Intensive surveillance of acute respiratory infections (ARI) in primary care with a focus on respiratory syncytial virus (RSV): prospective sentinel network observational study

Version 1.0, Date: 08/04/2023

Introduction:

Whilst most respiratory infections, including respiratory syncytial virus (RSV), are commonly managed in primary care by general practitioners (GP), some result in serious infections particularly in children under one year. [1] In Western countries, mortality due to an RSV infection is rare, however, annual hospitalization rates in the first year of life are estimated to be 3.2-42.7 cases per 1000 children, with a hospital stay length ranging between 2 to 11 days, and 2-12% of cases requiring an intensive care unit admission. [2, 3] Globally, it is estimated that more than 33 million young children are infected with RSV, resulting in 3.2 million hospitalizations and around 60,000 in-hospital deaths.[4]

A number of new vaccines and therapies for respiratory syncytial virus (RSV) are poised to be approved for use in the US and EU.[5] Creating a prospective linked dataset of virologically confirmed RSV cases can help to transform our understanding of RSV epidemiology post COVID-19, including the seasonal patterns and dominant strains in circulation. It will also be vital to further our understanding of the take up of new therapies and coverage by new vaccines especially in individuals at risk for severe RSV disease. This will contribute to the calculation of real-world vaccine and drug effectiveness [6], provide valuable information about adverse events of interest (AEIs) [7, 8], and will be key to further vaccine development, and health services resource allocation including addressing health inequalities.

Presentations of RSV include bronchiolitis, bronchitis, pneumonia and other lower respiratory tract infections (LRTI). [1] Contemporary data shows RSV continues to affect all age bands, and has a range of clinical presentations. Data from 5,171 swabs taken between 1/9/2022 and 20/2/2023 by the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) sentinel network [9] suggests RSV infection occurs across all age bands, though with most in children (Figure 1). Most RSV presented as upper respiratory tract infections (URTI), with lower respiratory tract infection (LRTI) the next most frequent, and ILI the least frequent (Figure 2).

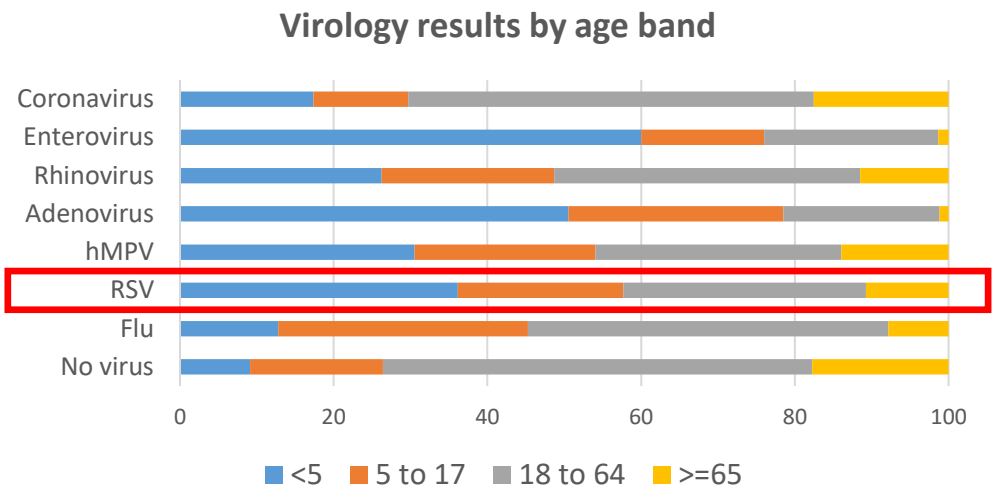

Figure 1. Virology results are subdivided by age band. The viral panel includes: COVID (SARS-COV-2 and other coronaviruses), Human metapneumovirus (hMPV), Respiratory syncytial virus (RSV, highlighted), and Influenza, combining all subtypes and lineages (flu).

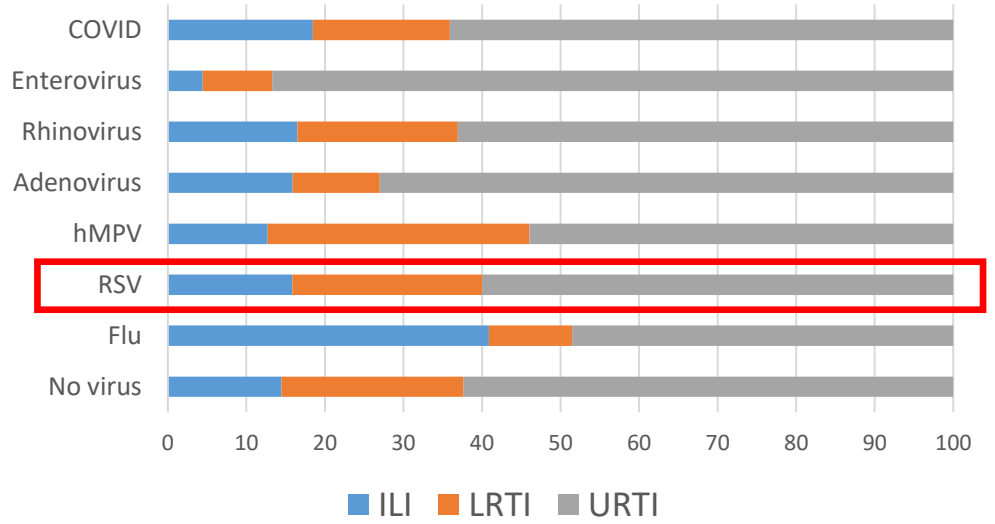

Figure 2. Acute respiratory infection (ARI) diagnosis is subdivided into influenza-like-illness(ILI), lower respiratory tract infection (LRTI) and upper respiratory infection (URT) for each virus tested. The viral panel includes: COVID (SARS-COV-2 and other coronaviruses), Human metapneumovirus (hMPV), Respiratory syncytial virus (RSV, highlighted), and Influenza, combining all subtypes and lineages (flu).

Historically, the interest of the RSC in collaboration with the UK Health Security Agency (UKHSA) is to monitor [10] acute bronchitis and bronchiolitis in under 5-year-olds. Our recent data also shows 37% of children under five years old who present with acute bronchitis and bronchiolitis and have a virology sample testing positive for RSV (Table 1).

Characteristic	No virus	Flu	RSV	hMPV	Adenovirus	Rhinovirus	Enterovirus	Coronavirus
Overall population	46.5	16.7	8.1	5.0	3.2	16.0	1.4	10.3
Bronchiolitis or Bronchitis in under 5's	10.0	7.5	37.5	15.0	12.5	37.5	2.5	10.0

Table 1. Distribution of proportion of respiratory virus identified in the overall population and under 5 years old, between 1st September 2022 and 24th February 2023

In this study, we plan to use virology in addition to point of care testing (POCT) testing to extend the number of samples for RSV and other respiratory viruses. We aim to have virological samples tested at the UKHSA reference virology laboratory. We will also aim to deploy POCT at scale. In primary care, POCT has not been deployed at scale, and rates of testing have been low.[11] Recent systematic reviews report POCT's accuracy and cost-effectiveness and identify integration into clinical workflow, supporting clinicians, quality assurance and funding as the barriers to adoption.[12, 13] We have recently shown that POCT for respiratory viruses can increase swabbing rates of virological surveillance in primary care.[14] POCT can be used to estimate influenza vaccine effectiveness and improves antimicrobial stewardship within primary care, allowing GPs to make an early and accurate diagnosis.[15]

The primary aim of this study is to provide more contemporary data about the clinical presentation and disease burden of virologically proven RSV. However, in addition, we plan that this study will provide data on other viruses for which vaccination or other treatments might be introduced in future. It will also make the RSC ready for post-marketing vaccination benefit-risk studies of the RSV vaccine once introduced.

There will be three studies, the principal study is the Intensive Surveillance study. We will recruit practices that will capture higher-quality data about the presentation of people with ARI. This will be the main focus of our work. The learning from this study will enable these practices and the network to transition to conducting high-quality post-marketing surveillance of vaccine benefit-risk for RSV.

We will additionally update the cohort studies being carried out across the wider RSC cohort. This will provide further years of data in the post-pandemic / COVID-19 endemic period. The second study will extend our understanding of the epidemiology of RSV, and the third will describe the severe outcomes of RSV. We will include the most recent data since 1st September 2017 to conduct our initial analysis. However, we plan to report data from the post-pandemic / COVID-19 endemic period starting September 2022.

Research aims

Study 1a: Intensive surveillance from a small sample of research-ready practices (n=21)

This study is the principal area of interest.

Aim: Describe the incidence of RSV (identified as a POCT-confirmed RSV case) in terms of demographic and clinical characteristics.

Objective:

1) *To record more details about the clinical presentation of ARI, and to provide more data about the virology of these presentations, using both POCT (for RSV, SARS-CoV-2 and Influenza viruses) and reference laboratory virology (for enterovirus, rhinivirus, adenovirus and hMPV in addition to RSV, SARS-CoV-2 and Influenza). We will ask clinicians to code relevant symptoms from the NICE guidelines on the diagnosis of ARI, e.g. fever, cough, sore throat etc.*
2) *The objective would be to estimate medical burden of disease, health care resource use and costs associated with a positive POCT RSV swab.*
3) *To report the sociodemographic and clinical risk factors for an RSV-related infection and RSV-related adverse outcomes.*
4) *To describe the disease burden of RSV.*
5) *To improve the uptake of sampling by exploring the facilitators and barriers to incorporating POCT into clinical workflow, and systematically recording the clinical features associated with respiratory illnesses related to RSV (with sub-analysis on SARS-CoV-2 and Influenza), their differential diagnoses, and their management.*
6) *To compare the reliability of molecular POCT with reference laboratory tests for RSV, (with sub-analysis on SARS-CoV-2 and Influenza), to assess its suitability for use in post-marketing surveillance.*
7) *Demonstrating data quality at the end of the data collection year in preparation for post-marketing surveillance.*
8) *To determine the scale and cost of continuing this study in future during the post-marketing surveillance seasons.*

Study 1b: Intensive surveillance cohort – VE of the updated COVID-19 booster vaccines

Aim: Conduct a vaccine effectiveness (VE) analysis of the COVID-19 booster vaccines for COVID-19 related infection and COVID-19 related severe outcomes.

Objectives:

1) *Describe the sociodemographic and clinical risk factors for individuals with COVID-19 related infection and COVID-19 related severe outcomes.*
2) *Conduct a VE of the COVID-19 booster vaccines for COVID-19 related infection and COVID-19 related severe outcomes. COVID-19 boosters are rolled out in individuals who are older and or with certain pre-existing conditions.*

Study 2: Epidemiology of RSV from our virology sampling practices

Aim: Describe demographic and clinical characteristics of the RSV incidence and co-infection (identified as a laboratory-confirmed RSV case).

Objectives:

1) *To describe the sociodemographic and clinical risk factors for an RSV-related infection and RSV-related severe outcomes?*
2) *To report the clinical presentation (including URTI, LRTI, ILI, and exacerbation of chronic disease) among individuals with RSV-related infection?*
3) *To identify the sociodemographic and clinical risk factors for co-infections related to an RSV infection.*
4) *To conduct a VE analysis of the RSV vaccines for RSV-related infection and RSV-related severe outcomes.*

Study 3: Severe outcomes from RSV, RSC sentinel network study

Aim: Describe the uptake of RSV treatments and vaccinations (identified using the diagnostic codes).

Objective:

1) *To describe severe RSV-related outcomes across the RSC.*
2) *To report the uptake of treatments for respiratory infection including RSV and distribution by socio-demographic and clinical characteristics.*
3) *To conduct a VE analysis of the RSV vaccines for RSV-related infection and RSV-related severe outcomes.*
4) *Define and estimate the burden of disease, estimating health care resource use and costs associated with RSV (using Primary care data and Secondary care data).*
5) *Define and estimate the burden of disease, estimating health care resource use and costs associated with RSV (using England wide incidence of RSV cases extrapolated from incidence of RSV cases from Study 1a and Study 2.*

Cohorts

To conduct the prospective observational study of confirmed RSV cases, we will create three cohorts described below (and shown in Figure 3):

1) **Intensive surveillance cohort.** This cohort will be recruited from our virology sampling practice, and will comprise up to 21 practices (three per region, recruited from the virology swabbing practices within the Oxford RCGP RSC network) who will be undertaking intensive respiratory surveillance including virology testing with POCT (for RSV, SARS-CoV-2 and Influenza). Primary healthcare data of these individuals will be linked with secondary care data to create one dataset called the *intensive surveillance cohort.* To provide details of clinical presentation, and illness duration and understand how to run POCT at scale for the possible post-marketing study +/- can be ready to collect AEI data. We would look for practices to have sessions that do detailed assessments of 4 to 6 ARI on at least 3 days per week.
2) **Virology sampling cohort.** This cohort will be drawn from our virology sampling practices without practices participating in the *intensive surveillance cohort*. This cohort will comprise individuals who have had a virology sample taken for reference laboratory testing, which is either positive for RSV infection or other respiratory viruses (i.e. coinfections) or reported as no virus detected. Primary healthcare data of these individuals will be linked with secondary care data to create one dataset the *Virology sampling cohort.*
3) **RSC sentinel cohort.** This cohort will comprise all the individuals registered with any of our general practices in the Oxford RCGP RSC network i.e. RSC. The primary healthcare data of individuals in the RSC will also be linked with the secondary care dataset to create the *RSC sentinel cohort*.

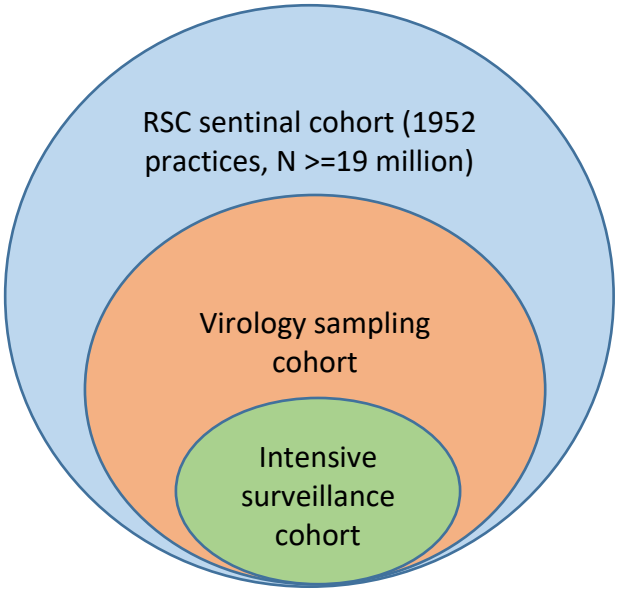

Figure 3. Venn-diagram representations of the study cohorts

Study designs and outcomes

Study 1a: Intensive surveillance cohort – Surveillance of RSV infection using POCT

This is the main area of effort, the study proposed will extend our contemporary understanding of RSV infection, as well as prepare the RSC to conduct post-marketing surveillance.

Introduction to Study 1a

Presentations with acute respiratory infection (ARI) including RSV:
People presenting with ARI, currently have high-quality data recorded and virology sampling is offered as part of the usual RSC practice in virology sampling general practices. We ask HCPs consulting ARI patients to record what on the balance of probabilities; the clinician thinks is the most specific ARI diagnosis. This should be recorded in the patient's record as a "problem" following the standard RSC process (Figure 4).

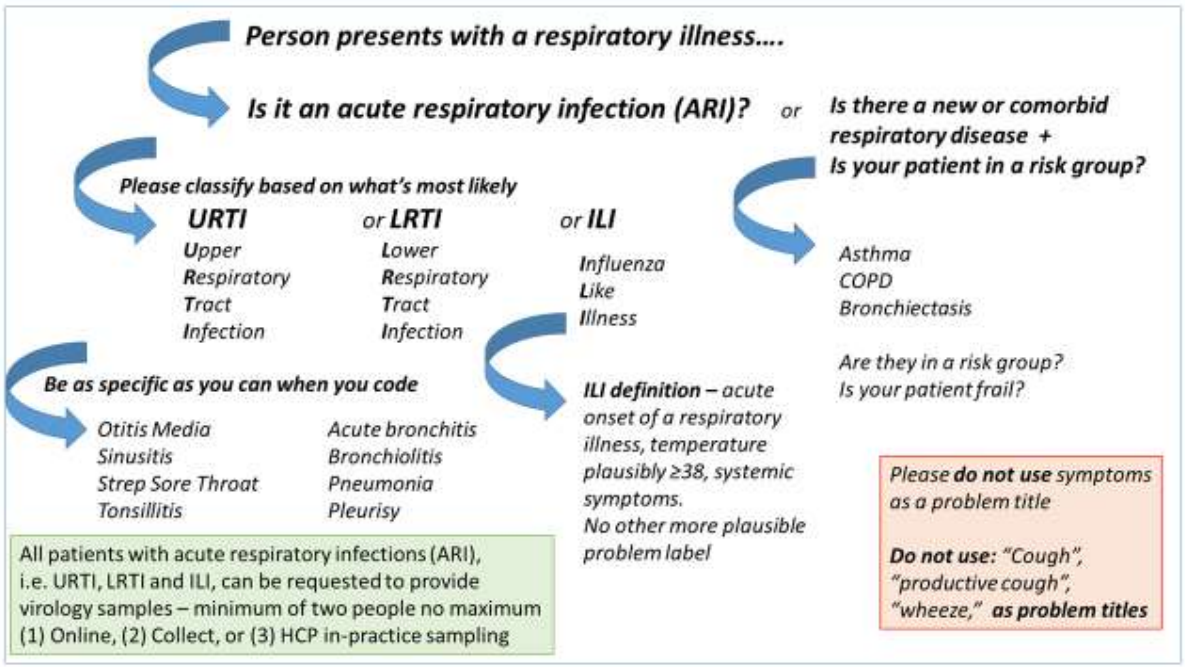

Figure 4. Research and Surveillance Centre (RSC) process for recording acute respiratory illness diagnoses

We also currently ask that as much relevant data should be coded as possible. Important information for the RSC includes (1) The patient's temperature level or if a fever is reported, (2) Presence of cough, (3) Myalgia, (4) Sore throat, if purulent and if any cervical lymphadenopathy. As described above, current surveillance also includes a request to collect a virology swab, which is sent to the UKHSA Reference Virology Laboratory at Colindale. This standard surveillance will continue for all ages attending with ARI. The recording of these elements is particularly important in this study as they are components of the risk prediction scores we are looking to evaluate as part of this study.

Design

For study 1a, we will recruit 21 practices from the virology swabbing practices in the RSC, with at least 2 practices in each of the seven health regions in England.

Practices in this POCT cohort will be asked to swab a total of 3,600 patients suspected of having respiratory virus infection during the 2023-24 winter season. This equates to 6 swabs per practice per week between September 2023 and March 2024.

We will conduct a prospective matched test-negative case-control study. The cases are defined as individuals with a positive POCT RSV swab, and the controls are selected among those with a negative POCT RSV swab including both already recorded RSV.

- Cases will have positive RSV swabs since 1st September 2023, and controls will have negative swabs.
- Matching will be done by, age-band, region and if feasible by GP practice.
- Odds ratio for all the sociodemographic and clinical factors for RSV related infection will be computed.

Period of observation:

- Starting date for POCT swabbing will be between 1st Sept 2023 to 31st March 2024, with the aim of taking in excess of 3,600 swabs in eligible patients.
- All events and non-events between these dates will be included for that season.

Training:

- **Enhanced surveillance to run in a pilot group of 21 general practices:**
    - Practices who join the enhanced surveillance pilot will be advised to manage and treat patients according to their usual clinical practice.
    - We will recruit 21 sentinel surveillance practices who are actively involved in virology sampling, and with previous experience of using POCT or are willing to consider its use in clinical workflow.
    - We will be looking for practices with either a high proportion of young people or larger practices that sample at least 20 children and young adults per week. We will ask practices to create 2 to 6 slots per day, or at least three days per week.
- **Enhanced surveillance practice training:**
    - Our surveillance training for the 21 study practices will be in two parts. Firstly, we will reinforce our standard approach to respiratory surveillance – coding of the "problem" (Figure 4), and key symptoms and offering a virology swab. Feedback from practices is that initial sampling does not change clinical

management, but that if the patient returns positive, or negative test results are helpful in patient management.

- Secondly, we will train the practice in the new additional elements that make up enhanced surveillance. These are to code a swab for POCT. We suggest that the swabs are offered in sequence – (1) Sentinel virology, and (2) POCT.
- We will discuss the incorporation of microbiology and POCT into clinical workflow. We have seen three models for including POCT in clinical workflow: (1) General practitioner (GP) run and led; (2) GP assisted by a health care assistant (HCA); or (3) Triage nurse or other health care professional (HCP) led services where testing is incorporated into the practice triage process.
- Our preferred approach is that practices create slots into which people presenting with ARI of recent onset can be booked. A trained member of staff or clinician will then systematically record the data required and conduct the sampling.

- **Timing of the availability of test results:**
  - Part of the workflow within the practice will include the management of results. POCT results will be available in 20 to 30 minutes and will need to be fed back to the managing clinician, in the practice. Practices may decide to let the patient go home while testing is done and phone with the result and send any prescription electronically. This result be recorded in the computerised medical record, we recommend including the concept clinical term for POCT (Clinical finding, SNOMED CT identifier (SCTID) 404684003).
  - Though the AegisPOCTM application will give the surveillance team a count of test results and results by practice so that we can check test results are recorded.
- **How results are linked to the sentinel network database:**
  - We will install a software interface, AegisPOC™ in the participated practices. AegisPOC™ will automatically provide a real-time update on sampling and results from each of the study practices. AegisPOC™ will provide information from the POCT machines directly back to Oxford-RCGP RSC, about the number of tests and results, but does not share any personal data. AegisPOC™ will allow real-time monitoring of swabbing rates and swabbing positivity rates within study practices and allow practices to be provided more training and help if sampling rates are low, or to be resupplied if rates are high. Whilst we will have the AegisPOC™ link we will still need practices to code results as in the section above. We will record differences in notification times between clinical, POCT and reference laboratory diagnoses.
- **Special, longer consultations should be created for enhanced respiratory surveillance:**
  - Each person presenting with an ARI will be offered an opportunity to have a

point of care test, up to the number of appointments a practice can offer that day by the participating practice. An updated Patient Information Sheet explaining POCT testing to patients will be provided. We recommend allowing 30 minutes for the consultation, or initial assessment and sampling with HCA running of the POCT test followed by a follow-up clinical review (20 minutes to be allowed for test running and recording the result).

- **Summary of the data to be recorded in an enhanced respiratory surveillance attendance. At the consultation, each person would have the following data recorded:**
    - ARI or Scarlet Fever diagnosis. The ARI diagnosis would be the most specific possible (Figure 4).
    - We will ask clinicians to code relevant symptoms from the NICE guidelines on diagnosis of ARI, e.g. fever, cough, sore throat etc..
    - An example consultation recording for acute tonsillitis (from a dummy patient's record) is shown in Figure 5).

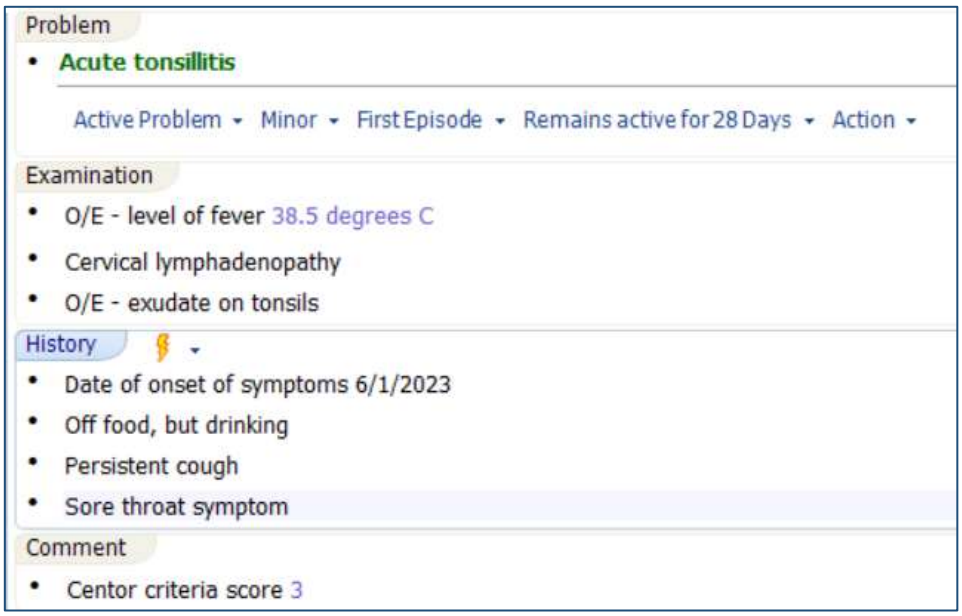

Figure 5. Example of minimum coded dataset required to describe the clinical findings in the EMIS computerised medical record (CMR) system

Outcomes

- Primary Outcome for Study 1a, objective 1:
    - We will set up enhanced surveillance clinics for respiratory illness where a trained nurse or healthcare assistant will be available for 3-5 hours sessions per week to assess patients with ARI using a standard method. More details are given in the training subsection of the design section.
    - In addition to the standard RSC ARI surveillance, practices participating in the enhanced surveillance will be asked to record components of the NICE

recommendation for the assessment of ARI in primary care.

- In addition to the standardised recording of these symptoms for all the eligible patients, we will also request for additional samples, including peripheral saturation test and POCT. Our experience of other POCT studies carried out in parallel with sentinel sampling is that patients are willing to give POCT and sentinel network samples. Additionally, feedback from our sentinel practices and our patient group is that the widespread sampling across the COVID-19 pandemic has resulted in far greater familiarity with and acceptance of sampling.

- Primary Outcome for Study 1a, objective 2:
  Burden of disease will include receipt of health care visits, antivirals, visits to the GP, antimicrobial therapy and virology result as an outcome (test positive or negative). The plan is to include the following costs:
  - Primary care costs: We will follow the guidelines reported by the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2021 compendium to calculate unit costs for contacts with healthcare professionals in primary care. The unit costs associated with categories of primary care use will thus be determined based on staff salaries, employer costs, capital/revenue overhead, number of patient contacts, by the type of consultation, for example, face to face vs online consultation, and by the primary care professional with whom the patient had contact, for example, the GP, nurse, other health care professional or administrative staff.
  - Prescription costs: Based on price of drug/appliance, informed by Prescription Cost Analysis database.
  - Medical tests costs: Secondary sources reported on NHS webpages.
  - Unit costs determined by type of consultation and primary care professional.
  - Secondary care costs: The use of secondary health care services will include attendances, and day cases and inpatient spell. To recover the cost of hospital admission, we will use the HRG4+2022/2003 Reference Cost Grouper, a software developed by NHS to calculate the cost of each hospital admission, hospital referrals and A&E visit. All costs will be expressed in pounds sterling and valued at 2022 prices with unit costs that are estimated at earlier price dates inflated to 2023 prices using the NHS Hospital and Community Pay and Prices Index.
  - Match HRG codes to costs in 2022/2023 Reference Costs Main Schedules, based on diagnostic/procedure codes, specialty, length of stay, type of admission, type and number of procedures.

  Any costs associated to secondary care will not be included in the interim analysis (to be delivered in March 2024) due to the time it takes for us to get the permission to access the data.

- Primary Outcome for Study 1a, objective 3:
    - Main outcome is describing factors associated with RSV infection, and clinical features on presentation ascertained from testing done with POCT.

- Primary Outcome for Study 1a, objective 4:
    - Burden of disease will include receipt of health care visits, antivirals, visits to the GP, antimicrobial therapy and virology result as an outcome (test positive or negative). The plan is to include primary care costs, prescription costs, medical tests costs, unit costs determined by the type of consultation and primary care professional and secondary care costs.
- Primary Outcome for Study 1a, objective 5:
    - We will assess where the equipment is placed and stored, who has access to this equipment and who uses and maintains the equipment. The testing location is important for the avoidance of transmission of respiratory infections to other potentially vulnerable staff and patients and these considerations will be explored to understand best practices for the pilot phase. We will also look at decisions made within teams about who receives POCT training, who will use the POCT with patients and who will make management decisions from POCT results, and how the test's diagnostic accuracy influences clinical decision-making. We will also explore differences in the testing rates between practices and assess factors influencing this, both environmental and in decisions to test made by primary care teams.
    - We will undertake ethnographic observations in a sub-set of 3-5 study sites, selecting those with diverse characteristics where possible and those who differ in how they intend to implement the POCT to observe where and how POCT equipment is incorporated into practice. A researcher will take opportunities to have informal discussions with health professionals about decisions made and any subsequent changes to workflows.
    - We will also conduct semi-structured interviews with clinicians and primary care staff (e.g., practice managers) to understand the decisions made about how to implement and use the POCT provided and any impact on other parts of the system. We will conduct approximately 4 interviews per study site seeking to gain insights from a variety of health professionals who played different roles in implementation, giving a total of approximately 28 interviews. Interviews will be informed by existing evidence and relevant theories from behaviour and implementation science, including the Behaviour Change Wheel and NASSS framework [16-18]. Data will be analysed using framework analysis [19].
- Primary Outcome for Study 1a, objective 6:
    - We will quality assure the POCT process by leveraging our long-standing RCGP-

UKHSA relationship and our existing virological surveillance protocol. We will utilise a dual testing model to achieve this, whereby a certain percentage of patients will be randomly selected to provide two samples: one for immediate assessment via POCT, the other for onward testing via established PCR-based testing pathways utilising UKHSA reference laboratories. This will help us to validate POCT outputs, monitor the extent to which results match and understand where there is disagreement. The use of vendor-neutral IT systems will support the generic future scalability of primary care POCT. This development of an automated pathway for POCT surveillance notifications would reduce barriers to implementation by removing the staff time burden that manual reporting would incur.

- We will compare the following metrics collected from POCT practices to virology practices: Number of swabs per week, positivity rates of RSV infection, appointment times, follow-up appointments, follow-up treatments, prescribing rates for individuals with confirmed RSV infection, quality of life, etc.

- Primary Outcome for Study 1a, objective 7:
  - We will provide study sites with training as specified above including POCT, guidelines, treatment, and options for incorporating into workflow. Based on the outputs, we will offer automated prompts embedded in the computerised medical record (CMR) system to flag patients in risk groups to prioritise for testing. We will also offer training in messaging patients in risk groups about POCT at their practice if they catch an ARI. The tools available include customised prompts from Ardens Healthcare Informatics and the EMIS Recruit tool. We will provide dashboards developed in-house from those in current use in our network, and also provide weekly reports to provide feedback to study sites.
  - To measure the quality of diagnostic data for respiratory illness related to RSV, we will adapt a method which was previously developed to measure data quality in primary care (for COPD). The steps would be as follows:
    - research the expected prevalence of the diagnosis and define audit criteria;
    - find out how the diagnosis might be coded--look at the terminology and the codes presented by the computer interface;
    - examine the characteristics of the practice population;
    - calculate the prevalence and infer its reliability;
    - investigate the completeness;
    - accuracy;
    - currency and consistency; and
    - calculate sensitivity and positive predictive value of the data.

- Primary Outcome for Study 1a, objective 8:
    - We will estimate the economic consequences associated with the targeted use of POCT. We will also estimate how this analysis can be further extended to three years during the post-marketing surveillance period.
    - To estimate the economic consequences associated with the targeted use of POCT, we will conduct an individual-level observational study. We will measure and value healthcare resource use associated with RSV infections. This will encompass the resource and cost implications associated with the identification of eligible patients, training staff to perform POCT, devices, equipment maintenance, follow-on management, and quality assurance.
    - To estimate how this analysis can be further extended to three years during the post-marketing surveillance period, we will develop an economic impact tool associated with the implementation of POCT for RSV infections in primary care. The methods adopted will follow the guidelines recommended by the National Institute for Health and Care Excellence (NICE) 'Assessing Resource Impact Process Manual' (NICE, 2017). The aim will be to provide estimates of the expected resource and economic cost impacts of the national implementation of POCT to allow effective financial planning.

Study 1b: Intensive surveillance cohort – VE of the updated COVID-19 booster vaccines

To conduct a VE analysis of the COVID-19 booster vaccines for COVID-19 related infection and COVID-19 related severe outcomes in the intensive surveillance cohort. We will also extend our analysis and target individuals with COVID-19 symptoms. including individuals with respiratory illness. COVID-19 boosters are rolled out in individuals who are older and or with certain pre-existing conditions.

Design

In addition to testing for RSV, we will also test for a COVID-19 infection in this cohort. Our approach to testing is described above in Study 1a. We will conduct a prospective matched test-negative case-control (TNCC) study. The cases are defined as individuals with a positive POCT COVID-19 swab, and the controls are selected among those with a negative POCT COVID-19 swab (either no infection or positive for other viruses but not COVID-19).

- Cases will have positive COVID-19 swabs since 1st September 2023, and controls will have negative swabs.
- Matching will be done by, age-band, region and if feasible by GP practice.
- Odds ratio for all the sociodemographic and clinical factors for RSV related infection will be computed.

Period of observation:

- Starting date for POCT swabbing will be between 1st Sept 2023 to 31st March 2024, with the aim of taking in excess of 3,600 swabs in eligible patients.
- All events and non-events between these dates will be included for that season.

Population

Our population of interest will be individuals aged less than 5 years, 5-17 years, 18-65 years and 65+ years.

Outcomes

The main outcome is as follows:

- To describe the sociodemographic and clinical risk factors for an COVID-19 related infection and COVID-19 related adverse outcomes?
- To report the clinical presentation (including URTI, LRTI, ILI, and exacerbation of chronic disease) among individuals with RSV-related infection?
- To evaluate the VE of updated COVID-19 booster vaccines in preventing COVID-19 infection and COVID-19 related severe outcomes using a TNCC design. If the numbers allow, we will also report the VE in subgroups of interest, such as persons with certain underlying conditions including those with chronic heart or lung disease and immunocompromising conditions.

Study 2: Virology sampling cohort – test negative case-control study

This is an extension of the retrospective study currently being conducted in the RSC virology cohort. We will include the most recent data since 1st September 2017 to conduct our initial analysis. However, we plan to report data from the post-pandemic / COVID-19 endemic period starting September 2022.

Design

We will conduct a prospective matched test-negative case-control design study. The cases are defined as individuals with a positive RSV swab, and the controls are selected among those with a negative RSV swab (either no infection or positive for other viruses but not RSV)

- Cases will have positive virology samples since 1st September 2023, and controls will have negative swabs (subject to confirmation of availability).
- We will include the most recent data since 1st September 2017 to conduct our initial analysis. However, we plan to report data from the post-pandemic / COVID-19 endemic period starting September 2022.
- Matching will be done by, age-band, region and if feasible by GP practice.
- We will also match on time either using the year of swab or by dividing the time into periods of pre-COVID-19, COVID-19 and post-COVID-19 vaccination.
- Predictors of RSV incidence will be ascertained retrospectively from the date of the swab.
- We will subdivide cases, where recorded into RSVA and RSVB subtypes, to conduct a subgroup analysis.
- Period of observation: All events and non-events between these dates will be included for that season.
- Sentinel network virology swabs: UKHSA Reference Laboratory virology results are generally back with practices in 5-7 days. These samples are currently posted by practices after in-practice sampling. Some patients do self-sampling, typically where patients' self-test results arrive 1-2 days later, this is because patients have to be posted a self-test kit. UKHSA virology includes the following viruses:
    - COVID-19 (strictly SARS-CoV2),
    - Influenza A divided into HIN1 And H3N2 subtypes, Influenza B,
    - Respiratory syncytial virus (RSV) reported as RSVA and RSVB subtypes
    - Human Metapneumovirus (hMPV)
    - Other coronaviruses
    - Adenovirus
    - Rhinovirus
    - Enterovirus
- How results are linked to the sentinel network database: There is already an established route for the pseudonymisation and linkage of test results into the sentinel network database.

- Carrying out a UKHSA virology reference lab nasopharyngeal swab. Please code in the usual way. A swab from nasopharynx taken for virology ("viral swab"… finds the correct clinical term)

Outcomes

- Primary outcome for study 2, objective 1:
    - Main outcome is describing factors associated with RSV infection ascertained by laboratory confirmation.
- Primary outcome for study 2, objective 2:
    - We will report the proportion of RSV by the syndromic presentation of ILI, upper and lower respiratory infections (URTI and LRTI respectively); or if an exacerbation of chronic respiratory disease (e.g. asthma and chronic pulmonary disease (COPD)). This will also be reported by age band and time period. We will additionally report the virology finding in children under 5 years old presenting with acute bronchitis and bronchiolitis.
- Primary outcome for study 2, objective 3:
    - We will report, descriptively, where there is co-infection reported. This may be viral or bacterial, and a description of the age band, sociodemographic and clinical presentation, and outcomes.
- Primary outcome for study 2, objective 4:
    - To evaluate the VE of RSV vaccines in preventing RSV infection and RSV related severe outcomes using a TNCC design. If the numbers allow, we will also report the VE in subgroups of interest, such as persons with certain underlying conditions including those with chronic heart or lung disease and immunocompromising conditions.

Study 3: RSC sentinal cohort – Describe the uptake of RSV treatments including vaccination if available, and severe outcomes.

This is an extension of the retrospective study currently being conducted in the RSC virology cohort. We will include the most recent RSV diagnostic codes since 1st September 2017 to conduct our initial analysis. However, we plan to report data from the post-pandemic / COVID-19 endemic period starting September 2022.

Design

- We will describe the sociodemographic and clinical factors of individuals who had a confirmed RSV infection and the subsequent treatment they receive.
- A prospective cohort study of the clinical presentation of patients with RSV infection as ascertained by primary care diagnostic codes (see Appendix Table 2 – please suggest additional symptoms or disease codes)
- A prospective cohort study of patients with evidence of RSV infection as ascertained by secondary care codes (see Appendix list of ICD-10 codes – please suggest additional disease codes)
- Registered with primary care (with linked individual-level data) since 1st September 2023 (this is subject to change).
- The burden of disease will be quantified within this period of follow-up for each season. We will consider the following variables to calculate the burden of disease (health service resource use and costs) associated with,
  primary care:
  - number of GP, practice nurse, and other healthcare professional consultations
  - number of prescriptions
  - number of tests in primary care

  secondary care:
  - number of hospital outpatient attendances,
  - number of hospital admissions
  - length of stay
  - treatments and procedures and in-hospital

Follow-up:

- We will include the most recent RSV diagnostic codes since 1st September 2023.
- We will include the most recent RSV diagnostic codes since 1st September 2017 to conduct our initial analysis.

Population

The RSV sentinel cohort will serve as the basis for this study. Cases are defined by primary or secondary care RSV diagnostic codes or by a combination of a respiratory diagnosis and positive virology or we may find a recording of treatment. We will also identify people with severe RSV related outcomes from primary care and secondary care data and describe their

sociodemographic and clinical characteristics. To establish a control group, we will select true a propensity score matching, individuals with similar sociodemographic and clinical characteristics but without a suspected RSV infection. The control group will provide a comparison to understand the differences in outcomes between those with RSV and those without the infection.

RSV infection will be ascertained by:

- Primary care diagnostic codes (see Appendix Table 2 – initial list of symptoms or disease codes)
- Secondary care codes (see Appendix Table 3 – initial list of ICD-10 diagnostic codes and Appendix Table 4 – initial list of OPCS-4 codes for details).

Outcomes

- Primary outcome for study 3, objective 1:
    - Main outcome is describing factors associated with RSV infection ascertained by laboratory confirmation.
- Primary Outcome for study 3, objective 2:
  The main outcome is the receipt of vaccination or treatment with antimicrobials and report the uptake of treatments for RSV infection using:
    - GP follow up attendances, prescription of antimicrobials, steroids, inhalers and sick notes.
    - RSV hospitalisation is defined as admission with an ICD-10 code for RSV related illness, or with a respiratory illness and a positive test or treatment for RSV in any position of the episode; or this event reported in the primary care record.
    - RSV ICU admission is defined as admission to ICU unit during the RSV associated hospital visit.
    - Occurance of co-infections including Influenza
    - Calculate and compare vaccine effectiveness from the data collected from two different cohorts i.e. POCT cohort and virology cohort.
- Primary outcome for study 3, objective 3:
    - To evaluate the VE of RSV vaccines in preventing RSV infection and RSV related severe outcomes using a TNCC design. If the numbers allow, we will also report the VE in subgroups of interest, such as persons with certain underlying conditions including those with chronic heart or lung disease and immunocompromising conditions.
- Primary Outcome for study 3, objective 4 and 5:
  Burden of disease will include receipt of health care visits, antivirals, visits to the GP, antimicrobial therapy and virology result as an outcome (test positive or negative). The plan is to include the following costs:
    - Primary care costs: We will follow the guidelines reported by the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2021 compendium to calculate unit costs for contacts with healthcare professionals

in primary care. The unit costs associated with categories of primary care use will thus be determined based on staff salaries, employer costs, capital/revenue overhead, number of patient contacts, by the type of consultation, for example, face to face vs online consultation, and by the primary care professional with whom the patient had contact, for example, the GP, nurse, other health care professional or administrative staff.

- Prescription costs: Based on price of drug/appliance, informed by Prescription Cost Analysis database.
- Medical tests costs: Secondary sources reported on NHS webpages.
- Unit costs determined by type of consultation and primary care professional.
- Secondary care costs: The use of secondary health care services will include attendances, and day cases and inpatient spell. To recover the cost of hospital admission, we will use the HRG4+2022-23 Reference Cost Grouper, a software developed by NHS to calculate the cost of each hospital admission, hospital referrals and A&E visit. All costs will be expressed in pounds sterling and valued at 2023 prices with unit costs that are estimated at earlier price dates inflated to 2023 prices using the NHS Hospital and Community Pay and Prices Index.
- Match HRG codes to costs in 2022-23 Reference Costs Main Schedules, based on diagnostic/procedure codes, specialty, length of stay, type of admission, type and number of procedures.

Covariates

Our covariates will include:

- Age: will be analysed both as a continuous variable as well as a categorical variable (provided there are sufficient numbers in the following categories): 0-6 months, 6-12 months, 12-24 months, 24-36 months, 36-48 months, 48 months-59 months, 5-18, 18-49, 50-64, 65-79, 80+. Please note this is subject to change and will depend upon a number of positive events in each category.
- Ethnicity: Asian, Black, Mixed, Others and White, Missing Catergory
- Sex: Male, Female
- BMI: <18.5, 18.5-24.9, 25.0-29.9, 30.0-39.9, 40.0+
- Deprivation quintile with range 1-5, with 1 being most deprived and 5 being least deprived
- Urban/rural classification of residence
- NHS appropriate geography (e.g. NHS Regions)
- Number of clinical conditions classified using Cambridge multimorbidity score (CMMS) quartiles
- Presence of individual conditions including cancer, immunosuppression, autoimmune disease, chronic heart diseases, chronic lung diseases, CKD, diabetes

and other relevant conditions suggested by the team of clinicians and epidemiologists.
- Influenza, COVID-19 and Pneumococcus vaccine exposure
- Co-infections (list of relevant infections/pathogens to be defined by a team of clinicians/epidemiologists) including evidence of COVID-19 (either from diagnosis in primary care records or from positive PCR tests) and Influenza infections.
- Data of registration with the practice
- Household number

Data Sources

The Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) is the national primary care sentinel network. The RSC database covers more than 19 million (around 33% of the English population) individuals and has a near real-time feed of primary care data and is nationally representative, covering around 32% of the English population (N>19 million). Our data is representative of the national population and links together individual patient-level primary care data with the national immunisation management service for vaccine uptake, Hospital Episode Statistics (HES) for hospitalisation and intensive care unit admissions, and Office for National Statistics (ONS) data for certificated cause of death. This linkage is done using an NHS number, which is a unique identifier assigned to every individual in England. [20] This linked dataset then sits in the RSC's secure environment. The primary care RSC data are recorded using SNOMED clinical terms (CT) and secondary care data are recorded using the International Classification of Disease version 10 (ICD-10) for disease, and the Office of Population Census and Surveys version 4 (OPCS) codes for procedures, More details regarding the coding systems and data collection is in the data sources section.

Data for the **intensive surveillance cohort** will be collected using the results of the intensive standardised clinical assessment and POCT machines in the 21 study practices. This POCT data will contain information on a panel of viruses including RSV, influenza and COVID-19.

Data for the **virology sampling cohort** is collected using reports from the UKHSA reference laboratories. This data contains information on a wide variety of viruses including influenza, RSV and COVID-19 samples taken by virology swabbing practices in the English primary care sentinel surveillance network and included virus type and sub-typing.

Primary care data are recorded using the SNOMED clinical terminology and the secondary care data are linked using the ICD-10 coding systems. We will link individual-level primary care data in the ORCHID database to secondary care and mortality data to create the **RSC sentinal cohort.** Routine clinical data from individual patient records at the practice level is

transformed into an accessible repository of data for health research – the Oxford-RCGP RSC database. It includes data from three sources:

1) Primary care computerised medical record (CMR) data
2) Surveillance data about infectious diseases collected by UKHSA
3) Data collections supplied by NHS Digital, and linked pseudonymised at the individual record level:
    - Hospital Episode Statistics (HES) of the same scope/granularity as SUS
    - Office of National Statistics (ONS) Mortality

Statistical Analysis

Study 1a:

- Our data analysis will be descriptive and enable us to understand the potential to conduct post-marketing surveillance in the future years. We will report the number and proportion of:
    - People with an ARI or RSV and have standardised symptom recorded.
    - Cases of ARI or RSV in people attending who have done the POCT tests.
- Descriptive analyses will be conducted to show the demographics and clinical factors among those with and without RSV infection in the intensive surveillance cohort.
- Cumulative health care resource use and health care resource costs covering primary and secondary health care services (for the final analysis) for the cohorts will be calculated for each patient by attaching unit costs to each service encounter. This will enable us to present initial estimates of the burden of health care utilization and cost across each group in terms of means, SD, medians, IQR, minimum and maximum. We will examine the distribution of the total health care costs to identify outliers.
- We anticipate applying a generalised linear model (GLM) with total health care cost as the dependent variable. The specific distributional form and link function for the GLM will be informed by the Akaike Information Criterion (AIC) and other diagnostic tests.
- We will also report outcomes:
    - Antibiotic prescriptions
    - Re-attendance in primary care for a respiratory illness
    - Hospitalisation
    - Death
    - The data analysis will enable to develop a plan for respiratory surveillance that includes RSV and other pathogens of interest. It will inform how many practices might be need in the future winter to run effective post-marketing surveillance.
- Comparison of trends of factors, including the number of swabs per week, positivity rates of RSV infection, follow-up treatments, prescribing rates for individuals with confirmed RSV infection, etc., with virology sampling cohort.
- We aim to analyse results of dual testing by comparing the proportion of patients for whom a POCT swab with virology swab submitted to the national reference

laboratory. These outcomes in pilot practices will be compared to historical submissions from the same practices and contemporaneous submissions from non-pilot practices that are not part of the POCT practices. The results will be used to predict sample sizes available for respiratory disease surveillance and vaccine effectiveness monitoring with national roll-out of POCT in primary care.

Study 1b:

- Descriptive analyses will be conducted to show the demographics and clinical factors among those with and without COVID-19 infection in the intensive surveillance cohort.
    - We will also report on severe outcomes which include Hospitalisation and Death
- Comparison of trends of factors, including the number of swabs per week, positivity rates of COVID-19 infection, rates of severe COVID-19 outcomes, etc.
- We conduct a TNCC study design to analyse the VE of the COVID-19 booster vaccines for COVID-19 related infection and COVID-19 related severe outcomes.

Study 2:

- Descriptive analyses will be conducted to show the demographics and clinical factors among individuals in the virology cohort. We aim to estimate:
    - Proportion of patients presenting with ILI/ARI for whom a PCR sample is submitted to the UKHSA reference laboratory;
- Conditional logistic regression will be used to identify independent predictors of RSV incidence.
- Moreover, trends of incidence will be visualised using graphs.
- Descriptive analyses will be conducted to show the demographics and clinical factors among those with and without RSV infection.
    - We will also report on severe outcomes which include hospitalisation and death
- Comparison of trends of factors, including the number of swabs per week, positivity rates of RSV infection, rates of severe RSV outcomes, etc.
- We conduct a TNCC study design to analyse the VE of the RSV vaccines for RSV related infection and RSV related severe outcomes.

Study 3:

- Descriptive analyses will be conducted to show the demographics and clinical factors among those with and without vaccine and antimicrobial treatments.
- Moreover, trends of incidence will be visualised using graphs.
- Descriptive analyses will be conducted to show the demographics and clinical factors among those with and without RSV infection.
    - We will also report on severe outcomes which include hospitalisation and death

- Comparison of trends of factors, including the number of swabs per week, positivity rates of RSV infection, rates of severe RSV outcomes, etc.
- We conduct a TNCC study design to analyse the VE of the RSV vaccines for RSV related infection and RSV related severe outcomes.
- Cumulative health care resource use and health care resource costs covering primary and secondary health care services for the cohorts will be calculated for each patient by attaching unit costs to each service encounter. This will enable us to present initial estimates of the burden of health care utilization and cost across each group in terms of means, SD, medians, IQR, minimum and maximum. We will examine the distribution of the total health care costs to identify outliers.
- We anticipate applying a generalised linear model (GLM) with total health care cost as the dependent variable. The specific distributional form and link function for the GLM will be informed by the Akaike Information Criterion (AIC) and other diagnostic tests.
- We will also repeat the burden of disease estimates by extrapolating the number of RSV cases to England wide population using the incidence of RSV cases from Study 1 and Study 2 by adjusting for relevant covariates including age, sex and deprivation.

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Appendix

Table 2 – Example list of conditions

TADDS variable	Description
1055	LowerRespiratoryTractInfection-WRpt
1020	Influenza-likeIllness-WRpt
1007	UpperRespiratoryInfection-WRpt
.	Acute bronchitis and bronchiolitis
.	Acute bronchiolitis
.	Chronic respiratory disease
.	COPD
.	Exacerbation of COPD
.	Asthma
.	Exacerbation of Asthma
We will include common cold, acute laryngitis/ tracheitis, pneumonia/ pneumonitis, pleurisy and respiratory system disease, please refer to: https://www.rcgp.org.uk/clinical-and-research/our-programmes/research-and-surveillance-centre/public-health-data	

Taken from here: https://orchid.phc.ox.ac.uk/index.php/orchid-data/

Table 3 – Example list of ICD-10 codes

ICD-10 codes	Description
J12.1	RSV-Pneumonia
J20.5	RSV- acute bronchitis
J21.0	RSV- aute bronchiolitis
B97.4	RSV as the cause of disease classified to other chapters

Taken from here: https://pubmed.ncbi.nlm.nih.gov/34754948/

Table 4 – Example list of OPCS codes

OPCS codes	Description
X86.4	X86.4 Respiratory syncytial virus treatment and Hepatitis C treatment drugs Band 1
X86.5	X86.5 Respiratory syncytial virus prevention drugs Band 1

Refer to:
https://www.gov.uk/government/publications/respiratory-syncytial-virus-rsv-symptoms-transmission-prevention-treatment/respiratory-syncytial-virus-rsv-symptoms-transmission-prevention-treatment#:~:text=Palivizumab%2C%20a%20monclonal%20antibody%20therapy,at%20high%20risk%20of%20infection

HES codes all the following as discharge destinations;

19 = The usual place of residence, including no fixed abode
29 = Temporary place of residence when usually resident elsewhere, for example, hotels and residential educational establishments
30 = Repatriation from high security psychiatric hospital (from 1999-2000)
37 = Penal establishment - court (from 1999-2000)
38 = Penal establishment - police station (from 1999-2000)
39 = Penal establishment - court and police station excluded (from 1999-2000)
48 = High security psychiatric hospital, Scotland (from 1999-2000)
49 = NHS other hospital provider - high security psychiatric
50 = NHS other hospital provider - medium secure unit
51 = NHS other hospital provider - ward for general PATIENTS or the younger physically disabled
52 = NHS other hospital provider - ward for maternity PATIENTS or Neonates
53 = NHS other hospital provider - ward for PATIENTS who are mentally ill or have learning disabilities
54 = NHS run Care Home
65 = Local Authority residential accommodation i.e. where care is provided
66 = Local Authority foster care
79 = Not applicable - PATIENT died or still birth
84 = Non-NHS run hospital - medium secure unit
85 = Non-NHS (other than Local Authority) run Care Home
87 = Non-NHS run hospital
88 = Non-NHS (other than Local Authority) run Hospice
98 - Not applicable - Hospital Provider Spell not finished at episode end (i.e. not discharged) or current episode unfinished
99 - Not Known