



Surveillance towards preventing paediatric incidence of respiratory syncytial virus attributable respiratory tract infection in primary and secondary/tertiary healthcare settings in Merseyside, Cheshire and Bristol, UK

Fred Fyles ,¹ Helen Hill,¹ Gregory Duncan,¹ Emma Carter,¹ Carla Solórzano,¹ Kelly Davies,¹ Lauren McLellan,¹ Maia Lesosky,¹ James Dodd,¹ Adam Finn,² Paul Stephen McNamara ,^{3,4} David Lewis,⁵ Mathieu Bangert,⁶ Natalya Vassilouthis,⁶ Matthew Taylor,⁷ Daniela M Ferreira,^{1,8} Andrea M Collins^{1,9}

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FF and HH contributed equally.

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For numbered affiliations see end of article.

Correspondence to

Dr Andrea M Collins;
Andrea.Collins@lstm.ac.uk

ABSTRACT

Introduction Respiratory syncytial virus (RSV) is a common respiratory virus, particularly affecting children, and can cause respiratory infections such as croup and bronchiolitis. The latter is a leading cause of paediatric hospitalisation within the UK. Children <3 years of age and/or with underlying health conditions are more vulnerable to severe RSV infection. There are currently limited data on the incidence of laboratory-confirmed RSV, particularly within primary care settings and outside the typical 'RSV season', which in the Northern hemisphere tends to coincide with winter months. There is also a lack of data on the health economic impact of RSV infection on families and healthcare systems. This observational surveillance study aims to collect data on the incidence of laboratory-confirmed RSV-attributable respiratory tract infection (RTI) in children aged <3 years presenting to primary, secondary or tertiary care; it also aims to estimate the health economic and quality of life impact of RSV-attributable infection in this cohort. Such data will contribute to informing public health strategies to prevent RSV-associated infection, including use of preventative medications.

Methods and analysis Parents/carers of children <3 years of age with RTI symptoms will consent for a respiratory sample (nasal swab) to be taken. Laboratory PCR testing will assess for the presence of RSV and/or other pathogens. Data will be obtained from medical records on demographics, comorbidities, severity of infection and hospitalisation outcomes. Parents will complete questionnaires on the impact of ongoing infection symptoms at day 14 and 28 following enrolment. The primary outcome is incidence of laboratory-confirmed RSV in children <3 years presenting to primary, secondary or tertiary care with RTI symptoms leading to health-seeking behaviours. Recruitment will be carried out from December 2021 to March 2023, encompassing two UK winter seasons and intervening months.

Ethics and dissemination Ethical approval has been granted (21/WS/0142), and study findings will be published

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Respiratory syncytial virus (RSV) is recognised as a leading cause of healthcare resource utilisation within paediatrics, including hospitalisations and critical care admissions. Rates of RSV infection are monitored by the UK Health Security Agency. In previous years, epidemiological patterns of RSV infection were well established, peaking in the UK over the winter months; however, since the start of the COVID-19 pandemic this pattern has been disrupted.
- ⇒ Data on rates of laboratory-confirmed RSV among children presenting to primary care, or outside the typical RSV season, are limited in the UK. The economic and quality of life impact of RSV-associated respiratory infection on children and their families in the UK is unknown.

WHAT THIS STUDY ADDS

- ⇒ This observational UK study will be the first to collect data on the incidence of RSV-attributable respiratory tract infection in infants aged <3 years old across a range of healthcare settings, outside of the typical RSV season, and to estimate the health economic and quality of life impact in these settings.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ In the future, these data may impact public health policy/guidelines relating to preventing RSV in infants; it may also impact future clinical research into novel preventative therapies for RSV across age ranges.

as per International Committee of Medical Journal Editors' guidelines.

INTRODUCTION

Respiratory syncytial virus (RSV) is a seasonal respiratory virus that, while able to cause



infection throughout life,¹ is a leading cause of childhood lower respiratory tract infections (RTIs).^{2–4} In Northern hemisphere countries, prior to the COVID-19 pandemic,^{5–7} RSV typically occurred in epidemics each winter,^{8,9} causing bronchiolitis, an inflammatory condition of the small airways, as well as ‘colds’, croup and pneumonia. RSV-associated RTI is a leading cause of hospitalisation among infants within the UK¹⁰ and is responsible for up to 10% of paediatric intensive care unit (PICU) admissions.¹¹ The median duration of stay for children hospitalised with bronchiolitis is 66 hours (IQR: 38–99), but can be prolonged in those with severe disease.¹² Very young children, those with underlying conditions and premature children^{13,14} have higher rates of mortality and morbidity from RSV infection.

Diagnosis of bronchiolitis is typically clinical,¹⁵ relying on history and clinical examination, with clinical features including coryza, breathing difficulties, cough and crepitations on auscultation.^{15,16} RSV may be identified as a causative pathogen through PCR testing; within the UK, however, these tests are rarely used for children treated within the community. Even within UK hospitals, systematic screening for causative organisms for RTIs is often not routinely performed outside of peak viral seasons.¹⁷

Given RSV is an RNA virus, samples need to be processed as soon as possible or stored at -80°C to prevent degradation, again limiting community or hospital testing. Multiple sampling methodologies are available, including nasopharyngeal aspiration (NPA) and nasal swabbing (NS). Existing studies are conflicted on the sensitivity and reliability of NS-based PCR compared with NPA,^{18–24} but NS is associated with reduced infant distress and increased acceptability to parents/carers²² and is currently the clinical standard among many paediatric units within the UK.

Many other pathogens can also cause bronchiolitis or exist as a co-infection with RSV,^{25–28} with a viral co-infection rate of approximately 6%.² RSV is also associated with a higher incidence of co-infection with *Streptococcus pneumoniae* (Spn),^{16,29} and recent studies have demonstrated RSV is able to augment bacterial growth and density in Spn co-infection.^{30,31} Data on co-infection in paediatric RTIs are limited within the UK, as are data on circulation of RSV outside the typical RSV season.

Similarly, data on RSV-associated RTI and associated economic costs in the UK outside a hospital setting are scarce, largely due to a lack of systematic testing with sensitive, wide-spectrum PCR assays, which are costly and difficult to implement on a large scale. To our knowledge, only three studies have been published exploring the socioeconomic burden of RSV within primary care—two outside of the UK^{32,33} and one within the UK that was significantly limited by the COVID-19 pandemic.³⁴

Currently, the only approved preventative therapies for RSV-associated RTI within the UK are monoclonal antibodies (mAbs), which may be classed as a ‘passive vaccine’. Two are currently available: palivizumab and nirsevimab. Palivizumab is an mAb that binds to and inactivates the

fusion glycoprotein on the surface of RSV, preventing entry into cells.^{35,36} A recent meta-analysis demonstrated reduced risk of hospitalisation due to RSV infection (risk ratio 0.44, 95% CI 0.30 to 0.64),³⁷ and palivizumab has been shown to be cost-effective in certain groups.^{38,39} Within the UK, it is only available for children considered at high risk of severe disease, for example, children with congenital heart disease. It is administered to children at highest risk of severe disease as an injection each month of the RSV season and costs around £5000 per child per season. Nirsevimab, which was recently approved for use in the UK,⁴⁰ also binds to the fusion glycoprotein, but has a longer half-life, requiring once-off administration as opposed to monthly. Recent studies have demonstrated efficacy in reducing medically attended RSV infection, with a relative risk reduction of 79.5% (95% CI 65.9 to 87.7).^{41–44} Further large-scale studies into use of nirsevimab are ongoing, and as of yet the UK has not released guidance on its use; however, given the reduction in dosing requirements, it is hoped that nirsevimab may prove a more attractive option for wide-scale clinical use than palivizumab.⁴⁵

Development of a novel RSV vaccination has been a public health goal for many decades, and there are currently a raft of potential candidates in development with a range of mechanisms of action.⁴⁶ At the time of writing, only four candidates for paediatric vaccines have reached phase II trials, with none in phase III development. Similarly a maternal vaccine, conferring immunity in early infancy through trans-placental antibody transfer, may be a potential preventative option in the future,⁴⁷ provided it is cost-effective.⁴⁸ An improved understanding of RSV Protein F⁴⁹ has provided a potential candidate for a maternal vaccine (NCT04424316) developed by Pfizer, which is currently undergoing phase III trials. As of yet, however, no maternal, adult or paediatric RSV vaccines are commercially available.

Given the increasing speed of development of preventative treatments for RSV, accurate and granular data on the burden of RSV disease in both hospitals and primary care are needed to inform public health policies and immunisation programmes for these vaccines.

Here, we describe our observational study of incidence of laboratory-confirmed RSV-associated RTI within primary, secondary and tertiary healthcare settings in Merseyside, Cheshire and Bristol. We aim to collect data on the incidence of RSV and other pathogens (including Spn carriage) in patients presenting to healthcare settings with RTI from December 2021 to March 2023, encompassing two UK winter periods and the intervening months. We will also gather information on health economic and quality of life (QoL) burden that RSV-associated RTI has on parents/carers, families and healthcare settings. These data will be used to help inform the discussion around future prevention strategies for RSV.

Table 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> ▶ Aged <3 years of age ▶ Evidence of RTI (any of the following): <ul style="list-style-type: none"> – Feels hot or temperature of >37.8°C – Cough – Nose: Snotty, stuffy, blocked – Earache – Sore throat – Sneezing ▶ Evidence of lower RTI (any of the following)*: <ul style="list-style-type: none"> – Audible wheezing (without auscultation) – Shortness of breath, rapid or shallow breathing for age – Oxygen saturations <94% on air – Crackles, wheeze or diminished breath sounds on auscultation – Respiratory distress: apnoea, nasal flaring, chest recession, grunting, head bobbing – Central cyanosis – History of above symptoms if intubated prior to site admission 	<ul style="list-style-type: none"> ▶ Parent/carer unable to provide informed consent on behalf of the child ▶ Parent/carer unable to conform to study requirements ▶ Participated within STOP RSV within the last 30 days ▶ (SAM Strip subgroup only): nasal flaring on examination

*Not necessary for upper RTI subgroup.
RSV, respiratory syncytial virus; RTI, respiratory tract infection; SAM, synthetic absorptive matrix.

METHODS

Study design and settings

STOP RSV is a pragmatic, observational surveillance study of the incidence of RSV-attributable RTI in children <3 years of age presenting to primary, secondary and tertiary healthcare settings in Merseyside, Cheshire and Bristol (representing urban and rural areas). Study sites will include tertiary care sites with dedicated level 2/3 paediatric units, including PICU. Additional sites may be added to the study throughout, subject to Health Research Authority (HRA) approval.

Participants

A total of 1800 (with ethical approval to increase to 2000 to allow for ongoing recruitment over the summer) children aged <3 years presenting to healthcare services with symptoms of lower RTI will be recruited in line with inclusion criteria outlined below (table 1). A subgroup may be recruited from primary care with evidence of upper RTI only (see Upper RTI subgroup, below). Recruitment will take place over a 16-month period, from December 2021 to March 2023, with adequate representation over two winter seasons. Patients will be recruited from primary, secondary and tertiary care. Emergency department (ED) discharges who were not admitted to a hospital ward and

were in ED for under 24 hours will count towards the primary care recruitment target.

In previous years, peak RSV season has been between October and March; however, the impact of lockdown measures and subsequent resocialisation during the COVID-19 pandemic has led to a change in this pattern, with numbers in 2021 peaking in July. Therefore, in order to provide accurate data on viral positivity rates, this study will run continuously over a period of 16 months, from December 2021 to March 2023, including two UK winter seasons and intervening months.

Participation within the study in the last 30 days is an exclusion criterion given the potential that, without an adequate time difference between recruitment periods, presenting symptoms will be from the same disease episode. Allowing for a period before re-recruitment will ensure subsequent symptoms represent a new episode of infection.

Objectives

The primary objective of this study is to estimate the incidence of laboratory-confirmed RSV over a 16-month period in children <3 years of age presenting to primary, secondary and tertiary care with RTI symptoms leading to health-seeking behaviour.

Secondary objectives:

- ▶ To report the incidence of laboratory-confirmed RSV-associated RTI in children <3 years in relation to the type of healthcare service provided (primary, secondary or tertiary care)
- ▶ To describe the co-circulation of RSV and other respiratory viruses in participants with symptomatic RTI
- ▶ To describe the healthcare utilisation and associated economic burden associated with RTI (with or without RSV) at recruiting sites
- ▶ To describe the health economic burden in wards, High Dependency Unit (HDU) and PICU in relation to RTI at secondary/tertiary care sites
- ▶ To describe incidence of RTI presentations to primary, secondary and tertiary care and associated health economic burden, using existing anonymised healthcare data

Exploratory objectives:

- ▶ To describe the family burden of participants with RTI symptoms (with or without RSV) leading to health-seeking behaviours;
- ▶ To describe the incidence of RSV+/-other respiratory viruses in a subgroup of children presenting to primary care with RTI symptoms without evidence of lower respiratory tract involvement
- ▶ To assess the sensitivity and specificity of synthetic absorptive matrix (SAM) swabs (nasal strips) for detection of RSV for children <3 years old with lower RTI symptoms presenting to secondary/tertiary care

Table 2 Pathogens detected by the BIOFIRE Respiratory 2.1 plus panel

Viruses	Bacteria
Adenovirus	<i>Bordetella pertussis</i>
Coronavirus 229E	<i>Bordetella parapertussis</i>
Coronavirus HKU1	<i>Chlamydomphila pneumoniae</i>
Coronavirus OC43	<i>Mycoplasma pneumoniae</i>
Coronavirus NL63	
Middle East Respiratory Syndrome	
CoronaVirus (Mers-CoV)	
Severe Acute Respiratory Syndrome	
Coronavirus 2 (SARS-CoV-2)	
Human Metapneumovirus	
Human Rhinovirus/Enterovirus	
Influenza A	
Influenza A/H1	
Influenza A/H1-2009	
Influenza A/H3	
Influenza B	
Parainfluenza 1	
Parainfluenza 2	
Parainfluenza 3	
Parainfluenza 4	
RSV	

Patient and public involvement statement

Patient and public involvement and engagement was used to shape the design of study materials such as the Participant Information Leaflet (PIL), as well as giving feedback on the appropriateness of the consent process and validated study questionnaires. The aims of the study were stated to the parents of participants during the consent process. A lay report or newsletter of our findings will be made available to all parents/carers of participants.

Study procedures

Consent from parents/carers will be requested to collect an NS from children presenting to healthcare settings with symptoms of RTI. The NS will be inserted into one

nostril, held in place for 5s and rotated 180 degrees. In the event, an NS, nasopharyngeal swab or NPA has already been obtained for clinical care, consent will be sought to ‘scavenge’ this sample for use within the study. In the event, a participant has left the healthcare setting prior to swabbing (eg, a GP telephone consultation or ED discharge), a home sample pack may be posted out to parents/carers with clear instructions on how to take a swab of their own child; this will be returned in a pre-paid package, consistent with regulations on transport of infectious substances.

While current evidence suggests NPA may be a more sensitive modality compared with NS for the detection of RSV, the use of NS sampling within this study reflects current UK practice and has been pragmatically chosen to reduce infant distress, improve parent/carer compliance, improve recruitment rates and allow for the provision of home sampling as detailed above.

Clinical samples will be transported to local NHS-associated laboratories for testing using the ‘BIOFIRE Respiratory 2.1 plus panel’, which tests for a range of viral and bacterial pathogens (detailed in table 2). As samples will be processed at laboratories associated with recruiting sites, results will be made available in real-time to clinicians involved with participant care.

Following this, samples will be transported to our centre and stored, following which they will be analysed for Spn carriage at our site’s laboratory. Data on Spn carriage will not be made available to clinicians.

At the time of consent, baseline data will be collected from medical records, including demographics and baseline health economic data; a short clinical Case Report Form (CRF) will capture clinical symptoms and parameters. Parents/carers will be asked what healthcare utilisation they have required (for this disease episode specifically) up to the point of recruitment, for example, previous attendance to primary care, use of NHS 111 service.

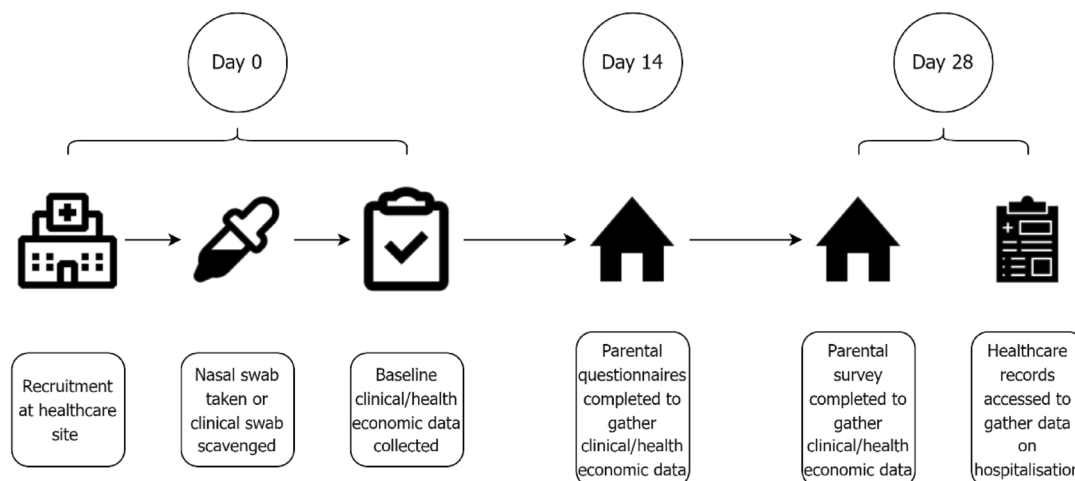


Figure 1 Patientflow diagram.

At day 14, the parent/carer will be asked to complete three questionnaires:

1. Healthcare Survey: Collecting data on clinical course (duration of symptoms, level of care), further medically attended visits due to respiratory symptoms and indirect costs associated with the illness (eg, transport to hospital)
2. EQ 5D 3L Quality of Life Questionnaire: A validated questionnaire assessing the QoL of the primary parent/carer at day 14
3. Peds QL Family Impact Module: A validated questionnaire assessing the impact the illness has had on the parent/carer and on the family unit as a whole

At day 28, parents/carers will be asked whether their child has had further symptoms/healthcare utilisation from day 14 onwards, and if so, will complete a further short survey asking about symptom duration, medically attended visits and indirect costs of the illness. Further medical data will be collected at day 28 from pre-existing healthcare records, recording data on healthcare utilisation for this infection episode, including whether a participant recruited in primary care has gone on to require secondary/tertiary care support. Patient flow is outlined in [figure 1](#).

Upper RTI subgroup

A subgroup of infants (n=180) <3 years old with RTI symptoms but without evidence of lower RTI will be recruited from primary care services over a minimum period of 3 months. An interim analysis will be carried out to estimate point prevalence of RSV in the first 180 participants, assessing whether RSV rates are significantly different compared with those with evidence of lower respiratory tract involvement. Results of this analysis, alongside data on monthly viral circulation rates, will be used by the trial steering committee to determine whether eligibility criteria are relaxed across all of primary care, which may potentially improve recruitment.

SAM nasosorption subgroup

A subgroup of infants (n=150) recruited at tertiary care sites will undergo concurrent NS and SAM nasosorption strips, to assess sensitivity and reliability of SAM sampling for RSV and other respiratory pathogens within this cohort compared with NS. Initially, as a subgroup, 30 participants will have the SAM strip inserted for a period of 10s only (shorter than the current recommendation of 30–120s) which may be better tolerated by infants. If reliable, this shorter time may be adopted in future work. In order to ensure those within the subgroup represent a range of disease severity, a target of n=100 will be set for patients discharged directly from ED (likely to have less severe disease), and n=50 for patients admitted to hospital (likely to have more severe disease).

SAM samples will be transported to clinical laboratories, where they will be run using the same analysis methods as NS. Following this, they will be transported to our facility

Box 1 Study outcome measures

Main study outcome measures

Laboratory measures

- ⇒ Frequency and proportion of RSV-positive cases in each category of healthcare:
 - ⇒ Primary care (GP and ED discharges)
 - ⇒ Secondary/tertiary care: PICU vs HDU vs hospital wards
- ⇒ Detection of other respiratory pathogens in respiratory samples measured by molecular methods

Clinical measures

- ⇒ Summary of demographic data, medical history, baseline observations, severity of illness score and RTI-related healthcare utilisation prior to recruitment
- ⇒ Summary of patient pathway of recruits with RTI, including:
 - ⇒ Proportion of patients with ongoing symptoms at D14±D28
 - ⇒ Hospital length of stay (days)
 - ⇒ Level of care (ED/ward/HDU/PICU)
 - ⇒ Duration and type of respiratory support (days)

Health economic measures

- ⇒ Summary of existing healthcare data on presentations of children aged <3 years to healthcare settings for RTI symptoms over the study period
- ⇒ Summary of data from questionnaires at recruitment, D14 and D28, including:
 - ⇒ Family socioeconomic indicators
 - ⇒ Frequency of children with ongoing symptoms
 - ⇒ Impact on childcare
 - ⇒ General carer burden
 - ⇒ Frequency of GP or other primary care visits
 - ⇒ Parent/carer days off work and leave taken
 - ⇒ Parent/carer costs of travel and accommodation

RTI without lower RTI subgroup

- ⇒ Proportion of samples positive for RSV and/or other respiratory pathogens, measured by molecular methods, compared with those within the main study

SAM nasosorption subgroup

- ⇒ Estimation of SAM swab test sensitivity and specificity compared with nasal swabs as gold standard
- ⇒ Comparison of agreement between nasal swabs and SAM swabs
- ⇒ Comparison of tolerability, sensitivity and specificity of insertion of SAM swab for reduced time (10 s) compared with 30–120 s PICU, paediatric intensive care unit; RSV, respiratory syncytial virus; RTI, respiratory tract infection; SAM, synthetic absorptive matrix.

and stored, ahead of analysis of Spn carriage detection. Results from SAM analysis will be cross-referenced with those from NS analysis to determine sensitivity/specificity.

Outcome measures

Study and substudy outcome measures are shown in [box 1](#). The primary outcome measure is point prevalence (95% CIs) of RSV-positive respiratory samples measured by molecular methods over 16 months collection.

Consent

To meet HRA guidance on applying a proportionate approach to seeking parental/carer consent and to



prevent information overload for parents/carers, we will offer two approaches to consent:

- ▶ Signed study consent at the time the child presents with RTI symptoms (paper or electronic);
- ▶ Verbal consent to obtain a swab, access minimal amounts of patient data and to be contacted by the research team, followed by deferred signed study consent as above

Given infants approached for inclusion within the study will likely be suffering from some form of respiratory distress, thus limiting parental capacity to process large amounts of information or complete immediate signed consent, this design allows parents/carers to have time to read information within the PIL and make an informed decision on whether to participate, while also allowing researchers to obtain a timely sample.

Signed study consent will be obtained only by staff delegated the role by the chief/principal investigator and will have sufficient good clinical practice (GCP) training. Staff obtaining verbal consent will require attendance of study-specific training, but will not need full GCP qualifications, again in line with HRA guidance on proportional approaches to research.

MONITORING AND ANALYSIS

Safety monitoring

Safety monitoring of the study is consistent with NHS REC requirements. Study staff will monitor for serious adverse events (SAEs) during study duration and report any unexpected SAEs or any SAEs directly related to the study, using the approved HRA form to REC within 15 days of the chief investigator (CI) becoming aware. These will be followed up by medical assessment as soon as possible and until the event is resolved. Adverse events (AEs) not meeting the criteria for SAE will not be reported/recorded. Adverse events of special interest (AESIs) are limited to anything directly related to the nasal sampling process.

Statistical analysis plan

The study sample size is dictated by the expected rate of RSV in the study population and the number of RTI cases typically seen by recruiting sites. The study target of $n=1800$ would allow a precision (95%) CI in the point estimate of RSV of ± 0.016 if proportion in population is 0.15 or of ± 0.021 if proportion in the population is 0.35. Analysis will be guided by a prepared statistical analysis plan, but briefly, prevalence of RSV (95% CIs) will be estimated on a monthly basis. Descriptive analyses will summarise the frequency and proportion of RSV cases presenting at different healthcare settings and describe demographic and clinical history by RSV status.

A Health Economic Model will be developed alongside the statistical analysis plan, consistent with requirements for use by the Joint Committee on Vaccination and Immunisation. EQ-5D-3L will be converted to utility scores

using UK preference weights, which will be combined with the duration of impact to estimate the overall quality-adjusted life year (QALY) outcomes, compared against age-adjusted population norms. This will generate estimates for the QALY-loss impact of RSV, both at a per case level and for the population as a whole.

Data monitoring

All source data produced in the study will be maintained by the PI at the NHS site and made available for inspection if required. Anonymised source data may be transferred to the eCRF system REDCAP by the NHS research team at study sites. Access to REDCAP is strictly controlled by the LSTM Data Management Team, and new users will require necessary delegation from PI prior to access rights. Patient confidentiality will be maintained as required under the Data Protection Act 2018 and UK GDPR.

Ethics and dissemination

This study is subject to approval from the NHS Research Ethics Committee (REC) and HRA. It will be conducted in line with ethical principles in the Declaration of Helsinki. Substantial amendments requiring review by NHS REC will not be implemented until REC grants a favourable opinion. The sponsor will report to the REC any serious breaches of the protocol or principles of good clinical practice.

Within 1 year after the end of the trial, the CI will submit a final report with the results, including any publications/abstracts, to the REC. Publication will be consistent with the Consort Guidelines and checklist.

Author affiliations

¹Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK

²University of Bristol Medical School, Bristol, UK

³Department of Child Health, University of Liverpool, Liverpool, UK

⁴Alder Hey Children's Hospital, Liverpool, UK

⁵Vauxhall Primary Health Care, Liverpool, UK

⁶Sanofi SA, Paris, France

⁷York Health Economics Consortium, Heslington, UK

⁸Oxford Vaccine Group, University of Oxford, Oxford, UK

⁹Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK

Correction notice The article has been corrected since it was published online. The co-author Daniela Ferreira's name has been amended to Daniela M Ferreira.

Contributors HH—conceptualisation, study design, protocol drafting, protocol amendments, writing and editing; reviewer responses and amendments. AMC—conceptualisation, study design, protocol drafting, protocol amendments, manuscript editing. DMF—conceptualisation, study design, manuscript editing. CS—conceptualisation, study design, protocol drafting, manuscript editing. GD—study design, manuscript writing and editing. EC—manuscript editing. KD—study design, protocol drafting, protocol amendments, manuscript editing. LM—protocol amendments, manuscript editing, writing and editing; reviewer responses and amendments. JD—Manuscript editing. ML—study design, manuscript editing. AF—study design, manuscript writing and editing. PSM—study design, manuscript editing. DL—study design, manuscript editing. MB—conceptualisation, study design, manuscript editing. NV—conceptualisation, study design, manuscript editing. MT—study design, manuscript editing. FF—study design, protocol amendments, manuscript writing and editing; original draft preparation, reviewer response and amendments. DMF and AMC are joint last authors.

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Competing interests Neither the CI nor any collaborator has any direct personal involvement in organisations sponsoring or funding the research that may give rise to a potential conflict of interest. Professor Adam Finn is a member of the Joint Committee for Vaccination and Immunisations, UK.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by REC Reference Number: 21/PR/1428IRAS Number: 304483. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iDs

Fred Fyles <http://orcid.org/0000-0002-5141-6220>

Paul Stephen McNamara <http://orcid.org/0000-0002-7055-6034>

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