD and 75 (22%) were admitted to the ICU for more than 4 h; corresponding numbers for infants whose mothers received RSVpreF during pregnancy were 53 (33%) and 23 (14%), respectively (table 2). All three RSV-associated LRTD in-hospital deaths occurred among infants whose mothers had not received RSVpreF during pregnancy (table 2).

Effectiveness of RSVpreF vaccination during pregnancy against RSV-associated LRTD leading to hospitalisation among infants from birth to age 3 months was 78·6% (95% CI 62·1–87·9) and from birth to 6 months was 71·3% (53·3–82·3; table 3). Results from prespecified sensitivity analyses of the primary outcome to age 6 months were consistent with the main results (appendix 2 p 13). Vaccine effectiveness against RSV-associated severe LRTD requiring hospitalisation from birth to age 6 months was 76·9% (45·0–90·3); in sensitivity analyses, vaccine effectiveness was 81·2% (63·9–90·2) when using all 219 control infants from the primary outcome and 77·4% (52·9 –89·2) when using an alternative SpO_2 threshold of less than 93% (appendix 2 p 13). Although the study was underpowered to evaluate effectiveness against RSV-associated severe LRTD requiring hospitalisation from birth to age 3 months in this first season, we assessed this age interval in post-hoc analyses, yielding a vaccine effectiveness of 70·9% (95% CI 21·7–89·2); estimates were 77·9% (56·1–88·9) when using all control infants and 81·2% (56·5–91·8) with the alternate SpO_2 threshold of less than 93% (appendix 2 p 14). Post-hoc analyses assessing the robustness of the results for the primary outcome to different methodological approaches yielded results consistent with the main analyses (appendix 2 p 15).

Among 235 case infants whose mothers did not receive RSVpreF during pregnancy, 120 (51%) progressed to severe LRTD, 38 (16%) required mechanical ventilation, and 59 (25%) were admitted to the ICU for more than 4 h (table 4). Among 51 case infants whose mothers received RSVpreF during pregnancy, 22 (43%) developed severe LRTD, seven (14%) required mechanical ventilation, and ten (20%) were admitted to the ICU for more than 4 h (table 4).

	Infants hospitalised for LRTD aged ≤6 months and tested for RSV		Maternal RSVpreF vaccination status during pregnancy	
	Case infants (RSV positive)	Control infants (RSV negative)	Received RSVpreF vaccine	Did not receive RSVpreF vaccine
Number of infants	286	219	160	345
Length of hospitalisation, days	7 (4–10)	5 (3–7)	5 (3–7)	6 (4–9)
Severe LRTD hospitalisation	142 (50%)	65 (30%)	53 (33%)	154 (45%)
Intensive care unit admission >4 h	69 (24%)	29 (13%)	23 (14%)	75 (22%)
In-hospital death	3 (1%)	0	0	3 (1%)

Data are mean (SD) or n (%), unless otherwise indicated. LRTD=lower respiratory tract disease. RSV=respiratory syncytial virus. RSVpreF=respiratory syncytial virus prefusion F vaccine.

Table 2: **Illness severity by infant case–control status and by maternal RSVpreF vaccination status during pregnancy**

Discussion

In March, 2024, Argentina became the first country to implement a national maternal RSVpreF vaccination programme as the primary approach for RSV prevention in infants.[5,7] The resulting real-world findings from the first RSV season post-RSVpreF implementation show high vaccine effectiveness against RSV-associated LRTD leading to hospitalisation, which supports maternal RSVpreF vaccination as an effective strategy for reducing the substantial burden of RSV among infants. Importantly, this study highlights the sustained effectiveness of maternal RSVpreF vaccination in protecting infants up to age 6 months—the most vulnerable period for RSV hospitalisation and severe disease in children. The demonstrated feasibility of implementing a large national maternal immunisation

	Case infants (RSV positive)		Control infants (RSV negative)		Crude odds ratio (95% CI)*	VE (95% CI)
	Mother received RSVpreF vaccine n/N (%)	Mother did not receive RSVpreF vaccine n/N (%)	Mother received RSVpreF vaccine n/N (%)	Mother did not receive RSVpreF vaccine n/N (%)		
RSV-associated LRTD leading to hospitalisation						
0 to ≤3 months (0 to ≤90 days)	39/201 (19%)	162/201 (81%)	82/145 (57%)	63/145 (43%)	0·18 (0·11–0·30)	78·6% (62·1–87·9)†
0 to ≤6 months (0 to ≤180 days)	51/286 (18%)	235/286 (82%)	109/219 (50%)	110/219 (50%)	0·21 (0·14–0·32)	71·3% (53·3–82·3)‡
RSV-associated severe LRTD leading to hospitalisation						
0 to ≤6 months (0 to ≤180 days)	22/142 (15%)	120/142 (85%)	31/65 (48%)	34/65 (52%)	0·19 (0·10–0·38)	76·9% (45·0–90·3)§

Data are n (%) unless stated otherwise. LRTD=lower respiratory tract disease; RSV=respiratory syncytial virus. RSVpreF=respiratory syncytial virus prefusion F vaccine. VE=vaccine effectiveness. *Crude OR calculated using multi-level logistic regression model with site-specific random effect. †VE calculated as (1–adjusted OR)×100, where the adjusted OR was generated using a multilevel logistic regression model with site-specific random effect, conception date, and calendar date of hospitalisation as natural cubic splines, inverse probability-of-treatment weights, and a fixed effect for infant sex (see appendix 2 p 8 for information on inverse probability-of-treatment weight methodology). ‡VE calculated as (1–adjusted OR)×100, where the adjusted OR was generated using a multilevel logistic regression model with site-specific random effect, conception date, calendar date of hospitalisation, and infant age at hospitalisation as natural cubic splines; and inverse probability-of-treatment weights. §VE calculated as (1–adjusted OR)×100, where the adjusted OR was generated using a multilevel logistic regression model with site-specific random effect, calendar date of hospitalisation and infant age at hospitalisation as natural cubic splines, inverse probability-of-treatment weights, and a fixed effect for complete exposure window.

Table 3: **Effectiveness of maternal RSVpreF vaccination during pregnancy against RSV-associated LRTD and severe LRTD leading to hospitalisation among infants from birth to 6 months of age**

programme—achieving approximately 60% coverage during the first seasonal campaign—underscores the public health impact that this vaccine could have on reducing the burden of RSV-associated disease. Indeed, the full public health impact of RSV-associated LRTD reduction in the earliest months of life is potentially even more substantial than evaluated in this study, given evidence of longer-term respiratory morbidity (such as subsequent respiratory infections or recurrent wheeze) following RSV-associated LRTD in early infancy.[3,24]

The first season findings from this study are consistent with those of the phase 3 pivotal MATISSE trial,[6] which used similar endpoints to this study. In both studies, maternal immunisation with RSVpreF was highly effective at preventing RSV-associated LRTD from birth to age 6 months. Nevertheless, it was challenging to predict how real-world effectiveness would align with efficacy given key differences between MATISSE and BERNI, including design (randomised clinical trial *vs* test-negative design), time period (during the COVID-19 pandemic when RSV circulation was disrupted *vs* 2024), gestational age at vaccination ($24^{+0/7}$–$36^{+0/7}$ weeks [mean 31 weeks] in MATISSE *vs* $32^{+0/7}$–$36^{+6/7}$ weeks [mean 34 weeks] in this study), population (clinical trial with healthy pregnant participants and their singleton newborns *vs* real-world population of infants hospitalised with LRTD), and setting (27% of participants from upper-middle-income country [UMIC] *vs* 100% from UMIC). Although the MATISSE endpoint of medically attended severe RSV-associated LRTD used different thresholds for tachypnoea and SpO_2 compared with the comparable endpoint in our study, and did not require hospitalisation (61·7% were hospitalised in MATISSE *vs* 100% in BERNI), vaccine effectiveness against RSV-associated severe LRTD leading to hospitalisation from birth to age 6 months in BERNI (76·9%, 95% CI 45·0–90·3) was similar to efficacy against medically attended severe RSV-associated LRTD in MATISSE (69·4%, 97·58% CI 44·3–84·1). BERNI vaccine effectiveness results for prevention of RSV-associated LRTD requiring hospitalisation through the first 3 months and 6 months of life were higher than efficacy against medically attended RSV-associated LRTD in MATISSE, which was expected given that all infants in BERNI were hospitalised for this outcome, versus 32·2% in MATISSE, and vaccines—including RSVpreF—generally provide higher effectiveness against more severe outcomes.

Although not currently available in Argentina, nirsevimab (another product approved for prevention of RSV disease in infants) has also been shown to be effective against RSV-associated outcomes in recent studies from high-income settings. Real-world effectiveness evidence is crucially important for countries as they evaluate RSV prevention options and decide which product(s) to implement, either independently or as part of a complementary strategy. However, it is important to highlight that for several reasons, effectiveness estimates for maternal RSVpreF and nirsevimab are not directly comparable. Although both products provide passive immunity, maternal RSVpreF vaccination provides infant protection from birth and is reported by age at illness, whereas nirsevimab is administered after birth and effectiveness has been reported by days post-immunisation or by age at immunisation (which might not be at birth). Direct comparison of available nirsevimab effectiveness estimates to BERNI study results is also limited by differences in outcome definitions, population and health system characteristics, and study methodologies. Nevertheless, among individual-level comparative observational studies that evaluated RSV-confirmed LRTD hospitalisation outcomes by use of approaches

most similar to BERNI, nirsevimab effectiveness ranged from 70% to 82%.[25–27] Studies of nirsevimab effectiveness against hospitalisation specifically due to RSV-associated bronchiolitis reported estimates ranging from 83% to 88%.[28–30] Recently released preliminary data from the 2024 RSV season in Chile are contextually relevant to the BERNI study given a similar geographical location and RSV circulation pattern and showed an estimated nirsevimab effectiveness of 76% (95% CI 69–81) against RSV-associated LRTD hospitalisation.[31]

Although RSVpreF is the first built-for-purpose maternal vaccine, immunisation during pregnancy has been a successful public health strategy for decades, leveraging the natural process of transplacental transfer of maternal antibody to provide immediate protection to infants from birth and through the early months of life, when infants are most vulnerable to severe morbidity and mortality from infectious diseases.[32] Moreover, maternal immunisation has unique advantages, including potentially providing direct protection to pregnant or postpartum individuals and prolonged protection to infants via vaccine-induced antibodies transferred via breastfeeding.[32] Argentina has been a pioneer in implementing maternal immunisation,[5] achieving moderate-to-high coverage in pregnancy for influenza and pertussis-containing vaccines after their incorporation into the national immunisation programme,[33] with subsequent reduction of morbidity and mortality in young infants.[33,34] In Argentina, maternal vaccines are provided free of charge, without a prescription, and as part of routine antenatal care; moreover, multiple points of access to immunisation clinics enhance vaccine coverage, thereby increasing access and health equity while minimising costs.[5,35,36] The swift roll-out and acceptance of RSVpreF in 2024 built on Argentina's previous successes with maternal immunisation and illustrates that achieving high coverage rapidly, even during the first year of implementation, is possible. Nevertheless, implementation in settings with resource constraints might require strategies tailored to their unique barriers to achieve optimal uptake and public health impact.

Strengths of this study include use of a test-negative design, a widely used approach for vaccine effectiveness evaluation, which reduces bias due to differential health-care-seeking behaviour compared with other observational designs.[12–14] Assuming equivalent vaccine effectiveness for infants who would not access hospital-based care for similar RSV-associated LRTD severity, our study findings can be generalised to the source population of infants for whom medical attention would be sought for serious respiratory illness.[12] Participating hospitals were broadly representative of geographical diversity in Argentina and sector (public, private, social security), there were no exclusions based on maternal or infant risk factors, and the study relied on standard-of-care data collection and RSV testing. These findings are therefore probably generalisable to other settings within Latin America and beyond, particularly settings with similar sociodemographics and health-care systems (eg, other UMICs) and with the same gestational age window for RSVpreF vaccine administration. Results might be less generalisable, however, to resource-limited LMICs, especially settings where prevalent maternal comorbidities (eg, maternal HIV infection or hypergammaglobulinaemia) could affect immune response to vaccination or transplacental transfer.[37]

	Total case infants (RSV positive)	Maternal RSVpreF vaccination status during pregnancy	
		Received RSVpreF vaccine	Did not receive RSVpreF vaccine
Number of infants	286	51	235
Age at hospitalisation, days	73·6 (33·1)	69·7 (32·5)	74·4 (33·2)
Age at hospitalisation			
0 to ≤2 months (0 to ≤60 days)	115 (40%)	19 (37%)	96 (41%)
>2 to ≤4 months (>60 to ≤120 days)	141 (49%)	27 (53%)	114 (49%)
>4 to ≤6 months (>120 to ≤180 days)	30 (10%)	5 (10%)	25 (11%)
Any comorbidity, n (%)			
No	274 (96%)	48 (94%)	226 (96%)
Yes	9 (3%)	3 (6%)	6 (3%)
Unknown	3 (1%)	0	3 (1%)
Clinical features at hospital admission			
Cough	259 (91%)	50 (98%)	209 (89%)
Difficulty breathing	269 (94%)	46 (90%)	223 (95%)
Tachypnoea	232 (81%)	37 (73%)	195 (83%)
Chest wall indrawing	232 (81%)	39 (76%)	193 (82%)
Oxygen saturation <95%	260 (91%)	43 (84%)	217 (92%)
Clinical features at any time			
Oxygen saturation <93%	158 (55%)	23 (45%)	135 (57%)
Oxygen saturation <90%	68 (24%)	11 (22%)	57 (24%)
Illness severity			
Severe LRTD hospitalisation	142 (50%)	22 (43%)	120 (51%)
ICU admission >4 h	69 (24%)	10 (20%)	59 (25%)
Required high-flow oxygen	122 (43%)	21 (41%)	101 (43%)
Required mechanical ventilation	45 (6%)	7 (14%)	38 (16%)
Required mechanical ventilation or high-flow oxygen	132 (46%)	23 (45%)	109 (46%)
In-hospital death	3 (1%)	0	3 (1%)
Use of health-care resources			
Length of hospitalisation, days	7 (4–10)	5 (3–9)	7 (4–11)
Length of ICU admission, days	10 (8–13)	10 (6–19)	10 (8–13)
Days of mechanical ventilation	9 (6–12)	8 (6–19)	9 (7–11)
Days of high-flow oxygen therapy	4 (2–5)	3 (2–4)	4 (2–5)
Any antibiotic use during hospitalisation	136 (48%)	25 (49%)	111 (47%)
Days of antibiotic use	6 (4–7)	5 (2–7)	6 (4–7)

Data are mean (SD), n (%), or median (IQR). LRTD=lower respiratory tract disease. RSV=respiratory syncytial virus. RSVpreF=respiratory syncytial virus prefusion F. ICU=intensive care unit.

Table 4: **Clinical features, illness severity, and use of health-care resources among case infants ≤6 months of age, overall and by maternal RSVpreF vaccination status during pregnancy**

This study has several limitations. Although we used a comprehensive analytical approach, we cannot rule out residual confounding by unmeasured factors, such as maternal medical history. Such factors could bias vaccine effectiveness estimates towards or away from the null value, depending on prevalence and strength of association with maternal RSVpreF vaccination and infant RSV outcomes. We also cannot completely exclude residual temporal confounding despite having used multiple mitigation strategies in the design and analysis. Although non-differential misclassification of RSVpreF vaccination status could have occurred and attenuated vaccine effectiveness estimates, this is unlikely given that the national vaccine registry was used to ascertain maternal RSVpreF vaccination status for all infants. As this study was done retrospectively, we were unable to standardise the laboratory testing method for RSV. To mitigate potential misclassification of cases as controls due to a false negative result from a non-PCR method, we required a PCR-confirmed negative RSV test for control infants; a sensitivity analysis imposing the same requirement for cases (ie, limited to PCR-confirmed positive RSV tests) yielded results consistent with the main analysis. As this study was done in hospital settings, it was not possible to evaluate vaccine effectiveness against less severe RSV disease, nor against out-of-hospital deaths associated with RSV-LRTD. Given that RSV is responsible for the largest proportion of hospitalised LRTD among infants in Argentina (and globally),[1,5] an ideal case-to-control ratio of at least 1:1 was not achieved with one season of data; in the 2024 season, the ratio was approximately 1:0·8 for the primary outcome and 1:0·5 for the key secondary outcome. Although results for the primary outcome were robust across sensitivity analyses, the key secondary outcome showed higher variability across sensitivity analyses; data from additional seasons will be crucial to increase robustness of results and clarify whether such variability is due to statistical instability of estimates or other substantive reasons. The BERNI study is continuing across multiple seasons; additional objectives important for guiding policy and maximising public health impact will be assessed in the future, including duration of protection, need for revaccination, and vaccine effectiveness stratified by gestational age at vaccination, time from vaccination to birth, finer intervals of infant age, simultaneous administration of other vaccines, infant feeding status, and infant high-risk status. Finally, although it was not feasible to exclude infants with other viral infections from the analysis in the first year, a prespecified sensitivity analysis excluding control infants with other viral respiratory diseases preventable through maternal immunisation (eg, influenza, SARS-CoV-2) will be done in future years.

In summary, this study shows that maternal RSVpreF vaccination during pregnancy is an effective strategy for preventing RSV-associated LRTD requiring hospitalisation in infants from birth through the early, vulnerable months of life. Additional studies assessing vaccine effectiveness in other settings and that use different methods will be important for describing and quantifying additional benefits of RSVpreF vaccination during pregnancy; such studies could include those capable of assessing the effect on all-cause respiratory outcomes in infants, as well as short-term, medium-term, and long-term sequelae from RSV infection (eg, secondary or bacterial co-infections and recurrent wheeze). As the first country to implement a national maternal RSVpreF vaccination programme for the primary RSV prevention strategy, Argentina's experience provides a valuable framework for other countries in Latin America and elsewhere. The high real-world effectiveness of RSVpreF shown in this study underscores the potential public health impact of this RSV prevention strategy, which might also have unique advantages, most prominently, protection from the first day of life.

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Contributors
GPM, AR, LDN, and CV conceived and supervised the study. GPM, SWM, VB, and AB were in charge of the project administration. GPM, AR, LDN, CV, BDG, DBF, SWM, and JEA conceptualised the study. AR, DBF, and NF wrote the original draft. AR, DBF, NF, SO, RR, GPM, SWM, LDN, CV, JEA , RZ, GV, MGA, GdCM, LJ, and RL reviewed and edited the manuscript. AR and VB accessed and verified the data. AR, SO, VB, AB, and RR accessed, cleaned, and analysed the data. SO and RR did the formal analysis. AR, GPM, DBF, SO, RR, SWM, JEA, CV, BDG, and RF did the investigation and designed the methods. SO and RR designed the figure. All authors reviewed the manuscript, approved the final version of the manuscript, and authorised the submission of the manuscript for publication.

Declaration of interests
GPM, LDN, VB, AB, RZ, GV, and RL are employees of iTRIALS, which has received funding from Pfizer, Merck, Moderna, and Sanofi for studies related to the topic of this Article. GPM has also received fees for advisory boards from Enanta and Pfizer, and speaker fees from Pfizer and Moderna. DBF, SWM, JEA, MGA, RF, BDG, and LJ are employees of Pfizer and hold shares or stock options in the company. All other authors declare no competing interests.

Data sharing
De-identified individual participant data that underlie the results reported in this Article will be available immediately following publication and for up to 5 years after publication, on reasonable request, to researchers who provide a methodologically sound proposal, and whose proposed use of the data has been approved by an independent review committee identified for this purpose. Proposals should be directed to the corresponding author. To gain access, data requestors will need to sign a data-access agreement.

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