STUDY PROTOCOL

REVISED 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"

[version 4; peer review: 6 approved]

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Abstract

Background

In 2021 we launched the BronchStart study, which collected information on 17,899 presentations in children with serious respiratory tract infections following the release of lockdown restrictions. Our study informed the Joint Committee on Vaccination and Immunisation's decision to recommend the introduction maternal respiratory syncytial virus (RSV) vaccination, which was introduced in the United Kingdom in August/September 2024.

Study question

We modified our original protocol to conduct a United Kingdom-wide assessment of maternal vaccination against RSV.

Methods and likely impact

We will conduct a multi-centre study, utilising the PERUKI network used in the original BronchStart study, to assess the effectiveness of maternal vaccination using a test-negative study design. We will gather detailed clinical information on children admitted with bronchiolitis in the post-RSV vaccination era, and understand possible reasons for incomplete vaccine uptake.

Keywords
COVID-19, Respiratory Syncytial Virus, Bronchiolitis, Infants, Children, Palivizumab

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Any reports and responses or comments on the article can be found at the end of the article.

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REVISED **Amendments from Version 3**

In responding to comments from our peer reviewers, we have added some text to clarify the background to the study, and added some text to the Methods section to make this clearer. We have added a link to a real-time dashboard for the study, and directly addressed some of their questions/comments in the "Notes to Reviewers" section.

Any further responses from the reviewers can be found at the end of the article

Introduction

The BronchStart study[1–3] was launched in 2021, anticipating an increase in serious respiratory infections in children following the release of lockdown measures implemented to limit the spread of the Covid-19 pandemic. Since then it has documented serious early life respiratory disease in the United Kingdom for the past three years, collecting detailed information bronchiolitis admissions, and feeding into the Joint Committee for Vaccination and Immunisation (JCVI) decision to introduce widespread RSV immunisation to the UK[4]. Maternal RSV vaccination has now been recommended across the United Kingdom, and was rolled out from August 12th 2024 (Scotland[5]) and September 1st 2024 (England[6], Wales[7], Northern Ireland[8]) for pregnant women who are at a gestation of 28 weeks or more.

Once vaccination is introduced, understanding vaccine effectiveness (VE) will be a key clinical and policy priority. National approaches to assessing VE will be conducted by the public health agencies of the Four UK Nations (England, Scotland, Wales and Northern Ireland). However, these are likely to be complicated by data linkage methodological issues that will delay analyses and release of data to well after the end of the winter RSV season; equally these analyses will be unable to collect detailed clinical information on demographics and outcomes for those who have/have not been the recipients of maternal vaccination. In addition, they will not be able to understand barriers to uptake of maternal RSV vaccination.

The aim of this update to the BronchStart protocol is to leverage the research infrastructure created for BronchStart to evaluate effectiveness of RSV maternal vaccination in a real-world setting during the first season (2024–2025) of maternal RSV introduction in the UK. To achieve this the BronchStart protocol has been amended to include a test-negative design (TND) VE study. Below we list key modifications to the original protocol required to conduct a test-negative VE study, with an embedded survey of mothers to understand potential barriers to vaccine uptake.

Study protocol

The original study protocol[1] was structured in keeping with the principles of the STROBE statement (strobe-statement.org/). This update to the protocol details any changes made to this original protocol for a study of maternal RSV vaccine effectiveness (VE) in the 2024/2025 winter season.

Sample selection

A national multi-centre prospective observational cohort study will be carried out under the auspices of the PERUKI (Paediatric Emergency Research in the UK and Ireland) Network[9]. All children meeting the inclusion criteria below will be eligible for the vaccine effectiveness study, which will be nested within the original study.

Inclusion criteria: The maternal RSV vaccine has been made available to all pregnant mothers from August 12th 2024 (Scotland) and September 1st 2024 (England, Wales, Northern Ireland). Therefore eligible participants will be infants born after the August 12th 2024 (Scotland) or September 1st 2024 (England, Wales, Northern Ireland) admitted to a hospital with clinical features of bronchiolitis (cough, tachypnoea or chest recession, and wheeze or crackles on chest auscultation)[10], lower respiratory tract infection (clinical diagnosis) or a first episode of acute viral wheeze (for the detailed rationale for only recruiting infants/children presenting with their first episode of wheeze, please refer to V2 of the protocol).

Exclusion criteria: Children with previous episodes of wheeze responsive to bronchodilator, suggesting an underlying diagnosis of recurrent wheeze of early childhood; this is likely to represent a much smaller patient group than the original BronchStart study, due to a focus in this updated protocol on infants born after the 12th August 2024 (Scotland) or 1st September 2024 (England/Wales/Northern Ireland) entering their first RSV winter season (2024/5).

Data collection

We will collect data at two time points: baseline (date of presentation to a participating hospital) and seven days later. Informed consent will be sought from mothers of eligible infants for permission to conduct a questionnaire, and access their medical records for their immunisation status. Clinicians identifying a case for inclusion will keep a local log of participants that contain patient identifiable characteristics cross referenced to a study number. An email after 7 days to the submitting clinician will prompt data entry at this point.

Data on the vaccine effectiveness sub-study will be entered to a secure online database (REDCap data capture tool)[11,12] (see below).

Variables to be measured

At baseline, data including patient demographics, presenting characteristics, acuity and results from point of care virology testing will be collected (see Supplementary File 1). An external link will enable clinicians to enter a full postcode derived index of multiple deprivation score for database entry.

At 7 days data will include the infant's length of stay (if this is longer than 7 days, further reminder emails will be sent on a weekly basis) highest acuity dependency (the ward they were placed on if admitted: Observation Unit, Normal, High Dependency or Intensive Care), whether care the patient was discharged or died and (if obtained) what viruses were identified by PCR (see Supplementary File 1).

RSV status will be identified by nasopharyngeal aspirate/swab (NPA/NPS) tested by either (a) point of care testing (rapid viral testing where available) at baseline presentation to ED, or (b) by laboratory PCR testing, if either is performed as part of standard care.

To understand factors associated with maternal RSV vaccine uptake, we consulted with a medical anthropologist (DI) to design a questionnaire for mothers of infants participating in the study. The final questionnaire included questions that adhered to the principals of the Five 5C's model[13,14] of vaccine hesitancy, which posits that psychological antecedents such as confidence, complacency, constraints, calculation, and collective responsibility influence vaccine uptake on an individual level.

Sample size calculation

Two approaches were taken for sample size calculations: one based on the WHO recommendations for the evaluation of Covid-19 vaccine effectiveness[15], and a second simulating a variety of different vaccine effectiveness and coverage rates in the populations recruited in our previous studies, bootstrapping our proposed analyses methods to determine the confidence intervals we would obtain of the 'known' vaccine effectiveness.

Calculations based on WHO recommendations for evaluation of VE. Calculations were based on the precision of the VE estimated by the test-negative design, as recommended by the WHO, and implemented using their VE calculator[16]. The maternal vaccine coverage of Tdap is just under 60% in England[17] and maternal RSV vaccine coverage could be as low as 30% in the first season. Assuming the true VE for RSV-associated bronchiolitis/LRTI hospitalisation among infants from birth through 6 months of age is 70%, the study would need to recruit 145 RSV-associated hospitalisations, with 1:1 matching with test-negative controls to achieve a precision width of 40% (+/-20%) for the VE.

Calculations based on varying assumptions. Using an alternative method (epiR:epi.sscc)[18] it can be seen (Table 1) that the number of cases required is very dependent on these assumptions being correct; the exact number is lower than previously as a precision width for the VE is not specified. As VE or uptake rates decline, the number of cases required rapidly rise.

Sample size feasibility and number of recruitment sites required. Reviewing case recruitment for infants aged 0–6 months for the 2021/2 BronchStart season showed that for the top 5 recruiting centres between 54–111 RSV positive cases, and 40–78 RSV negative cases, were recruited by site over the peak 6 months of the season. For the 2024/5 season, a limited eligible patient population (infants born after August 12th 2024 [Scotland] and September 1st 2024[England/Wales/Northern Ireland]) and a likely reduction in respiratory presentations with the introduction of vaccination means that multiple recruiting centres will be required to meet the proposed sample sizes. Assuming a worst-case scenario of 20% uptake and 60% effectiveness (218 cases, 218 controls, total 436 cases), and that each centre were able to recruit 50 patients (25 cases, 25 controls), we aimed to identify at least 10 recruiting centres (~500 recruits) for this study.

Table 1. How the number of cases required varies by different assumptions of vaccine effectiveness and uptake. Calculated using epiR::epi.sscc[18] with following parameters: OR = 1-VE, p0 = coverage, power = 0.9).

	Vaccine Effectiveness					
Uptake	**40%**	**50%**	**60%**	**70%**	**80%**	**90%**
5%	2,161	1,287	828	560	391	280
10%	1,114	659	420	281	195	137
15%	768	451	285	189	129	90
20%	597	348	218	143	97	66
25%	498	287	178	116	77	52
30%	433	248	153	98	64	43
40%	361	203	123	77	49	31
50%	329	182	108	66	40	24
60%	326	177	102	61	36	20

Study registration

The study will be registered on ISCRTN Registry (https://www.isrctn.com/).

Outcomes

Primary outcome: Estimate vaccine effectiveness (VE) of RSV maternal vaccination during pregnancy against RSV-associated LRTD hospitalization among infants from birth through 6 months of age.

a. Cumulative from birth through 6 months

b. Stratified by from birth to 3 months and from >3 to 6 months

Secondary outcomes

a. Describe level of care among hospitalized cases and controls (observation unit, hospital ward, high-dependency unit, paediatric intensive care unit)

b. Describe respiratory support among hospitalized cases and controls (low-flow oxygen, high-flow oxygen therapy, continuous positive airway pressure, bilevel positive airway pressure, and invasive mechanical ventilation)

c. Describe treatment modalities and frequencies (antibiotics, intravenous fluid, nasogastric fluid)

d. Evaluate RSV testing rates and modality during the 2024–2025 RSV season in ED and hospital settings across the PERUKI network to inform feasibility of

VE assessments against other outcomes in future RSV seasons using test negative designs.

e. Describe predictors of maternal vaccine uptake (including but not limited to prematurity, logistical challenges, maternal choice).

Data analysis and statistical plan

Our primary analysis will be an un-matched conditional logistic regression stratified by site and calendar month of attendance with age, prematurity and sex as co-factors. Stratifying by site and month is important to control for local differences in vaccine uptake. We will also carry out a matched (by site, age and date of attendance) analysis as a secondary analysis, but anticipate that close chronological matching of cases and controls may prove not possible due to the sharp peaks in attendance, due initially RSV cases as the epidemic spikes, then due to non-RSV disease caused by other viruses as RSV recedes. We will look at vaccine effectiveness for all infants and also the subgroup of those whose mother received a vaccine >14 days before birth.

A thematic analysis will be conducted on free text responses collected in the maternal questionnaire. Data will be coded to identify patterns and themes, and a codebook developed comprising codes and sub-codes generated from etic and emic categories, descriptions of each, and examples of representative data.

Ethical issues

The original BronchStart study was a non-consented study which only used routinely collected clinical data on the infant with respiratory disease. However, as for this study we would be accessing maternal, as well as infant, health records, we felt that consultation with a parent and patient group was necessary to understand how to collect this information in a way that was acceptable to parents of children with serious respiratory disease.

Prior to designing the study, we therefore launched a consultation with a patient and public involvement (PPI) group for parents of children affected by viral wheeze, Fourteen parents responded, located in England and Northern Ireland. We asked whether, as a mother, respondents would be happy for researchers to check maternal medical records to verify their vaccination history. None of the respondents stated that they would not be happy for a researcher to access their medical records. Five out of 14 (36%) stated that they would be happy for researchers to access their medical records without needing to be told about it; 7/14 (50%) were happy for researchers to access their medical records with verbal consent; 2/14 (14%) were happy for researchers to access their medical records, as long as they were provided with written information and able to provide written consent. We therefore proceeded on the basis of providing appropriate information and eliciting consent for the VE sub-study. 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 a favourable opinion from the Research Ethics Committee on the 8th August 2024. The consent form for the study is available as Supplementary File 2, and the study information leaflet as Supplementary File 3.

Data input, storage and management

Data will be entered using the validated online data entry software REDCap. (Research Electronic Data Capture tools) following the clinical report forms provided in the appendix (Supplementary Files 1). This software (REDCap) is hosted on the University Hospitals Bristol and Weston NHS Foundation Trust (UHBW) secure server, accessible on the Health and Social Care Network (HSCN) that is managed by NHS Digital. All research data reside within the hosting institution. The study Sponsor Organisation (University Hospitals of Leicester NHS Trust) will be the Data Controller throughout, and University Hospitals Bristol and Weston NHS Foundation Trust will have Joint Controllership for the duration of data entry and cleaning. REDCap uses a granular security model so that users can only review the data they have been explicitly authorised to access. REDCap also provides a comprehensive log/audit feature that records all individual changes with a date/time stamp and a change owner. Data that are captured and stored will only be available via the information technology systems linked to the HSCN which is the current validated system used by NHS Trusts to share and store patient information.

Dissemination

Data will be presented in:

- A real-time study dashboard (https://bronchstop.netlify.app/)
- Data submissions to the regulatory authorities, public health agencies and local study teams.
- A study preprint
- A peer reviewed scientific journal
- Engagement with the PPI group involved as part of study design, and the Resvinet Patient Network, who were involved in the original BronchStart study

Conclusions

Within a rapid timeframe, we anticipated that this study will generate estimates of vaccine effectiveness which will help to inform planning for subsequent RSV seasons. In addition, detailed information will be collected on infant demographics, clinical presentations and outcomes in the post-RSV vaccination era. Additionally, insights into associations with incomplete maternal vaccine administration will facilitate future efforts to boost vaccine uptake.

Data availability

Underlying data

As this is a study protocol no data are yet available. Study data will be stored on a RedCap server hosted by University of West of England, Bristol, United Kingdom (See Data input, storage and management). Anonymised, aggregate data

will be shared with interested parties upon reasonable request following approval from the sponsor institution (UHL NHS Trust).

Extended data

Edinburgh Research Archive: BronchStart Study Extended Data [https://era.ed.ac.uk/handle/1842/37604?show=full]

Available here will be:

- BronchStop_supplementary_file1.pdf (Consent form for BronchStop sub-study)
- BronchStop_supplementary_file2.pdf (Parent information leaflet for BronchStop sub-study)
- BronchStop_supplementary_file3.pdf (BronchStop sub-study CodeBook)

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Open Peer Review

Current Peer Review Status: ✔ ✔ ✔ ✔ ✔ ✔

Version 4

Reviewer Report 18 January 2025

https://doi.org/10.21956/wellcomeopenres.25971.r115143

✔ **Ram Hari Chapagain**
National Academy of Medical Sciences (NAMS), Kathmandu, Nepal

The Introduction ,methodology along with inclusion and exclusion criteria and variables need to be collected is clearly mentioned. the outcome variable is mentioned clearly. The statistical plan is also clear.

It is better to have consent form parents before collecting the data as consenting is major in any form of study.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Vaccine trials , Burden study , economic study

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 27 December 2024

https://doi.org/10.21956/wellcomeopenres.25971.r116019

Michael G Ison
National Institute of Health, Rockville, MD, USA

The authors propose collecting a range of data that will inform maternal decision making about RSV vaccine (retrospectively), rates of testing for RSV and VE from this observational cohort. Similar RWE studies have been helpful in understanding the clinical utility of these new vaccines. Some issues that were unclear to me:

1. How well does the cohort reflect the UK population that it is targeting to assess?
2. There are differences in sensitivity of antigen-based vs. PCR-based testing. It is unclear how that will be factored in as a negative antigen test could miss a case.
3. Likewise, involvement requires consent - what is the expected consent rate and will the consented patients likely reflect the overall population or be skewed?
4. Is there variability of level and type of care across hospitals - this could result in skewed data if there is heavier enrollment in some centers.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Expert in RSV vaccines, respiratory viruses in adults and immunocompromised hosts.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 23 December 2024

https://doi.org/10.21956/wellcomeopenres.25971.r115941

Susan Hopkins
UK Health Security Agency, London, UK

The updates to this article address my major concerns.

Competing Interests: I am employed by UKHSA. I confirm that this potential conflict of interest did not affect my ability to write an objective and unbiased review of the article.

Reviewer Expertise: Infectious Diseases, Epidemiology, Vaccine Effectiveness studies.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 3

Reviewer Report 13 November 2024

https://doi.org/10.21956/wellcomeopenres.25532.r107417

Susan Hopkins
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This is an important study which aims to assess vaccine effectiveness of maternal RSV vaccine to prevent serious RSV illness (by reviewing hospitalisations) in babies from 0-6 months). It also aims to provide some assessment of level of care required, respiratory support, associated treatment, evaluate testing and maternal factors in uptake of vaccination.

The introduction states that national datasets will be unable to assess vaccine effectiveness. I am unsure how this statement is made as UKHSA provides vaccine effectiveness estimates for influenza, COVID-19 and would be expected to do that for RSV.

The additional qualitative overlay in this study is beneficial and would not be performed by routine national studies.

Given this PERUKI group is UK and Ireland, I would observe it was an opportunity to compare the different policy approaches to vaccination - maternal vaccination in the UK and neonatal

vaccination in Ireland - it would enable an assessment of the different approaches in similar health systems and provide a natural experiment.

The precision width of 40% (+/- 20%) is very wide. Why is it only possible to recruit 10 sites? Improving the precision estimate would be much better.

The number of cases and controls recruited is small and therefore the ability to determine the impact of vaccination at various points in pregnancy, lack of ability to provide chronological matching and improved matching of cases and controls will be a limiting factor.

I did not have access to the data variables detected and therefore could not assess the suitability of the data collected. There was no assessment on how well the data collection planned has been completed in previous studies.

Overall, this study will add value particularly on describing the detail of healthcare delivery, the testing approaches within hospitals and the qualitative work on maternal vaccination. However, it will only provide a limited assessment on VE.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Partly

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Partly

Competing Interests: I work in UKHSA - the organisation that conducts national vaccine effectiveness studies for vaccines.

Reviewer Expertise: Infectious Diseases, Epidemiology, Vaccine Effectiveness studies.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 16 Dec 2024

Thomas Williams

We did not mean to imply in our introduction that public health agencies such as UKHSA or Public Health Scotland would not be conducting studies to evaluate vaccine effectiveness. We have therefore edited the wording of the Introduction to make this clearer (additions underlined): “Once vaccination is introduced, understanding vaccine effectiveness (VE) will

be a key clinical and policy priority. National approaches to assessing VE will likely be conducted by the public health agencies of the Four UK Nations (England, Scotland, Wales and Northern Ireland). However, these are likely to be complicated by data linkage methodological issues that will delay analyses and release of data to well after the end of the winter RSV season." Initially we had hoped to compare, using the same methodology, outcomes in both the UK and the Republic of Ireland with the introduction of maternal RSV vaccination/nirsevimab, but unfortunately issues related to funding and the timing of ethical approvals made this impractical. We have applied for funding to perform this comparison, if this is successful the protocol will be amended for next season. The accuracy of the VE in our study was based on the worst-case scenario that maternal RSV vaccine coverage is 30%. This means that, in the worst-case scenario, the study can provide a VE with a lower confidence interval >50% assuming the true VE is 70%, i.e. we will have 95% confidence to conclude the VE is >50% based on the above assumptions. The lower boundary of VE in pivotal vaccine trials is normally between 0% - 30%. Therefore, we felt the precision of VE in our study is acceptable. If the vaccine coverage is as high as the Tdap coverage, the precision of VE will be +/- 15%. The rapidly evolving nature of the study meant that we could only guarantee that a limited number of sites would be able to come on board in time to start recruiting for the 2024/5 RSV season. However, although we aimed for a minimum of 10 sites, we recognised that the larger the number of sites, the higher the prevision of estimates, and we are pleased to report that we currently have over 20 sites recruiting to the study (https://bronchstop.netlify.app/)

We recognise that the small planned sample size is likely to limit our ability to conduct sub-analyses of study data.

We apologise for the lack of access to the data variables: there was a delay in uploading the data variables sheet to the University of Edinburgh repository. This is now available at this link: http://dx.doi.org/10.7488/era/885 We agree that the most comprehensive assessment of VE will come from a large national study of routinely collected data on hospital admissions. However we hope that our study will offer additional value over and above the information that can be established from such a national study.

Competing Interests: No competing interests were disclosed.

Reviewer Report 29 October 2024

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In this protocol the PERUKI research group present an important and timely update to the BronchStart study. With this update, the group will aim to evaluate vaccine effectiveness of maternal RSV vaccine against RSV associated LRTD hospitalization in infants from birth through 6 months and also stratified from birth to 3 months and 3-6 months. This is a timely and important study, particularly given the UK will be among one of the only countries this season to implement a maternal vaccine strategy alone. Data on vaccine effectiveness of the RSV maternal vaccine as well as determinants of maternal vaccine uptake are much needed to help inform RSV immunization policy.
The authors should be commended for their efforts to make their study protocol and data collection tools available and to rapidly disseminate data via a real-time study dashboard.

Suggestion:
The Inclusion and exclusion criteria are outlined, however the rationale for exclusion of children with previous episodes of wheeze responsive to bronchodilator is not described, I suggest the authors include their rationale for this decision in the published protocol.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Vaccine implementation. Clinical Epidemiology. Vaccine uptake.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 16 Dec 2024

Thomas Williams

We thank our reviewer Dr. Geoghegan for their positive response to the updated protocol. In the updated version of the protocol we have added a link to the study dashboard for this

winter season: https://bronchstop.netlify.app/

In the initial BronchStart study, we were interested to see whether a change in the age at which infants/children experienced their first RSV infection was associated with a change in phenotype. Due to the lockdown measures implemented to prevent the spread of respiratory viruses, we speculated that many children would experience their first RSV infection between the ages of 1 and 2 years, rather than, as in a normal season, between the age of 0-1. We speculated that this might manifest as a wheezing phenotype rather than typical bronchiolitis. However, we did not want to capture repeat attendances for the children who present with frequent wheeze episodes, so limited this group by specifying that we only wanted to capture the first wheezing episode (which could be a manifestation of first RSV infection). For this updated version to the protocol, the oldest child likely to be recruited to the proposed vaccine effectiveness study is around 6 months of age, as we will only capture children born from the 12th August onwards who present at any point up until the end of the RSV season, which tends to come to a close in February/March. Therefore we felt that this was likely to be less of a concern than in earlier iterations of the study, but we have maintained this wording to ensure consistency with previous versions of the protocol. Please see the changes to the wording below, with additions underlined. "Inclusion criteria : The maternal RSV vaccine has been made available to all pregnant mothers from August 12 th 2024 (Scotland) and September 1 st 2024 (England, Wales, Northern Ireland). Therefore eligible participants will be infants born after the August 12 th 2024 (Scotland) or September 1st 2024 (England, Wales, Northern Ireland) admitted to a hospital with clinical features of bronchiolitis (cough, tachypnoea or chest recession, and wheeze or crackles on chest auscultation) 10 , lower respiratory tract infection (clinical diagnosis) or a first episode of acute viral wheeze (for the detailed rationale for only recruiting infants/children presenting with their first episode of wheeze, please refer to V2 of the protocol). Exclusion criteria : Children with previous episodes of wheeze responsive to bronchodilator, suggesting an underlying diagnosis of recurrent wheeze of early childhood; this is likely to represent a much smaller patient group than the original BronchStart study, due to a focus in this updated protocol on infants born after the 12th August 2024 (Scotland) or 1st September 2024 (England/Wales/Northern Ireland) entering their first RSV winter season (2024/5)."

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 19 August 2021

https://doi.org/10.21956/wellcomeopenres.18503.r44077

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With a primary objective to assess the impact of COVID-19 on RSV transmission and disease severity, this surveillance study in the UK is topical and important. The protocol is well designed and the methods are fully described. I have just minor comments.

1. Introduction: Reference(s) for statements on long-term effects RSV is missing. Kindly add.

2. Data analysis: Please confirm if you will use multivariate analysis or if it will be multivariable logistic regression with binary outcomes of hospitalization, level of ventilatory support and PICU admission examined separately. Currently it is not clear.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: RSV; Infectious disease epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 23 June 2021

https://doi.org/10.21956/wellcomeopenres.18503.r44084

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This is a protocol for a timely study in the UK. The study is well planned and pragmatic for busy EDs. I have minor comments only:

- Collection of data on participants' attendance at childcare / nursery etc would be useful.
- For the 7 day follow up, I assume families are not being contacted again but researchers are just looking at their local hospital record. Will you know if they attend at a different hospital (or GP) in the follow up period? This may need to be noted as a limitation.
- For the stratification of severity did you consider also using a scoring system (e.g. the ReSViNet score - I think you are collecting all the required data anyway?).
- It is unclear to me how "excess morbidity" will be defined / measured.
- On the supp file 2: units for H+ (pH) listed as mmHg, is this correct? (not nmol/L on nM)?

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: I have sat on RSV advisory boards for Merck and have been an investigator on clinical trials of RSV therapeutics for various pharmaceutical companies. I work with various EFPIA partners as part of the RESCEU consortium. I confirm that this potential conflict of interest did not affect my ability to write an objective and unbiased review of the article.

Reviewer Expertise: RSV, respiratory viruses, paediatrics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.