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Estimating the burden of vaccine preventable lower respiratory tract disease in primary care, UK: protocol for a prospective surveillance study (AvonCAP GP2)

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Keywords

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Abstract (word count: max 250, current 250)

Background

The true burden of acute lower respiratory tract diseases (aLRTD; includes acute lower respiratory tract infection, acute exacerbation of pre-existing heart failure and chronic lung disease) among adults presenting to primary care, and the proportion that are potentially vaccine preventable, is unknown.

Aims

To describe aLRTD incidence in adults presenting to primary care; estimate proportions caused by RSV, SARS-CoV-2 and pneumococcus; and investigate disease burden from patient and NHS perspectives.

Design and Setting

Primary care prospective cohort study conducted in six representative General Practices (total ~83,000 registered adults) in Bristol, UK.

Methods

Adults (aged ≥18 years) registered at participating General Practices and presenting to primary care (in-hours or out-of-hours) or emergency department (if not admitted) with aLRTD will be eligible and identified by real-time primary care record searches. Researchers will screen electronic GP records, including free text, contact patients to assess eligibility, and offer enrolment in a surveillance study and an enhanced diagnostic study (urine, saliva and respiratory samples; physical examination; and symptom diaries). Data will be collected for all aLRTD episodes, with patients assigned to one of three arms: surveillance, embedded diagnostic, and descriptive dataset. Outcome measures will include clinical and pathogen defined aLRTD incidence rates, symptom severity and duration, NHS contacts and costs, health-related quality of life changes, and mortality (≤30 days post identification).

Conclusion

This comprehensive surveillance study of adults presenting to primary care with aLRTD, with embedded detailed data and sample collection, will provide an accurate assessment of aLRTD burden due to vaccine preventable infections.

How this fits in

There is a paucity of evidence, both in the UK and globally, regarding the true burden and aetiology of acute lower respiratory tract infection (aLRTI) among adults presenting to primary care. In this study, we will prospectively screen adults registered with one of six General Practices in Bristol, UK, and identify those with acute lower respiratory tract disease (including aLRTI and presumed non-infective exacerbations of chronic lung disease and heart failure). For eligible patients, data will be extracted from electronic GP records and, for a subset, samples and additional data will be collected, including examination findings, surveys and symptom diaries. Study findings will estimate the incidence and burden of aLRTI for adults presenting to primary care, and the proportion that could potentially be prevented by vaccines; data will be combined with a sister study of hospitalised adults to estimate the overall burden of aLRTI across primary and secondary care.

Introduction

Vaccines against respiratory pathogens *Streptococcus pneumoniae* (SP), Respiratory Syncytial Virus (RSV) and severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) are licensed in the UK. Traditionally, the burden of vaccine preventable illness has been estimated by studying the incidence of severe illness in secondary care.[1 2] While important in terms of morbidity and mortality, this underestimates the total disease and societal burden. This impacts calculations of vaccine cost-effectiveness since a high community incidence can offset the lower costs associated with less severe illness.

The healthcare cost of hospitalised community acquired pneumonia (CAP) across Europe and in the UK prior to the SARS-CoV-2 pandemic were estimated at £8.6 billion[3] and £731 million per annum, respectively.[4] The incidence of acute lower respiratory tract infections (aLRTIs) and CAP in Europe varies by country, age and gender; however, in all studies incidence increased markedly with age.[5-9] A large UK primary care study of adults aged ≥65 years reported annual incidences of CAP and aLRTI of 8/1000 and 123/1000 person years, respectively, though this study relied on retrospective review of coded data.[9]

The true burden and aetiology of aLRTIs within UK primary care is unknown[1 10] but is important to ascertain the potential benefit of vaccines to reduce disease burden for the patient (time off work and quality of life loss) [11], the NHS (healthcare utilisation costs and system capacity) and society (e.g. lost productivity costs) . Furthermore, vaccinating 'at-risk' cohorts, may help reduce antimicrobial resistance [12]. Partial burden estimates are available in the UK through: (i) routinely collected primary care data (but limited by incomplete and non-standardised coding, and lack of microbiological

data);[6 9] and (ii) bespoke prospective cohort studies (limited by recruitment selection bias and failure to collect data on patients not sampled).[13 14] A recent study investigating the appropriateness of antibiotic prescriptions in UK primary care found that 37% of antibiotics prescribed were not linked to a diagnostic code.[15]

Typically, people with aLRTI present to primary care with acute cough and symptoms/signs attributable to lower respiratory tract involvement, including sputum production, wheeze or shortness of breath. However, evidence suggests that exacerbations of heart failure (HF) and chronic lung diseases may be triggered by similar microbes in the absence of typical 'infection' symptoms. Here, we use the term 'acute lower respiratory tract disease' (aLRTD) to describe both aLRTI (e.g. pneumonia, acute bronchitis, infective exacerbation of chronic lung disease) and exacerbations of HF and chronic lung disease presumed to be 'non-infective'.

Aim

Describe the incidence and burden of aLRTD, in adults (≥18 years) presenting to primary care in Bristol, and estimate the proportion caused by vaccine-preventable infections, including SP, RSV and SARS-CoV-2.

Objectives

- Describe the demographic, clinical and microbiological characteristics for adults presenting to primary care with aLRTD.
- Investigate the natural history of aLRTD, including patient-reported symptom duration and severity; antibiotic/antiviral consumption; respiratory pathogen isolation; time off work, primary care consultations, hospital admission and quality of life for up to 12 months.
- Describe time trends in population-based incidence rates of aLRTD.
- Determine mortality rate at 30 days (and up to 12 months for those who have not recovered at 28 days) after primary care visit for aLRTD.
- Determine the pathogen distribution rates of RSV, SARS-CoV-2, and other viral pathogens among adults diagnosed with exacerbation of congestive heart failure, non-infective exacerbation of asthma and non-infective exacerbation of COPD.
- Estimate the financial costs of aLRTD from patient and NHS perspectives.
- Describe the proportion of presumed non-infective aLRTD diagnoses associated with respiratory pathogens.

Method

Study design and setting

This prospective cohort study will take place in Bristol, UK, from 14th February 2022 to 31st July 2024. Six General Practices (total ~83000 registered adult patients) serving populations with varying socio-demographics (deprived/affluent, urban/semi-urban, different ethnic groups) and covering a wide geographical area will be participating (see Supplementary File 1). Figure 1 shows the study summary.

Recruitment

To enable comprehensive surveillance, potential participants will be identified, screened, and invited to take part prospectively each day (Monday to Friday).

Eligibility criteria

Adults (aged ≥18y) registered at one of the six practices will be eligible if they present to the practice, out of hours (OOH) primary care (one provider in Bristol) or emergency department (ED, if not admitted to hospital) with an acute illness (onset or worsening of symptoms ≤28 days) and symptoms/signs consistent with a clinical aLRTD diagnosis. The full inclusion and exclusion criteria are shown in Box 1.

Optimising the use of diagnostic codes

In UK primary care, clinicians document consultations by using symptom or diagnostic codes and/or by entering 'free text' notes into the electronic GP records. Respiratory infections are generally poorly coded, with clinicians reluctant to use diagnostic codes (e.g. 'acute lower respiratory tract infections') and preferring to use symptom codes (e.g. 'cough') or to not provide a code, even when they suspect an infection.[16] To mitigate this, interventions (training, computer prompts) have been developed and implemented to optimise coding of aLRTD.

For adults with symptoms/clinical signs of respiratory infections and/or prescribed antibiotics, an electronic prompt will appear, asking whether the patient has a suspected aLRTD with onset of symptoms ≤8 days (Supplementary File 2). For those who select 'yes', a template will appear asking the clinician to select the relevant diagnostic code from a dropdown list and to rate the severity of the illness (mild/moderate/severe). The clinicians will be able to send a pre-prepared text message and/or briefly discuss the study with patients, recording their action in the template. Patients who

do not want to be contacted by the research team will be recorded by the clinician as having declined consent.

Identifying potential participants

Recognising that use of diagnostic aLRTD codes will be suboptimal, a search of the electronic GP records system has been developed to identify all adults with possible aLRTD, including those where a diagnostic code has not been used. The search identifies adults: (i) with a clinical diagnosis of aLRTD; (ii) with pre-existing asthma or COPD prescribed an antibiotic or oral steroid; (iii) with pre-existing heart failure prescribed a diuretic; or (iv) where respiratory symptoms (cough, shortness of breath, wheeze, chest pain) have been coded or an antibiotic used to treat aLRTI has been prescribed. The search will be run by the research team at least twice a day. Eligible participants presenting to OOH primary care or ED, will be identified through letters documented in their primary care records.

Screening

A researcher will manually review the electronic GP records of all potentially eligible participants, including free text, to assess eligibility against defined criteria (Box 1), and contact the patient to further assess eligibility and invite them to take part.

Inclusivity and consent

Online, phone, postal or face-to-face consent will be taken, depending on patient preference. Patients will be invited to consent to the surveillance arm only (i.e. electronic GP record data) or the embedded diagnostic arm (i.e. electronic GP record data plus samples/surveys/examination findings). To improve inclusivity, patients will be offered standard or 'Easy Read' versions of the information sheets and consent forms. Patients will be encouraged to watch two short films: a generic 'Why take part in research?' and a second explaining study participation specifics. For non-English speaking patients, study documents and short films have been translated into ten commonly spoken languages in Bristol. For patients who lack capacity to consent, we will endeavour to identify a consultee to determine the patient's willingness to take part and, where appropriate, obtain a consultee declaration.

Data collection

Data will be collected for all aLRTD episodes, with patients assigned to one of three study arms:

- a surveillance arm;
- an embedded diagnostic arm;
- and a descriptive dataset arm.

Surveillance arm

The index consultation date will be defined as the date the participant appears in the electronic GP record search (in-hours patients) and is assessed as eligible; or the attendance date (OOH and ED patients).

Information about socio-demographics, qualifying condition, severity of illness (mild/moderate/severe), smoking status, pregnancy status, vaccination history (SARS-CoV-2, influenza, pneumococcus) and long-term conditions will be collected (Table 1). Health utility data (hospital admission, ED attendances, outpatient appointments and primary care appointments) and final diagnosis will be collected for the 30-day period after the index consultation date.

Embedded diagnostic arm

A research visit will be conducted to collect: samples (nose/throat swab, saliva and urine samples); examination findings; surveys; and/or day one of a 28-day symptom diary (Table 1). Health related quality of life measures will also be assessed (EQ-5D-5L).

For the symptom diary, participants can choose to complete an online version, paper version or to receive daily phone calls from the research team. A validated measure will record presence and severity of symptoms,[17] recorded daily using a scale from 0 (no problem), 3 (moderately bad) to 6 (as bad as it could be). Weekly questions about quality of life (EQ-5D-5L[18]), recovery of illness and time off work, will be included. The symptom diary will be completed until resolution of symptoms for up to 28 days. Participants who have not fully recovered by 28 days will be invited to complete follow-up diaries (EQ-5D-5L and time off work) at 6 and 8 weeks, then 3, 4, 5, 6, 9 and 12 months until they have fully recovered.

Participants will be reimbursed with vouchers for each research visit and symptom diary.

Descriptive dataset

With ethics approval (see below), a small dataset, including age, gender, deprivation decile, ethnic group, clinical diagnosis, severity of illness, date of eligible condition and category of presentation (in-hours or OOH primary care, or ED) will be collected on participants who decline consent and other specified groups.

Analysis plan

Analyses will be based on available data pooled across participating GP practices and, unless otherwise indicated, will be characterised based on the collated demographic, clinical, and epidemiological variables (described above). The cohort will describe aLRTD, stratified by clinical diagnosis, as appropriate.

Continuous data will be described using median and interquartile range or mean and standard deviation for all variables collected from the entire cohort or specific subgroups. Categorical variables will be described using frequencies and proportions. The incidence of aLRTD will be calculated as the number of eligible cases divided by total number of adults registered at participating GP practices and presented as per 1000 person-years. Pathogen-specific rates will be calculated as the number testing positive divided by the total number tested and presented as percentages.

Specific analyses, including survival analysis, and univariate and multivariable regression models, will be used to explore the relationships between aLRTD and known risk factors (covariates), as appropriate. In addition, details of analytical methodology applied will be provided for each analysis. Handling of missing values will be decided based on the type and frequency of these. Results will be presented with 95% confidence intervals and, where applicable, p-values will be used to indicate statistical significance.

Discussion

Summary

In this comprehensive surveillance study, we will prospectively identify and collect data on adults presenting to primary care with aLRTD. For a subset of adults, we will collect nose/throat, saliva and urine samples, examination findings, surveys, and health utility data.

Strengths and limitations

A key strength of the study is the rigorous approach to identifying eligible patients and collection of data for all episodes of aLRTD, ensuring accurate incidence estimates. Potentially eligible patients will be identified using a search of electronic GP records, including patients where a diagnostic code has not been used. The electronic GP records will be screened, including free text consultation notes, and patients contacted prospectively where feasible to establish eligibility. These strategies will overcome a limitation of existing retrospective studies, which rely on routinely collected coded primary care data, which can lead to inaccurate incidence estimates, especially for infections.[15] Furthermore, all patients we contact will be invited to provide samples and surveys as part of the embedded diagnostic study. Lastly, incorrect incidence denominators may also result in inaccurate incidence estimates, however, in this study, they will be derived from the list of patients registered at participating GP practices. In the UK, this is a formal process and UK residents cannot register with multiple practices.

One limitation is that our searches rely on symptoms and diagnoses being coded or treatment prescribed, so some instances of aLRTD where the clinician has recorded only free text and not prescribed treatment will be missed. However, we have mitigated this through interventions and training as part of a previous study . A further limitation is the generalisability of the results, in that data will be collected from a small number of General Practices in one geographical area. However, we have selected practices serving populations with varying socio-demographic characteristics, and our analytic approach is designed to provide findings that are generalisable to the wider UK population.

Implications for research and/or practice

This study will provide accurate estimations of the incidence and burden of aLRTD for adults presenting to primary care in the UK. These data, combined with findings from a sister study of hospitalised adults, will provide important evidence to policy makers about the potential benefit of vaccines to reduce the burden of aLRTD disease.

Ethical approval

The study is called “Avon Community Acquired Pneumonia General Practice study Part 2 (AvonCAP GP2; ISRCTN64997989)”. This study received a favourable ethical opinion from Yorkshire and the Humber NHS Research Ethics Committee (ref 21/YH/0271), the HRA (ref CPMS 51111) and the Confidentiality Advisory Group (CAG) (ref 21/CAG/0173). Approval was obtained from the CAG for researchers from the University of Bristol, who were not part of the direct care team, to screen identifiable information from the electronic GP records before the planned consent process; and to include specific cohorts of patients without consent, including those we are unable to contact (at least 3 failed contact attempts over ≥24 hours) and end of life patients. Patients who speak to a clinician or researcher about the study will not be included in the surveillance arm without their consent.

A sister study, called “Avon Community Acquired Pneumonia (Avon CAP, ISRCTN 17354061)”, will estimate the incidence and burden of aLRTD for adults presenting to secondary care in Bristol over the same time.

Acknowledgements

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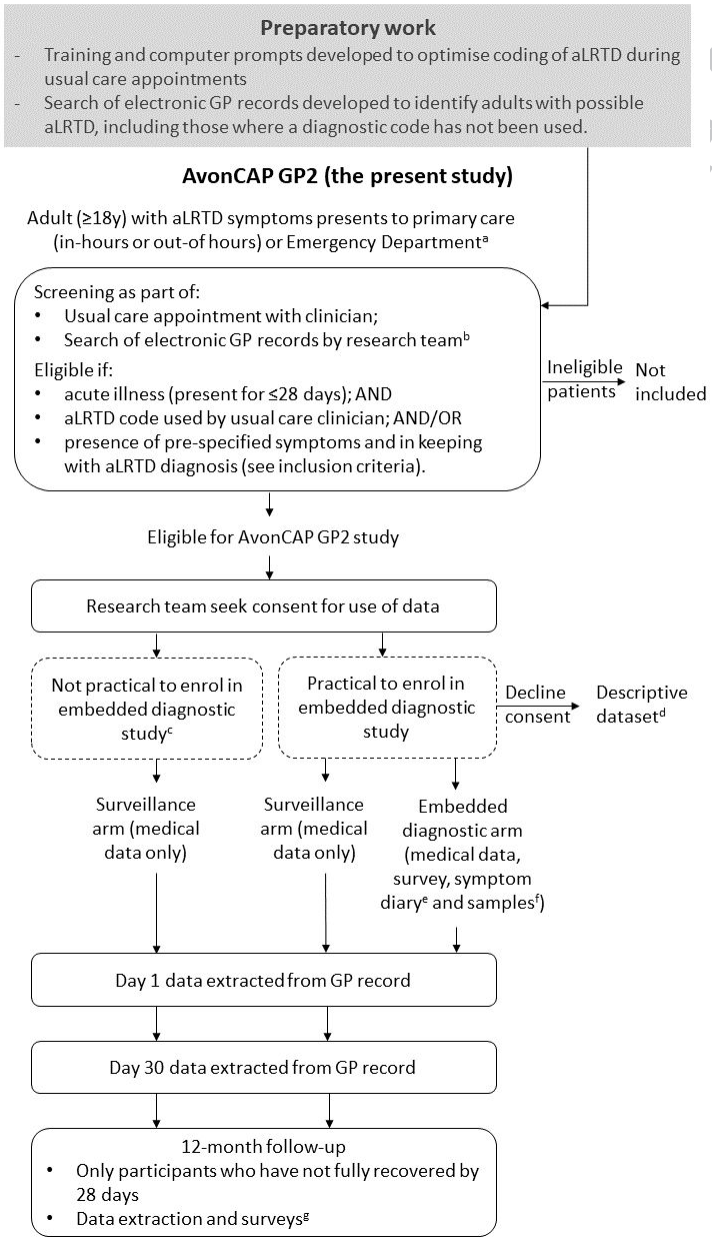
Competing interests

This study will be conducted as a university-guided collaboration between the University of Bristol (sponsor) and Pfizer (funder). AF is a member of the Joint Committee on Vaccination and Immunization (JCVI) subcommittees on pneumococcal and RSV vaccines. In addition to receiving funding from Pfizer as Chief Investigator of this study, he leads another project investigating transmission of respiratory bacteria in families jointly funded by Pfizer and the Gates Foundation. Authors with Pfizer affiliations are employed by Pfizer and may own Pfizer stock.

Abbreviations

aLRTD	Acute lower respiratory tract disease, comprising acute lower respiratory tract infection (aLRTI), exacerbation of chronic lung disease and exacerbation of heart failure.
aLRTI	Acute lower respiratory tract infection, including acute bronchitis, community acquired pneumonia and infective exacerbation of chronic lung disease.
CAP	Community acquired pneumonia
COPD	Chronic obstructive pulmonary disease
ED	Emergency Department
GP	General practitioner
OOH	Out of hours
RSV	Respiratory Syncytial Virus
SARS-CoV-2	Severe acute respiratory syndrome-Coronavirus-2
SP	Streptococcus pneumoniae

Figure 1: Study flow diagram



a. For adults who present to the Emergency Department, they will only be eligible if they are not admitted to hospital.
b. The research team will run a search of the electronic GP records at least twice a day to identify adults with aLRTD diagnosis, symptoms, clinical findings and/or prescribed antibiotics. They will manually review the consultation notes, including free text, and contact the patient to assess eligibility.
c. We have approval from the Confidentiality Advisory Group (CAG) to include specific groups of patients in the surveillance arm without consent, including those we are unable to contact (at least 3 failed contact attempts over ≥24 hours) and end of life patients. If a patient lacks capacity to provide consent (e.g. due to cognitive impairment or dementia), the research team will attempt to contact a family member, friend or unpaid carer of the patient (i.e. a personal consultee) to discuss the patient's willingness to take part. If they are unable to contact a personal consultee or if the person contacted does not want to take on the role of personal consultee, the research practitioner/nurse will attempt to identify and contact a nominated consultee. 'Medical data' refers to routinely collected data within the electronic GP records.
d. If a patient declines consent (or other specified cohorts of patient), descriptive data will be collected, including: screening ID, date of eligible condition, reasons for declining to participate, eligibility, qualifying condition, severity of illness, gender, age, deprivation decile, ethnicity and category of patient presentation (out of hours GP, in hours GP or Emergency Department).
e. Daily symptom diary until recovery from illness or for up to 28 days.
f. Nose/throat, saliva and urine samples collected on day 1.

g. Follow-up survey (quality of life, time off work, recovery) at 6 weeks, 8 weeks, 3, 4, 5, 6, 9 and 12 months (until fully recovered from illness).

Box 1: Eligibility criteria

Inclusion criteria (all must be met)

1. Aged ≥18 years of age; AND
2. Presenting to primary care with acute illness (i.e., present for 28 days or less); AND
3. Evidence of aLRTD* as guided by the following criteria:
    1. Evidence of aLRTI (including acute bronchitis, pneumonia and infective exacerbations of chronic lung disease):
        i. Clinical suspicion of LRTI and new/worsened cough with ≥1 of following signs/symptoms: sputum production or purulence, chest pain, wheeze, shortness of breath, tachypnoea or abnormal auscultatory findings suggestive of aLRTI; OR
        ii. Clinical diagnosis of aLRTI

    OR

    2. Evidence of acute exacerbation of pre-existing heart failure with respiratory symptoms:
        i. Clinical suspicion of acute exacerbation of pre-existing heart failure and new or worsening of ≥2 of following signs/symptoms: cough (including nocturnal cough), shortness of breath, wheeze, tachypnoea, abnormal auscultatory findings suggestive of exacerbation of heart failure; OR
        ii. Clinical diagnosis of acute exacerbation of heart failure with respiratory symptoms

    OR

    3. Evidence of non-infective exacerbation of pre-existing chronic lung disease:
        i. Clinical suspicion of presumed non-infective exacerbation of pre-existing chronic lung disease and new or worsening of ≥2 of cough, shortness of breath, wheeze, tachypnea, abnormal auscultatory findings suggestive of acute non-infective exacerbation; OR
        ii. Clinical diagnosis of non-infective exacerbation

Exclusion criteria (if any met)

1. Previously enrolled participants within 28 days of the onset of the study qualifying aLRTD illness.
2. At the time of enrolment, alternative non-LRTD working diagnosis suspected.
3. Presenting to primary care with the same episode of aLRTD for which they have been discharged from hospital.
4. Any patient who develops signs and symptoms of LRTD after being hospitalized for ≥48 hours.

Table 1: Summary of variables to be collected

Descriptive dataset arm	
Socio-demographics	• Age • Gender • Deprivation decile • Ethnicity (White and Black, Asian and Minority ethnic)
Illness episode	• Clinical diagnosis • Severity of acute illness (reported by clinician) • Date of eligible condition • Category of patient presentation (in hours or out-of-hours primary care, or Emergency Department)
Surveillance arm (data collected in addition to descriptive dataset arm variables)	
General health	• Long-term conditions* • Smoking status • Alcohol status • Pregnancy status • Rockwood frailty score • Risk factors for pneumococcal infection
Vaccinations	• Influenza • SARS-CoV-2 • Pneumococcal
Symptoms	• Upper and lower respiratory symptoms • Heart failure symptoms
Complications	• Acute renal failure, liver dysfunction, myocardial infarction, new atrial fibrillation, stroke, transient ischaemic attack, deep vein thrombosis, pulmonary embolus, new or worsening of congestive heart failure, fall, reduced mobility, increased care requirements.
Primary care attendances	• Number and type of primary care appointments (in-hour and out of hours)
Secondary care attendances	• Hospital admission (length of stay, treatment, outcome) • Outpatient appointments
Use of other healthcare services	• Emergency department attendances • 111 calls • Ambulance attendances
Investigations	• Radiology (e.g. CXR, CT scan) • Microbiology • SARS-CoV-2 test results
Treatment	• Antibiotics • Steroids • Inhalers • Diuretics

	• Antivirals
Vital status	• Date of death (if occurring within 30 days of index consultation date or for up to a maximum of 12 months for those who have not recovered at 28 days).
Embedded diagnostic arm (data collected in addition to descriptive dataset and surveillance variables)	
Surveys	• EQ-5D-5L (today, worst day of illness, before this illness) • Number of children and adults living in the household • Employed as a healthcare worker
Samples	• Nose and/or throat swab • Saliva • Urine
Physical examination	• Confusion screen** • Temperature** • Oxygen saturation** • Heart rate** • Respiratory rate** • Blood pressure** • Weight • Height • Body mass index
Symptom diary (until fully recovered from illness for up to 28 days)	• Presence and severity of symptoms[17] (completed daily) • EQ-5D-5L (completed weekly) • Time off work (completed weekly).

*Long term conditions from the 20 medical conditions included in the Cambridge multimorbidity score[19] and the Charlson comorbidity score[20]

**Examination findings collected from February 2022 to October 2023 only.

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