Avon Community Acquired Pneumonia Study (Avon CAP):

A Pan-pandemic Acute Lower Respiratory Tract Disease Surveillance Study

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This protocol describes the Avon CAP study and provides information about procedures for entering participants. Every care was taken in drafting this protocol, but corrections or amendments may be necessary in the future. Any amendments will be circulated to and approved by investigators in the study.

The study will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and other regulatory requirements as appropriate.

Study queries

Clinical and general queries should be directed to the Chief Investigator (Prof Adam Finn) via: 0117 342 0172; Primary Investigator (Dr Catherine Hyams) via 07966 208708; or the Clinical research team on 0117 414 8114 or 0117 342 0160.

Sponsor

The University of Bristol is the research sponsor for this study. For further information regarding sponsorship queries, please contact:

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Study Summary

Study Title	Avon Community Acquired Pneumonia Surveillance Study: A Pan-pandemic Acute Lower Respiratory Tract Disease Surveillance Study
Short Title	Avon CAP
Clinical Phase	N/A
Study Design	Observational
Study Participants	Patients presenting to North Bristol NHS Trust or University Hospitals Bristol NHS Foundation Trust with features of lower respiratory tract disease (LRTD)
Planned Sample Size	Feasibility phase: 500 per each hospital site Annual sample: 10-15,000 patients per hospital site per annum
Treatment duration	N/A
Follow up duration	1 -2 months following admission
Planned Study Period	3 years
Research question and objectives	The primary objective is to estimate population-based incidence of LRTI (including community-acquired pneumonia hospitalizations) during and after the COVID-19 pandemic, overall and for the subsets associated with SARS-CoV-2, *S. pneumoniae,* and respiratory syncytial virus. Additional epidemiological and outcomes measures will also be assessed.
Inclusion Criteria	1. Aged ≥18 years of age 2. Patients hospitalized with illness with following 2 characteristics: a. Acute illness (i.e., present for 28 days or less); AND b. Evidence of acute LRTD: i. Patients with current or suspected COVID-19, or previous proven COVID-19 within last 28 days; OR ii. Clinical or radiologic diagnosis of pneumonia or an acute LRTI; OR iii. New onset or worsening of ≥2 of following 8 LRTD symptoms or clinical findings: 1. fever (>38.0°C/100.4°F) or hypothermia (<35.5°C) before or within 24 hours of enrolment 2. pleuritic chest pain; 3. cough (including nocturnal only); 4. sputum production or purulence; 5. dyspnea (shortness of breath) including orthopnea/exertional only; 6. tachypnea (respiratory rate ≥20/min); 7. abnormal auscultatory findings suggestive of LRTD 8. radiologic finding that is consistent with LRTD, including pneumonia, and/or acute congestive heart failure.
Exclusion Criteria	1. Any patient who develops signs and symptoms of LRTD after being hospitalized for ≥48 hours (excluding suspected/proven COVID19) 2. Previously enrolled participants readmitted ≤7 days after discharge for their study qualifying admission (excluding suspected/proven COVID19) 3. At the time of enrolment, an LRTD-related diagnosis has been excluded or

	another diagnosis confirmed (for example, patient had a fever and tachypnea due to an intraabdominal process such as cholecystitis)

List of Abbreviations

Abbreviation	Definition
A&E	Accident and emergency
ARI	Acute respiratory illness
BNT162b2	Pfizer/BioNtech COVID-19 vaccine
BRI	Bristol Royal Infirmary
CAP	Community-acquired pneumonia
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
COVID	Coronavirus disease
CRF	Case report form [eCRF = electronic CRF]
CSA	Clinical study agreement
CT	Computed tomography
CVA	Cerebrovascular accidents
CXR	Chest x-ray
GCP	Good Clinical Practices
ICH	International Council for Harmonisation
ICU	Intensive care unit
IRB/EC	Independent Review Board/ Ethics Committee
LRTD	Lower respiratory tract disease
MRI	Magnetic resonance imaging
NP	Nasopharyngeal
NSTEMI	Non-ST-elevation myocardial infarction
OP	Oropharyngeal
PCV7	7-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PCV20	20-valent pneumococcal conjugate vaccine
PPV23	23-valent pneumococcal polysaccharide vaccine
RSV	Respiratory syncytial virus
SAP	Statistical analysis plan
STEMI	ST-elevation myocardial infarction
TND	Test Negative Design

UAD	Urinary antigen detection assay
VE	Vaccine effectiveness

1 Background

1.1 Acute lower respiratory tract disease

Acute lower respiratory tract disease (LRTD) encompasses pneumonia, lower respiratory tract infection (LRTI), acute bronchitis, exacerbation of underlying respiratory disease including asthma and chronic obstructive pulmonary disease (COPD). Throughout Europe before the COVID-19 pandemic, the healthcare cost of pneumonia is estimated at approximately €10 billion per annum, with inpatient care accounting for €5.7 billion (European Lung White Book). The indirect costs of lost work-days amount to €3.6 billion. Studies have shown that the incidence of pneumonia in Europe varies by country, age and gender; however, in all studies the incidence of pneumonia increases sharply with age. In the UK, pneumonia affects 0.5 to 1% of adults each year, and the incidence of LRTI is considerably higher with a recent study finding an incidence of 148/1000 person-years in patients ≥ 65 years of age (Millet ERC et al). Previous studies to define the disease burden attributable to acute LRTD have used either radiological or microbiological diagnosis to confirm disease, and hence may underestimate the true disease burden, or have been conducted using clinical coding data, which is both retrospective and subject to the errors associated with this methodology. Furthermore, all previous studies have been carried out before the COVID-19 pandemic, and the effect of this new emergent respiratory pathogen on acute LRTD remains unclear.

1.2 COVID-19 infection

In 2019 a novel coronavirus-induced disease (COVID-19) emerged in Wuhan, China. A month later the Chinese Center for Disease Control and Prevention identified a new beta-coronavirus (SARS coronavirus 2, or SARS-CoV-2) as the aetiological agent (Zhu et al, 2019). A worldwide pandemic is currently occurring, and as such the disease burden of acute LRTD will increase. As the responsible virus is a new human pathogen, relatively little is known about disease pathogenesis and the clinical spectrum of disease which it causes, including risk factors associated with poor outcomes in developed countries (Huang et al, 2020).

Furthermore, the interaction between SARS-CoV-2 and other respiratory pathogens including *Streptococcus pneumoniae* and Respiratory Syncytial Virus (RSV) is undefined. It is unknown if bacterial or viral co-infection, superimposed or subsequent infection is common in patients with SARS-CoV-2 infection. This is important in terms of understanding disease pathogenesis and being able to provide appropriate vaccination strategies to try to mitigate mortality and morbidity. It remains unclear how the disease burden of other acute LRTD will be affected, if at all, by the SARS-CoV-2 pandemic.

The UK began vaccinating its adult population in December 2020, using a Department of Health defined risk-based strategy by age, comorbidity and key worker status. Initially, only the BNT162b2 vaccine was used. This is a nucleoside modified messenger ribonucleic acid (modRNA) vaccine from Pfizer/Biontech that encodes the full-length, membrane-anchored spike (S) glycoprotein of SARS-CoV-2 with two introduced proline mutations to lock it in the prefusion conformation (Kariko et al. 2008; Pardi et al. 2015, Wrapp et al. 2020). BNT162b2 showed an acceptable safety profile in a Phase 1/2 study (Walsh et al 2020) and, in a Phase 3 trial conducted in Argentina, Brazil and the Unites States, was tolerable and demonstrated 95% efficacy against COVID-19 (Polack et al. 2020). At the time of writing, BNT162b2 currently has temporary authorisation for supply under MHRA regulation 174, and data confirming the effectiveness of the vaccine outside of the clinical trial setting are needed. Further, additional COVID-19 vaccines also now have temporary authorisation for supply under regulation 174 in the UK, including from AstraZeneca and Moderna.

1.3 Streptococcus pneumoniae

Pneumococcus is a leading cause of lower respiratory tract infections among adults, including community-acquired pneumonia (CAP) population wide (O'Brien, Wolfson et al. 2009, Said, Johnson et al. 2013, Torres, Cillóniz et al. 2018) and among immunocompromised individuals (Zhang, Van Werkhoven et al. 2018), and pneumonia among those with a history of healthcare contact such as long-term care facility residents (Carratala, Mykietiuk et al. 2007, Chalmers, Taylor et al. 2011, Ewig, Klapdor et al. 2012, Polverino, Torres et al. 2013, Parrott, Nebeya et al. 2017). *S. pneumoniae* is also the most frequent bacterial pathogen isolated from patients with acute bronchitis (Macfarlane, Holmes et al. 2001, Creer, Dilworth et al. 2006) and COPD exacerbations (Wilkinson, Aris et al. 2017).

However, previous studies that described the burden of vaccine-preventable pneumococcal pneumonia have largely focused on radiologically confirmed and microbiologically defined CAP only. A recent review of a UK CAP incidence described underestimation of CAP using this approach, potentially by as much as four-fold, due to study requirements for informed consent, study screening processes, radiologic confirmation, and requirement for collection of a dedicated study urine specimen for pneumococcal antigen testing (Chalmers et al., 2017). Correspondingly, a recent vaccine-probe study, performed in the Netherlands, documented that this limited scope appears to underestimate the true burden of respiratory infections prevented by the 13-valent pneumococcal conjugate vaccine (PCV13) (Gessner et al., 2018). The vaccine-preventable disease incidence was 2 to 3.5-fold higher for clinical CAP cases versus microbiologically and radiologically confirmed vaccine-type CAP.

Pneumonia study inclusion criteria are not the only source of underestimation of pneumococcal burden – under or alternate diagnosis also contributes. Presenting complaints as well as signs and symptoms in older patients with pneumonia are often atypical and may lead to missed or incorrect admission diagnoses (Henig & Kaye, 2017). Also, pneumonia may be a secondary to or an underlying cause of the main presenting complaint, such as in patients with altered level of consciousness, cerebrovascular accidents (CVA), congestive heart failure (CHF), or COPD exacerbations. In these scenarios, pneumonia may not be the primary diagnosis code recorded for the hospitalization or may not be coded as an associated diagnosis at all. On this basis, there is a need to assess the burden of pneumococcal disease in the larger group of patients presenting with acute lower respiratory disease – not just those with a formal pneumonia diagnosis. Acute lower respiratory tract disease (LRTD) in adults includes pneumonia (all types); bronchitis; exacerbations of chronic obstructive pulmonary disease, congestive heart failure, asthma, and other underlying pulmonary disease (e.g., cystic fibrosis); acute respiratory distress syndrome (ARDS); and other acute lower respiratory disease, i.e., any condition involving acute lower respiratory pathology (i.e., effects trachea, bronchi, bronchioles, or lungs in opinion of treating/study physician). Comprehensive assessment of all LRTD is needed to identify the disease burden due lower respiratory tract infection.

1.4 RSV infections in adults

RSV is also an important respiratory pathogen later in life, with severe disease occurring among those with compromised cardiac, pulmonary or immune systems and in the elderly (Falsey, Hennessey et al. 2005). Estimates of the RSV disease burden requiring hospitalization in adults are limited but suggest that up to 10% of adults presenting with acute respiratory illness (ARI) during the winter have RSV (Dowell, Anderson et al. 1996, Thompson, Shay et al. 2003, Falsey, Hennessey et al. 2005, Falsey, McElhaney et al. 2014, Jain, Self et al. 2015). The RSV season frequently does not completely overlap with the influenza season which confounds the ability to define RSV's clinical and epidemiological features, as viral pathogen testing is often driven by concerns regarding influenza. The limited available data show that age and chronic medical conditions (e.g., COPD, cardiac disease, immunodeficiency) are significant risk factors, and that fever is less commonly observed with RSV than with influenza infection, while cough, dyspnoea, and wheezing may be more common (Falsey 2013, Falsey, McElhaney et al. 2014).

1.5 Rationale for study

Accurate incidence rates of acute LRTD and its disease subsets, such as pneumonia and LRTI, remain elusive and the impact of COVID-19 on respiratory disease burden is unclear. Accurate incidence rates of vaccine-preventable infection are required to assess the potential population-level impact of vaccination recommendations. As discussed, current evidence suggests that the burden of pneumococcal and RSV lower respiratory infections is underestimated. Further, the current COVID-19 pandemic due to SARS-CoV-2 has dramatically increased the burden of LRTI worldwide. On this basis, we seek to conduct a study to measure the true burden of acute respiratory disease due to these pathogens during and after the COVID-19 pandemic within the limitations of currently available diagnostic testing.

This population-based multi-hospital, active prospective surveillance is designed to determine population-based incidence rates of hospitalized adults ≥18 of age with community-acquired LRTI (including CAP) in Bristol, England. The involved Bristol hospitals' nearly completely capture hospital admissions among residents of a well delineated geographic region allowing for calculation of population-based incidence rates of LRTI. Study data derived from surveillance activities will fully enumerate the number of acute LRTD cases in this region.

Persons identified as having LRTD in study hospitals will be offered participation in the consented portion of this study involving enhanced testing for pneumococcal, RSV, and SARS-CoV-2 infection. This will allow for more complete characterization the incidence of these infections than standard of care testing alone.

Additionally, real world vaccine effectiveness (VE) estimates for COVID-19 vaccines are needed to demonstrate their effect in general populations as well as in risk groups. These can be achieved using a test negative design (TND) case control analysis. For the purpose of these TND analyses, cases are individuals diagnosed with COVID-19 up to 14 days prior to admission or on admission to hospital and controls are those in whom COVID-19 was not detected in the same timeframe. Almost all data needed to conduct these analyses are already being collected in this study, including COVID-19 disease and vaccination status from standard of care records, alongside other medical history and current illness details. To allow for more complete multivariate adjustment for potential confounding differences between the cases and controls, additional information on COVID-19-related behavioural risk factors will be collected from some participants using a standardised questionnaire, such as occupation, frequency of mask use and inclusion in a social bubble. We plan to conduct VE assessments separately for different COVID-19 vaccine products.

1.6 Study Context

This study will undertake surveillance of lower respiratory tract disease (LRTD) including pneumonia in adults in a defined geographical area. This study combines NHS Hospital Trust-based surveillance of lower respiratory tract disease (LRTD) including pneumonia in adults in a defined geographic area with a University-sponsored research study which enhances the diagnostic accuracy in a subset of consented patients. The surveillance will be done in two large hospitals in Bristol and may later be expanded to include a third hospital in Bath. These surveillance activities will be done under NHS Trust governance and with full ethics approval in each hospital. Although originally planned to be stand-alone prospective, comprehensive case ascertainment of adult lower respiratory tract infections within the NHS space, occurring as it turns out in the midst of the coronavirus pandemic, which most commonly presents as pneumonia in adults, the work will be done alongside and overlapping with other observational studies focussed specifically on COVID-19.

The University-sponsored embedded study will recruit a subset of the patients identified during the surveillance activity. Patients who are enrolled, following informed consent, will have additional investigations performed for research purposes and surplus samples obtained during routine case will also be scavenged. The surveillance activity will serve, in effect, as the screening activity for the study as well as providing a comprehensive, anonymised dataset on the disease burden of pneumonia and LRTD in the adult population in the Bristol urban area over a defined time period.

HRA/ethics approval for this embedded study will be sought by the University and both the data from all consented subjects and all the anonymised screening/surveillance datasets will be unified from the databases held by the participating hospitals, with the agreement of those hospitals. These data will be reported on by the University at the end of the project. The combined anonymised dataset, along with the consented patient data and research samples, will belong to the University while the participating hospitals will retain ownership and control over their respective databases and their contents. Thus, the respective institutions will each have autonomy, control, governance oversight and ethical approval jointly and collaboratively for this programme of surveillance and research.

To accurately calculate disease burden and describe acute LRTD and its subsets, it is necessary to record all cases of adults hospitalised within the defined geographical area who meet study criteria. This study will systematically record and describe all adult patients admitted with acute LRTD and its subgroups, providing an accurate calculation of disease incidence, burden and outcome analysis in addition to other epidemiological analyses, including identifying risk factors for disease and poor outcome.

This study will recruit a subset of the patients identified during the surveillance activity into a consented arm. Patients who are enrolled, following informed consent, will have additional investigations performed for research purposes and surplus samples obtained during routine care will also be scavenged. Participants recruited to the embedded study will be asked to consent to the use of their data for clinical research, with a target enrolment of up to 80% of eligible admitted patients. Patients approached with information about the consented study will subsequently fall into 3 groups:

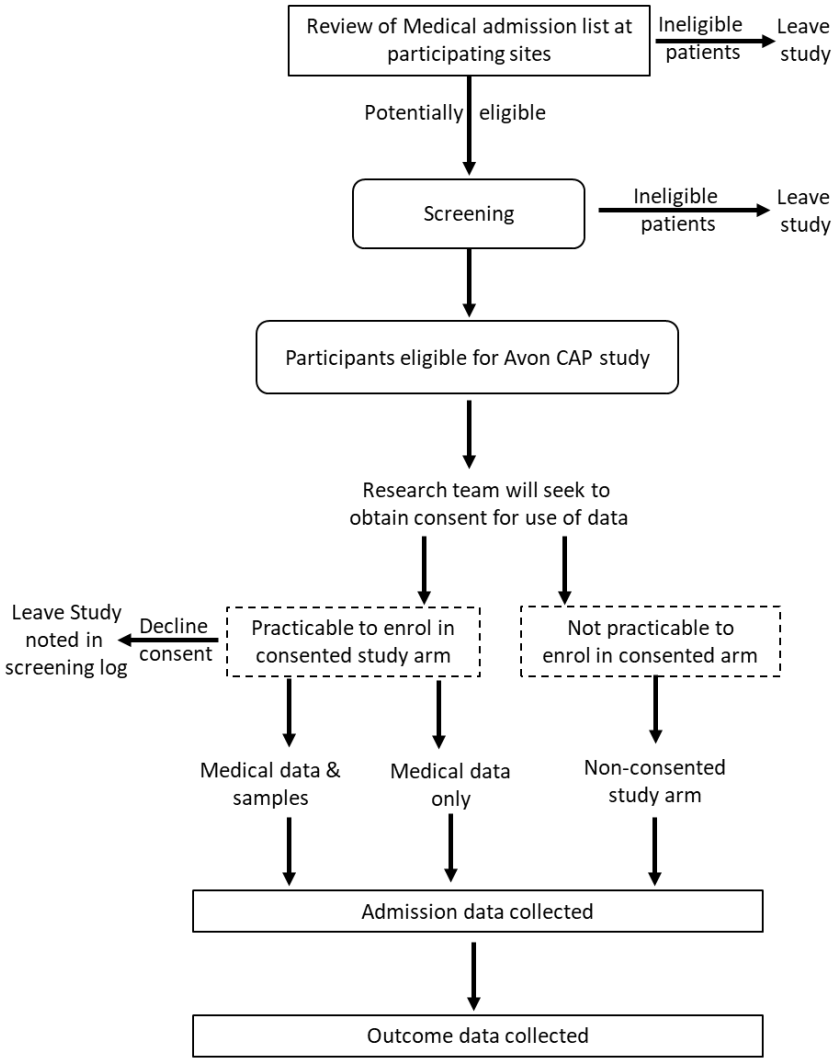
- Those who provide full consent to the study, including access to medical data
- Those who provide consent to access to medical data only (and not biological samples)
- Those who decline consent and are not enrolled in the study, and are only noted in the screening log

Individuals who decline consent for access to medical data will not be recruited to this non-consented study arm, thereby ensuring there is no contagion of the non-consented study arm. In this way, the non-consented surveillance will only collect medical data from individuals in whom it is not practicable to take consent.

However, as it is not practicable for the research team to approach and consent every individual hospitalised with acute LRTD into the consented arm, this study seeks approval for data collection to be undertaken on these individuals via a non-consented surveillance arm. We therefore will request and obtain authorisation for access to personal data under Section 251 of the NHS Act 2006 for the use of non-consented data. If patients are eligible, data fields from their routine clinical care would be collected to determine features of clinical presentation and disease, including co-morbidities, routine healthcare tests and outcomes (e.g. requirement for intensive care and/or organ support, mortality).

The data collected during the non-consented surveillance activity will be combined with the data obtained from the consented arm to provide a comprehensive dataset of patients with acute LRTD. In this way, all patients and disease will be captured and described, allowing for a complete and accurate estimation of disease incidence and burden.

Study Flow Diagram: Activities pertaining to data collection for consented study & non-consented surveillance arms, demonstrating how they work together.



1.7 Lay summary

Acute lower respiratory tract disease affects large numbers of people worldwide. Older people are more likely to have disease, suffering both reduced quality of life and increased mortality from respiratory infection. Previous studies have tried to define the burden of respiratory infection in adults, but these studies have been limited as they required patients to have either an identified cause of disease (microbiological diagnosis) or change on a Chest X-ray (radiological diagnosis). This has led to an underestimate in disease in adults, because other cases have not been counted.

In 2019, a new virus called SARS-CoV-2 (also referred to as coronavirus) that causes an illness known as COVID-19 emerged and is causing a worldwide pandemic. As the virus is new to humans, people do not have any immunity to it and large numbers of patients are expected to become infected. We do

not understand fully how this virus causes disease, nor the risk-factors for a poor outcome (including death). We also do not understand how this virus interacts with other bacteria and viruses that cause disease in humans. This is important, because if we can determine how these infections interact with each other and the consequences for the patients affected, we may be able to offer better vaccination strategies to prevent disease and treatments to help patients affected. Other diseases we know are important in adult respiratory infection are pneumococcus and RSV (a cold virus). There are potential new vaccines available for use in adults, but as we do not know the true amount of disease caused by these infections, we cannot determine if using these vaccines in adults would be worthwhile.

The Avon CAP study aims to record all patients admitted with respiratory illness at 2 hospitals in the Bristol area. We will gather data that has already been recorded by the clinical teams treating these patients, including demographics, co-morbidities, outcomes and the results of the investigations undertaken by the medical team. Persons with acute respiratory illness will also be offered participation in the consented portion of this study involving additional testing for pneumococcal and RSV infection, which will identify more cases of such infections than routine testing. We will then use these data to accurately define the true amount of disease caused by respiratory illness and be able to determine the subgroups of disease (for example by patient co-morbidity, microbiological and radiological diagnosis) and determine the impact of COVID-19 on respiratory disease.

COVID-19 vaccine was introduced in the UK in December 2020, with individuals called for vaccination by age and risk group (including certain key worker status). This study provides an ideal opportunity to assess how effective these COVID-19 vaccines are in preventing hospitalizations in a “real world” setting. Real world VE estimates from this study can be compared to those from blinded, randomised clinical trials with more limited numbers of participants. The assessment will be a case control study comparing participants who are hospitalised with LRTI and who have been diagnosed with COVID-19 (cases) or have not been diagnosed with COVID-19 (controls) on admission to hospital, or in the 14 previous days, using a method called the test negative design (TND). Almost all the data required for this assessment will be collected as part of the consented study, including COVID-19 disease, vaccination status, and sociodemographic and clinical characteristics of patients from standard-of-care records held by the GP and/or hospital. The only extra information needed will be some details about behaviours during the pandemic which will be collected from some participants via a short questionnaire. These questions may include occupation, household structure, inclusion in any social bubble and use of masks. It is anticipated the COVID VE assessment will continue for 12-24 months depending on vaccine uptake and COVID-19 attack rates during the study.

2 Schedule of activities

Please refer to

Study procedures and **Error! Reference source not found.** sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

Consented Arm

The investigator may schedule visits (unplanned visits) in addition to those listed in the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the participant. Collection of standard-of-care data will be done for all identified LRTD events in study hospitals and entered into the surveillance databases hosted by the Trusts. This will be conducted by appropriate members of the clinical team, and research team members will only have access to pseudonymised data. Sample collection and interview activities shown in bold below will be undertaken for consented participants only by members of the research team.

Table 1. Comprehensive List of Procedures by Visit for Consented-Arm, Including Visit Windows.

Procedure / Assessment [a]	**Screening/ Enrolment Visit [b]**	**Final Assessment/ Vital Status (Data Collection only)**	**Convalescent Visit ("Serology Subset" Only)[e]**	**Mortality Assessment (data collection only)**
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**
	Day 1	**Day 30**	**Day 45**	**Day 365**
Visit Window	**Within 48 hours of admission**	**Day 30 to 45**	**Day 22 to 60[c]**	**Day 365**
Screening (surveillance)	X			
Clinical symptoms	X			
Medical History[c]	X	X	X	
Vaccination History	X		X	
CRB-65 and pneumonia severity (PSI) score	X			
Informed Consent	X			
Eligibility confirmation for embedded study	X			
Patient Interview, including approved questionnaires[f]	X		X	
Collect urine specimen	X			

Procedure / Assessment [a]	**Screening/ Enrolment Visit** [b]	**Final Assessment/ Vital Status (Data Collection only)**	**Convalescent Visit ("Serology Subset" Only)**[e]	**Mortality Assessment (data collection only)**
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**
	Day 1	**Day 30**	**Day 45**	**Day 365**
Collect upper respiratory tract sample for SARS-CoV-2, RSV and other pathogens[d]	X		X[d]	
Collect blood specimen[e]	X		X	
Obtain residual (scavenged) standard care specimens from clinical laboratory	X	X	X	
Record SOC respiratory specimen testing results	X			
Record SOC blood culture results	X			
Record SOC chest imaging results	X			
Final acute LRTD Illness Diagnosis		X		
Cardiac complications		X		
Vital Status/Mortality		X		X
Hospitalization duration, readmission, & level of care		X		
Collect Research-related Injuries (RRIs)	X	X	X	

Abbreviations: SOC = standard of care; UAD = urine antigen detection assay; RSV= respiratory syncytial virus; RRI = research-related injury; CRB-65 = Confusion, Respiratory rate, Blood pressure, 65 years of age and older.

a. Sample collection and interview activities shown in bold above will be undertaken for consented participants only.
b. All participants in the consented enhanced diagnostic testing will have confirmation of their eligibility confirmed and be subsequently enrolled at Visit 1 / Day 1.
c. At Visit 2 and 3, relevant changes to medical history since the last visit will be documented.
d. Respiratory samples will be collected for RSV and other respiratory pathogen testing if such testing has not already been ordered or completed as part of standard-of-care testing. Details on the type and collection process for samples will be included in the laboratory manual. Another respiratory swab will be collected at the convalescent visit, only if the participant experienced a new ARI after hospital discharge.

e. For those that consent to participate in the Serology subset, a blood sample will be collected for serologic testing. A remnant of an appropriate blood sample from standard of care testing can be used if appropriate for this use per laboratory manual specifications. For this subset of patients, an additional convalescent visit will take place approximately 22–60 days after enrolment for collection of a convalescent blood sample. However, effort should be made to schedule this visit as close to day 42 as possible. If subject has another enrolment qualifying acute LRTD event(s) prior to their convalescent visit, they will have acute serology specimen taken at each enrolment and only one convalescent serology visit will be completed 42 days after last acute specimen was taken.
f. The applicable covid risk questionnaire will be completed for participants during relevant period, e.g. national lockdowns.

Non-consented arm

Collection of standard-of-care data will be done for all identified LRTD events in study hospitals and entered into the surveillance databases hosted by the Trusts.

Table 2. Comprehensive List of Information to be collected for non-consented arm.

Procedure / Assessment	**First Data Collection**	**Second Data Collection**	**Third Data Collection**
	Admission	**Outcomes and Results**	**Mortality**
	Day 1	**Day 30**	**Day 365**
Visit Window	**Within 48 hours of admission**	**Day 30 to 45**	**Day 365**
Surveillance	X		
Clinical symptoms	X		
Medical History[a]	X	X	
Vaccination History	X		
CRB-65 and pneumonia severity (PSI) score	X		
Record SOC respiratory specimen testing results	X		
Record SOC blood culture results	X		
Record SOC chest imaging results	X		
Final acute LRTD Illness Diagnosis		X	
Cardiac complications		X	
Vital Status/Mortality		X	X
Hospitalization duration, readmission, & level of care		X	

Abbreviations: SOC = standard of care; UAD = urine antigen detection assay; RSV= respiratory syncytial virus; RRI = research-related injury; CRB-65 = Confusion, Respiratory rate, Blood pressure, 65 years of age and older.

a. At Visit 2, relevant changes to medical history since the last visit will be documented.

2.1 Study type

Avon CAP is a prospective population-based multi-hospital epidemiological study in patients presenting to North Bristol NHS Trust, University Hospitals Bristol and Weston NHS Foundation Trust (hereon referred to as NBT and UHBW). Additional Trusts may be invited to participate as the study progresses, including the Royal United Hospital NHS Trust in Bath. All LRTD events will be included to ensure complete capture of LRTI events, which are the primary focus of the study. Bristol is a single geographical area with multiple hospitals, general practices (GP) and long-term care facilities (LTCF), which provide care to a defined population (the denominator) in that area.

The study collects simple demographic and clinical data on admission of patients to hospital, as well as the results of microbiological and radiological investigations undertaken as standard-of-care investigations in this patient group. Therefore, the study is non-interventional and a surveillance exercise with an embedded consented study (see Section 1.6).

2.2 Patient population

The patients that will be included in the cohort are all adult patients aged ≥ 18 years presenting to NBT and UHBW with clinical features (signs and symptoms) of acute LRTD. This will be determined by assessing all adult patients admitted to these 2 hospitals using the screening algorithm outlined in Section 4.

3 Research questions and objectives

3.1 Primary outcome

To estimate population-based incidence of community-acquired LRTI hospitalizations during and following the COVID-19 pandemic, overall and for community-acquired pneumonia.

3.2 Secondary outcomes

3.2.1 COVID-19/SARS-CoV-2 infection

1. To estimate the population-based incidence rates of COVID-19-related hospitalizations
2. To describe the proportion of LRTI hospitalizations (overall, standard-of-care pneumonia diagnosis, radiologically confirmed CAP only) attributable to COVID-19, both overall and by age/risk stratification
3. To describe demographics, clinical and epidemiological characteristics and outcomes within COVID-19 LRTI and the different subcategories, both overall and stratified by age/risk
4. To describe mortality rate at 30 days after admission to hospital for COVID-19 LRTI and its subcategories, overall and by age group and risk group status
5. To describe the association between COVID-19 and other respiratory pathogens, including but not limited to *S. pneumoniae*, influenza and RSV, both with co- and super-imposed infection and secondary respiratory infection.
6. To describe the length of hospital stay for COVID-19 LRTI hospitalizations and the proportion of COVID-19 admissions involving an ICU stay.
7. To assess whether *S. pneumoniae* LRTI is associated with more severe COVID-19 clinical outcomes (such as requiring invasive mechanical ventilation) among persons hospitalised with COVID-19 infection.

3.2.2 COVID-19 Vaccine Effectiveness

These measures may each be assessed per vaccine brand or manufacturer in the real-world setting. Definitions of exposure categories and details of the planned COVID-19 VE analysis can be found in Appendix 1.

Primary:

To estimate the effectiveness of 2 doses of COVID-19 vaccine (i.e. fully vaccinated) against hospitalization for acute respiratory infection due to SARS-CoV-2 infection by vaccine brand or manufacturer.

Secondary:

1. To describe the effectiveness of only 1 dose of COVID-19 vaccine (i.e., partially vaccinated) against hospitalization for due to SARS-CoV-2 infection by vaccine brand/manufacturer.
2. To describe the effectiveness of ≥1 dose of COVID-19 vaccine (i.e., ever vaccinated) against hospitalization for ARI due to SARS-CoV-2 infection by vaccine brand/manufacturer.
3. To determine the effectiveness of current and future COVID-19 vaccinations by COVID-19 variant in real-world settings

Exploratory:

1. To determine the effectiveness of current and future vaccinations against COVID-19, taking into account factors such as patient characteristics, number of doses and dose intervals, timing of doses relative to disease onset, virus variant and other potential confounding factors.
2. To describe further the effectiveness of COVID- 19 vaccines against hospitalization for ARI stratified by various patient characteristics (e.g., age, sex, chronic medical conditions, receipt of influenza vaccine, long term care facility residence, time since vaccination and time between doses).
3. To summarize the proportion of hospitalized patients who receive 0, 1, 2 or more doses of COVID-19 vaccine by number of vaccination doses (to update as vaccination program rollout changes)
4. To summarize the time between administration of the first and second dose of COVID-19 vaccine among hospitalized patients who received 2 doses
5. To summarize the time since vaccination with COVID-19 vaccine (most-recent dose) from illness onset
6. To describe demographic and clinical characteristics and disease severity of any COVID-19 vaccine failures
7. To assess the impact of COVID-19 on confirmed subsequent pneumococcal LRTI

3.2.3 *Streptococcus pneumoniae*

1. To estimate the population-based incidence rates of hospitalizations for the following 12 specified LRTI subcategories:
    a. all LRTI (overall, pneumococcal only, PCV13-type, and PCV20-type);
    b. any standard-of-care pneumonia diagnosis (overall, pneumococcal only, PCV13-type, and PCV20-type);

c. any radiologically confirmed CAP (overall, pneumococcal only, PCV13-type, and PCV20-type).

2. To describe the proportion of LRTI hospitalizations (overall, standard-of-care pneumonia diagnosis, radiologically confirmed CAP only) associated with any *S. pneumoniae,* PCV13, PCV20 serotypes and by individual serotypes, both overall and stratified by age/risk condition
3. To describe demographics, clinical and epidemiological characteristics and outcomes within LRTI and its 12 subcategories, both overall and stratified by age/risk condition
4. To determine mortality rate at 30 days after admission to hospital for LRTI (and its 12 subcategories), overall and by age group and risk group status
5. To describe the serotype and frequency and type of antibiotic resistance among *S. pneumoniae* isolates
6. To describe the length of hospital stay for LRTI hospitalizations and the proportion of LRTI admissions involving an ICU stay, overall and by 12 subcategories

3.2.4 RSV Infection

1. To determine the population-based incidence of RSV LRTI hospitalizations both overall and stratified by presence of underlying risk conditions
2. To describe the clinical and epidemiological characteristics and clinical outcomes of RSV-related LRTI hospitalizations both overall and stratified by presence of underlying risk conditions
3. To describe the proportion of LRTI caused by RSV in hospitalized patients both overall and stratified by presence of underlying risk conditions
4. To describe the difference between the population-based incidence of hospitalization, epidemiology, clinical presentation, and outcomes observed in RSV-positive adults versus those with other common respiratory viruses (eg, SARS-CoV-2 and influenza)
5. To determine the pathogen distribution rates of RSV, SARS-CoV-2, and other viral pathogens among adults admitted with congestive heart failure or chronic obstructive pulmonary disease exacerbations

3.3 Exploratory objectives

3.3.1 *S. pneumoniae* exploratory objectives

1. To describe the occurrence of cardiovascular events within 30 days of hospitalization for pneumonia for standard-of-care pneumonia diagnosis and radiologically-confirmed CAP only (overall, pneumococcal only, PCV13-type, and PCV20-type) including the following events: non-ST elevation myocardial infarction (NSTEMI), ST-elevation myocardial infarction (STEMI), cerebrovascular accident, new episode of atrial fibrillation or other significant cardiac arrhythmia; deep venous thrombosis or pulmonary embolism, new or worsening congestive heart failure, and cardiovascular-related death.
2. To describe time trends in population-based incidence rates of pneumococcal-related hospitalizations during and after COVID 19 pandemic

3.3.2 Respiratory syncytial virus exploratory objectives

1. To determine the rates of sero-response to RSV between acute and convalescent serology and the concordance with molecular test results
2. To determine the prevalence of RSV and other viral pathogens in control participants without acute LRTD
3. To compare the frequency of RSV and other viral pathogen detections among enrolled control participants (without acute LRTD) with the frequency of RSV and other viral pathogen detections among LRTD events
4. To describe time trends in population-based incidence rates of RSV hospitalizations during and after COVID 19 pandemic

3.3.3 Patient outcome and risk factors

1. To determine the risk factors for hospitalisation with aLRTD and its disease subsets
2. To determine the risk factors for poor outcomes following hospitalisation with aLRTD and its disease subsets
    a. stratified by aLRTD and its disease subsets
    b. stratified by patient risk factor (for example: age, gender, pre-existing risk factors e.g. COPD, pulmonary fibrosis)

4 Research methods

4.1 Study design

Adults with LRTD will be screened using population-level surveillance at study hospitals, and collection of standard-of-care data will be performed on all LRTD events. Patients presenting during the recruitment period of the study, with documented or suspected COVID-19 will fulfil study eligibility criteria, and therefore all references to LRTD also encompass documented or suspected COVID-19 cases who may not otherwise qualify as LRTD. LRTD patients will be offered participation in the enhanced diagnostic testing portion of this study with informed consent, which will involve collection of urine, respiratory, and in some cases blood samples, for additional testing, if necessary, for COVID-19, pneumococcus, and RSV as well as administration of a short patient questionnaire on COVID-related risk behaviours. The pneumococcal testing will include serotype to allow estimation of the proportion of the burden that is potentially vaccine preventable – either by the currently available PCV13 or the anticipated PCV20, which is currently in the final phases of clinical development. Information about the additional pneumococcal, SARS-CoV-2 and RSV infection testing will be integrated with the population-level surveillance data to allow for more accurate population-based estimates of vaccine-preventable pneumococcal and COVID-19 and RSV-related LRTD incidence. The epidemiologic data generated from the study may serve as the baseline for future vaccine effectiveness studies – either for expected PCV20 or investigational RSV and SARS-CoV-2 vaccines that are also currently under development at Pfizer.

Enhanced Diagnostic Testing. Patients who meet all inclusion criteria and no exclusion criteria with informed consent will be enrolled in enhanced diagnostic testing portion of the study. At the time of their enrolment visit, participants will be interviewed (if possible) and a urine for pneumococcal testing and a swab for respiratory pathogen testing will be obtained in all participants (unless refused at time of collection or the patient's clinical status prevents collection, e.g. an anuric participant cannot provide urine). Aliquots from the urine specimens collected from study participants will be frozen and stored for subsequent shipment to Pfizer laboratories for urinary serotype-specific antigen detection (UAD) and BinaxNOW® testing. Additional testing may be conducted on these specimens or portions of these specimens that may be stored at the Bristol Biobank only after obtaining appropriate permissions.

All LRTD events will have additional information collected at 30 days. Additional information on the participants' final clinical diagnosis, vital status, and cardiovascular complications of their current illness (pneumonia patients only) will be collected.

Study duration. The study is expected to enrol for three consecutive years with an option to extend should additional epidemiological data be needed. Yearly or seasonal interim analyses may be conducted.

Serology subset. All participants in the enhanced diagnostic testing group will be offered participation in the serology subset, which will involve the following additional visits/procedures: 1) serology specimen at enrolment visit/V1 (may be salvaged from SOC specimen if appropriate specimen available), and 2) additional in-person visit at Day 42 to collect a blood specimen for convalescent serology and possibly another respiratory pathogen swab (the later only if another intercurrent acute respiratory illness has occurred). Participation will require signature of an annex to the main study informed consent.

UAD and Viral Testing Controls. An additional group of approximately 400 contemporaneous control participants without acute LRTD, comparable by age group and season to subject in the enhanced testing group, will be enrolled participation. These participants will be identified as adults who are:

3. Patients attending outpatient clinics in participating hospitals in specialties other than respiratory or cardiology OR
4. Patients currently admitted at participating hospitals on non-medical wards with no current acute respiratory or cardiovascular conditions.

Control participants will provide urine for UAD and BinaxNOW testing and an upper respiratory swab sample for RSV/respiratory pathogen testing. UAD testing will help inform cut points for UAD positivity in this population.

COVID-19 VE assessment is described in Appendix 1.

4.2 Active surveillance and screening

The detailed screening methods to conduct active surveillance will be determined by the site and described in full in a Surveillance Manual which will be created and managed by the Investigator and reviewed by Pfizer collaborators. The feasibility studies conducted prior to the surveillance study implementation will inform the detail of surveillance activities and screening processes at both locations.

In essence, any adult inpatients ≥ 18 years old presenting to one of the participating hospitals displaying the specified symptoms of LRTD or with a clinical diagnosis consistent with LRTD will be included in the screening activities, including those with exacerbations of COPD and CHF accompanied

by respiratory symptoms. Screening for potential Avon CAP study participants will be undertaken by a member of the clinical team at each hospital site, usually a nurse, allied health professional (e.g. physiotherapist) or doctor. This should be performed at least once a daily during the working week (Mon-Fri), with the first screening round performed at the start of the day. Screening will involve reviewing the medical admission take list (primarily the 'presenting complaint/details' section) to screen patients for entry to the surveillance part of the study. The medical admission list is a real-time electronic based list (internet or other IT system) which can be searched using various parameters including admission time, enabling accurate checking of patient admissions (especially those occurring overnight and at weekends). The medical admission take list also records details of the presenting complaint and/or presumed diagnosis of each patient admitted to the hospital.

Patients admitted through the medical admission take will be excluded if they have a presenting complaint or diagnosis that is not compatible with the study inclusion/exclusion criteria. For example, patients without lower respiratory pathology such as acute pancreatitis, myocardial infarction (NSTEMI or STEMI), stroke or cellulitis would be excluded from entering the surveillance log.

Following consent, participants with LRTD events meeting the screening definition will undergo enhanced diagnostic tests and have their clinical data pseudonymised and entered into the eCRF. All potential participants will be approached regardless of time of admission if they are present during established recruitment periods.

4.3 Pseudonymisation

Each patient with an admission that may meet eligibility will be assigned a surveillance number within the database. This will be assigned by the research team following the screening of the medical admission list and will be used to pseudonymise patients. Throughout the study and on its completion, the database will be cleaned using the NHS number to identify individuals who have more than one qualifying admission, both within one NHS Trust and across participating study sites. These individuals will be identified in the pseudonymised database using the surveillance number of their first study eligible admission. The NHS number will subsequently be deleted following processing at the end of the study. This will provide a method of ensuring that there is an accurate calculation of disease incidence within a defined geographical area with multiple NHS hospitals providing acute care, whilst maintaining a pseudonymised database. A data flow diagram is included in Section 11.4.

4.4 Patient selection

4.4.1 Screening inclusion criteria

Patients must meet all the following inclusion criteria to be eligible for enrolment:

1. Aged ≥18 years of age
2. Patients with illness with following 2 characteristics:
    a. Acute illness (i.e., present for 28 days or less); **AND**
    b. Evidence of acute LRTD:
        i. Patients with current or suspected COVID-19 or previous proven COVID-19 within last 28 days **OR**
        ii. Clinical or radiologic diagnosis of pneumonia or an acute LRTI **OR**
        iii. New onset or worsening of ≥2 of following 8 LRTD symptoms or clinical findings:
            1. fever (>38.0°C) or hypothermia (<35.5°C) before or within 24 hours of enrolment;
            2. pleuritic chest pain;
            3. cough (including nocturnal only);
            4. sputum production or purulence;
            5. dyspnea (shortness of breath) including orthopnea or on exertion only;
            6. tachypnea (respiratory rate ≥20/min) documented by healthcare professional;
            7. abnormal auscultatory findings suggestive of LRTD (e.g., crepitations/rales or evidence of pulmonary consolidation including dullness on percussion, bronchial breath sounds, wheezing, or egophony);
            8. radiologic finding that is consistent with LRTD, including pneumonia, and/or acute congestive heart failure (e.g., pleural effusion, increased pulmonary density due to infection, the presence of alveolar infiltrates [multilobar, lobar or segmental] containing air bronchograms, or interstitial oedema).

4.4.2 Screening exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Any patient who develops signs and symptoms of LRTD after being hospitalized for ≥48 hours (either at current hospital, another transferring hospital, or a combination of these), unless admitted with current, previous proven, or suspected COVID-19 infection.
2. Previously enrolled participants readmitted ≤7 days after discharge for their study qualifying admission, unless admitted with current, previous proven, or suspected COVID-19 infection
3. At the time of enrolment, an LRTD-related diagnosis has been excluded or another diagnosis confirmed (for example, patient was found to have fever and tachypnoea due to an intraabdominal process such as cholecystitis)

4.4.3 Study inclusion/exclusion criteria

To participate in the enhanced diagnostic testing, individuals must meet all of the following:

1. Meet all screening inclusion criteria in section 5.2.2
2. Meet none of screening exclusion in section 5.2.3
3. Informed consent document signed and dated by patient (if written consent) or otherwise documented (as detailed below), or the requirements for patients unable to provide consent have been fulfilled (as detailed below)

4.4.4 UAD and respiratory pathogen control group

4.4.4.1 Control group inclusion criteria

Individuals must meet all of the following inclusion criteria:

1. Age 18 years and older.
2. Informed consent document signed and dated by patient
3. Individuals who are willing and able to provide urine and respiratory swab

4.4.4.2 Control group exclusion criteria

Individuals presenting with any of the following will not be included in the control group:

1. Individuals who are investigational site staff members or relatives of those site staff member or participants who are Pfizer employees directly involved in the conduct of the trial.

2. Individuals with suspicion of pneumonia or other respiratory infectious diseases or documented, concomitant infectious disease.
3. Individuals residing in any long-term care facilities (for example, nursing homes or respite care facilities).
4. Individuals with known bronchial obstruction or a history of post-obstructive pneumonia. (Chronic obstructive pulmonary disease (COPD) is permissible, provided there has not been an exacerbation within the 3 months prior to enrolment.)
5. Individuals with primary lung cancer or another malignancy metastatic to the lungs.
6. Individuals with fever (measured temperature of ≥38.0° C measured by a healthcare provider).
7. Individuals with significant immunosuppressive disease such as leukaemia.
8. Individuals with either pneumococcal conjugate vaccine (PCV) and/or pneumococcal polysaccharide vaccine (PPV) administration within the past 30 days

4.4.5 Patient consent and enrolment

Avon CAP is a disease surveillance study for acute LRTD illness events occurring in hospitalised patients recording clinical data and the results of investigations performed by clinical teams as routine standard-of-care. Therefore, specified individual patient consent is not required to collect data on acute LRTD events for screening.

Patients with LRTD illness event identified through screening will be offered the opportunity to participate in enhanced diagnostic testing portion of this study. This enhanced diagnostic testing requires informed consent to participate and involves collection of urine, blood and upper respiratory swabs, as well as extra interview data and access to data held in the surveillance database. Participants will have an opportunity to review information about what would be involved in full in the patient information leaflet and informed consent form.

This study anticipates that some patients who meet eligibility criteria may not be able to provide consent. For example, patients requiring ventilation on intensive care, or those with delirium or cognitive impairment and/or dementia may lack capacity. In this event, the research team will discuss the patient's capacity with the relevant clinical team and determine the opinion of the clinical team concerning the patient's capacity and willingness to participate. The research team will attempt to contact a family member, friend or unpaid carer of the patient (i.e. patient representative), in order to discuss the study and determine the patient's willingness to participate. The patient will not be enrolled in the study if the research team, clinical team or patient representative do not feel that this patient would be willing to participate if they had capacity, or that participating would adversely affect

their clinical treatment. We will conduct this aspect of the study in accordance with the Mental Capacity Act.

Consent or a consultee declaration can be taken face-to-face with individuals who are currently in the hospital or on hospital site. This study anticipates instances when face-to-face discussions and written documentation may not be possible. Such examples include infection control measures restricting hospital visiting, participants who have been discharged before the research team could approach and participants with difficulty in completing the consent form (e.g. osteoarthritis). In cases where face-to-face and/or written consent is not possible, alternate methods of consent and its documentation may be used: including (but not limited to) electronic, telephone or other verbal consent (e.g. teleconference). If a consent or declaration form is not completed and signed by the participant or consultee, then research staff will ensure that there is a witness to countersign the appropriate consent or declaration form.

Avon CAP is an observational surveillance study, and patients can, therefore, be enrolled in other studies or clinical trials. Furthermore, the study anticipates that one individual may have multiple study eligible hospitalizations throughout the duration of the study, as they may be admitted with multiple chest infections or respiratory exacerbations. If the research team become aware that a potentially eligible participant has previously consented to enrol in the study during a previous hospital admission, they will seek confirmation that the participant is willing to consent to ongoing participation during the relevant study eligible admission. This may be in the form of repeated consent to enrol or via a declaration that the previous consent is still valid as there has been no change in the study processes or protocols, and that the participant is still willing to consent to enrolment.

5 Justification for accessing data without consent

The Avon CAP surveillance study will undertake comprehensive surveillance on all adults hospitalised with an eligible condition (i.e. acute LRTD) without consent from all participants.

Avon CAP will undertake systematic and comprehensive surveillance of all adults hospitalized with acute lower respiratory tract disease within a well-defined geographical area. As the demographic and population of Bristol is well described, ascertaining the true burden of acute respiratory infection and describing disease in the context of COVID-19 will allow this study to calculate accurate estimates of incidence. In order to be able to determine the morbidity and mortality associated with acute lower respiratory tract disease, it is necessary that the data collected cover the entire population, as missing any cases within the study area would result in an inaccurate calculation of disease burden. Furthermore, by capturing and detailing precise clinical data, this study will be able to stratify disease by patient factors such as age, gender and ethnicity, as well as by risk factors, including smoking status and pre-existing co-morbid disease including chronic respiratory and cardiovascular conditions. Through this surveillance mechanism all acute respiratory infection in hospitalized adults will also be described by causative pathogen and radiological diagnosis, in addition to capturing patient outcome. The study has three important features:

1. The data will be comprehensive and complete over a defined time period for a defined population area and therefore not subject to the potentially biased ascertainment which weakens other large studies
2. The demographic of the study area is broad in terms of deprivation, minority groups, urban and rural distribution and is in many ways highly representative of the population of England, permitting results to be of value for nationwide planning.
3. The study has substantial confirmed funding which will underpin its viability and successful conduct and is fully embedded within the clinical services of the contributing hospitals, while the anonymised data handling and analysis will be undertaken within the University domain thus not competing for scarce research resources at a time of critical need within the NIHR and NHS research infrastructures.

This comprehensive surveillance platform will enable us to truly understand and describe adult respiratory infection in adults in the context of COVID-19. Should any vaccine providing protection against respiratory pathogens be introduced during Avon CAP, the design of this study enables it to act as a vaccine impact ecological study. The research team will seek to enrol as many participants as possible in the embedded study undertaking enhanced diagnostic tests, with a target recruitment of 80% of eligible participants.

5.1 Patients missed by consent

This study seeks to describe and ascertain the disease burden and outcomes attributable to acute LRTD in hospitalised adults, and by necessity the research will be undertaken on patients accessing secondary healthcare requiring acute medical care. Some patients will be admitted 'out of hours' (i.e. evenings, nights and/or weekends) and may be discharged or die before the research team have time to approach these individuals for consent. Those who are discharged home after a short interval are those most likely to represent mild disease. Individuals who die shortly after admission are likely to be either elderly, frail or have extensive/severe pre-existing medical conditions. These patients are those most likely to represent severe disease with adverse outcomes, and therefore most likely to benefit from any public health intervention or improvement in healthcare resource allocation that may be enabled by the insights provided by this study. However, not all elderly, frail or patients with co-morbid disease have severe disease, and it is therefore not possible to extrapolate or generalise the data obtained from individuals who consent to all patients admitted. To fully understand, describe and account for acute LRTD and its subgroups of disease it is essential to undertake comprehensive surveillance activity inclusive of all individuals requiring hospital-level care following presentation with acute LRTD. An accurate evaluation of disease incidence, including the incidence of pneumonia, LRTI and other disease subgroups or estimation of disease incidence by risk factor (such as age, gender, socioeconomic status), requires the inclusion and accurate data capture of all individuals admitted within the defined geographical area over a defined period.

5.2 Requirement for data points

To fulfil the study objectives, this study requires data from participants categorised as NHS number, date of birth, postcode (to sector level), date of death and health data. These are the minimum data required to ensure accurate ascertainment, processing and analysis. Additional fields such as the patients' names, addresses and/or hospital numbers may be seen by the research team in the review of clinical records to collate data to undertake this study, but will not be extracted or saved.

In order to meet the study objectives, the following data will be collated without consent under appropriate approvals:

1. NHS number
2. Date of birth
3. Sector level postcode
4. Date of Death
5. Health Data

The data will be held within a database in the IT domain of each participating NHS study site, accessible only to authorised research team members. The data will be processed and transferred to the central University IT domain as outlined in section 10 of this protocol. The requirement for the data is explained in the following paragraphs.

5.2.1 NHS Number

The NHS number is a unique identifying number that is issued to each individual and stays with that individual for life. It is therefore a single data point that can identify an individual both within a given NHS Trust (or study site) and across NHS Trusts. Each NHS Trust uses a local hospital number which is not transferrable or usable within the NHS IT system at another NHS site, and therefore this cannot be used to avoid duplication. Participant name would not be uniquely identifiable within a large and densely populated area and would require at least one additional data point for accurate identification.

This study aims to determine the incidence of acute LRTD with a defined geographical area with the acute care requirements of the population being served by more than one NHS Trust (or study sites). To calculate disease incidence accurately, each individual who meets study eligibility criteria must be counted correctly (i.e. not missed and not counted more than once for a single clinical episode), both within and across study sites. For example, a patient may be admitted to North Bristol NHS Trust, discharged home a few hours later but unexpectedly deteriorate and be taken by ambulance to University Hospital Bristol and Weston NHS Trust. In this example, the patient would have only one episode of disease, but unless there was a mechanism to identify this individual across the study sites they would be counted twice, and therefore lead to an inaccurate count.

5.2.2 Date of Birth

A participant's date of birth is required to calculate patient age at admission, age at death (if occurring within 30 days of study admission) and age at discharge. This is important to allow stratification of individuals affected by acute LRTD by age, with evidence suggesting disease increases with age. Vaccination strategy in the UK is currently stratified by age, with individuals over 65 years qualifying for PneumoVax® (PPV-23) vaccination and seasonal influenza vaccination. Therefore, estimating the disease burden by age will provide important information about the groups most likely to benefit from vaccination with current and novel vaccines against respiratory disease, in addition to other public

health interventions and healthcare resource allocation designed to improve outcomes in those most at risk.

Furthermore, current risk severity scores for respiratory disease recommended by the British Thoracic Society, NICE and American Thoracic Society/Infectious Disease Society of America require patient age at admission. These severity scores have not been well evaluated in the context of the emergent COVID-19 pandemic. Testing existing risk severity scores and identifying modifications that improve their accuracy at predicting disease outcomes would lead to improved clinical care for individuals with acute LRTD.

5.2.3 Postcode (to sector level)

Sector level postcode is required to estimate the socioeconomic status of individuals affected with respiratory disease, and to undertake geotemporal analysis of acute LRTD allowing for mathematical modelling of infection. Determining which localities and socioeconomic groups are most at risk of disease and adverse outcomes is important in determining the availability and distribution public health care interventions, including but not limited to vaccination programmes. Furthermore, the potential impact of other interventions designed to modify risk factors such as comorbid disease, environmental factors and access or availability of healthcare resources can be appropriately assessed and provided based on the data provided by this study.

Mathematically modelling disease patterns and spread in time and place allows for better understanding of how disease outbreaks and incidence of disease occurs in a population, and will provide a generalisable model that can be used both within this population and extrapolated to other populations. This will also not only provide better understanding of disease but also provision of better health care resources to reduce disease morbidity and mortality.

5.2.4 Date of Death

Date of death for participants in this study will only be recorded if occurring within 365 days of an eligible hospital admission. The date of death is used to (1) calculate survival and mortality statistics (2) determine if any death occurring within 365 days of admission is as an inpatient or following discharge. This is important in determining disease burden and outcome and determining whether mortality was as an inpatient or following discharge. This has significant impact on healthcare economics and provision of healthcare resources. It may also highlight patient groups at particular risk

of adverse outcomes, and thereby enable targeted interventions to reduce mortality in these groups. Notably, multiple disease severity scores are validated against all-cause one-year mortality, and multiple studies report mortality up to one-year following respiratory infection.

5.2.5 Health Data

Health data are data concerning individuals' demographics (gender, ethnicity), pre-existing medical conditions, signs and symptoms of disease on arrival at hospital, and investigation of (blood, microbiology and radiological test results) and outcomes (e.g. requirement for intensive care and/or organ support, length of hospital admission, etc.). Health data will be ascertained in order to characterise acute lower respiratory tract disease including: the patients that it affects; the presentation to hospital; its investigation, treatment and outcomes; to stratify disease into subgroups; and determine microbiological diagnosis. These will be used to investigate risk factors for disease and poor outcome (including morbidity and mortality) and to calculate disease burden and incidence of acute LRTD and its subgroups. This is important in determining the requirement and provision of healthcare resources and the potential benefit of public health initiatives (including current and future vaccines) in reducing morbidity and mortality

5.3 Public health benefit

Processing of these data will allow the study to determine:

- Incidence of acute LRTD and its subgroups in the Bristol area
- Risk factors for acute LRTD and its subgroups
- Outcome for acute LRTD and its subgroups in Bristol
- Incidence of vaccine-preventable respiratory disease in Bristol
- Identify risk factors with poor outcome, including those that may be modifiable
- Identification of differences between patients and their outcome at participating hospitals

Since the characteristics of the population of Bristol are known in detail, these data will be able to be extrapolated to national level. These data will therefore inform policy on public health interventions to improve the health of those whose data have been systematically collated, the wider Bristol population and the national population. Furthermore, these data can be analysed to provide insights into healthcare resource allocation, again benefitting the local population and those studied.

5.4 Lawful Basis for data processing

GDPR Article 6.1(e) – University of Bristol public task

Article 9.2(i) – public interest in the area of public health

Article 9.2(j) – scientific research

Public task: the processing of these data is needed to calculate a true disease incidence for acute LRTD, its subgroups and vaccine-preventable disease that will enable the better allocation and provision of healthcare resources and implementation of public health initiatives to reduce morbidity and mortality, including but not limited to vaccination.

6 Recruitment, data and sample collection

6.1 Patient selection

This study will be based at NBT and UHBW hospitals, and other hospital sites may be invited to participate at a future date. Patients will be selected from normal clinical care either from the inpatient or acute admissions setting. Furthermore, an audit of microbiological testing will be undertaken to ensure that patients were inadvertently missed through the clinical care selection pathway. If any additional healthcare settings are established to manage overflow patients with COVID-19 infection from these hospitals due to the pandemic, these additional hospital sites would be included in this study.

6.2 Data sources

Consent will be obtained to access data relating to outcomes of:

- Radiology tests
- Microbiology tests
- Clinical parameters regarding hospital admission (including co-morbidities, symptom type and duration, admission observations, etc)
- Vaccination status
- Patient treatment (including requirement for ventilation, renal support, etc)
- Patient outcomes (including hospital length of stay, requirement for intensive care, haemofiltration and complications arising from their LRTD).

Consent will also be obtained to record which GP practice the participant is registered with, in order to use this to generate a denominator for incidence calculation.

6.3 Sample and data collection

Data will be recorded on an e-CRF (REDCap), although a paper-based source document may be used under exceptional circumstances (such as computer failure) which will be entered to the e-CRF. In this instance, any paper-based records will be handled in keeping with due diligence of confidential medical information.

Consent will also be obtained for collection of the following samples:

6.3.1 Scavenging of Residual Standard of Care Specimens

Where possible for participants in enhanced diagnostic testing, aliquots of standard care specimens will be scavenged (e.g., sputum, tracheal aspirate, bronchoalveolar lavage, pleural fluid, or swab for MRSA testing) and sent to the appropriate local or national laboratories for pneumococcal, RSV, and other respiratory pathogen testing. Patients may undergo molecular testing for respiratory viruses; the surplus sample may be transferred to other diagnostic laboratories following testing in the NHS clinical laboratory, including laboratories governed by Public Health England. This study may therefore salvage excess or remnant biological specimens obtained for standard of care testing which are transferred to other facilities, including Public Health England laboratory facilities. The results of tests performed on any samples salvaged from Public Health England laboratories may be reported back to the Public Health England service in pseudonymized or aggregated form, although this would not affect the clinical care of the patient due to timelines for carrying out analyses on these samples.

6.3.2 *S. pneumoniae* isolates

Any *S. pneumoniae* isolates from standard of care bacterial cultures (such as, blood, respiratory tract, and pleural fluid) will be sent to the appropriate local or national laboratories for confirmation of S. pneumoniae, and serotype identification as outlined in the Laboratory Manual.

6.3.3 Respiratory swabs for respiratory pathogen testing (Study Procedure)

If not already requested or completed as part of standard of care testing, a respiratory swab will be collected as a study procedure for RSV RT-PCR and respiratory pathogen testing as soon after study enrolment as possible and preferably within 24 hours of study enrolment. Nasopharyngeal (NP) swab is currently the preferred approach. If the participant declines a NP swab, an alternative respiratory specimen such a midturbinate nasal swab may be collected. Any sample collection will be recorded in the CRF. Enrolled patients may decline respiratory swab collection and remain in the study. Full details of specimen collection and processing will be outlined in Laboratory Manual. The Serology subset will also have another respiratory swab collected at their convalescent visit if they have a new intercurrent acute respiratory infection before Visit 3.

6.3.4 Urine samples

As a study procedure, urine will be collected in a noninvasive manner from all participants as soon as possible following enrolment; it is preferred that the urine sample be collected within 24 hours following study enrolment. Any sample collection will be recorded in the CRF. If a bladder catheter

has been placed as part of routine medical care, a fresh urine sample may be collected from the lumen or the port. Any additional urine volume remaining after the UAD aliquots are saved, will be deposited in Bristol biobank or divided into falcon tubes and shipped to the Pfizer central laboratory for additional new assay development and UAD technology transfer. Urine will be frozen and stored at the local laboratory for subsequent shipment to the Pfizer central laboratory for UAD and BinaxNOW® testing or transfer to biobank at Bristol University. Specific instructions for the collection, processing and shipment of urine specimens will be described in the study laboratory manual. Patient unable or unwilling to provide a urine specimen may still be enrolled in the study.

As part of a program of rigorous control and continuous assessment of UAD assay performance, and ongoing monitoring of the studies which utilize the UAD assay, this study will collect urine samples from approximately 400, controls without acute LRTD that will be similar in age group distribution and month of collection to participants with acute LRTD. Analysis of these control samples will further support that the established positivity cut-off values of the UAD assays are applicable to this population. BinaxNow® will also be analyzed in control patients.

Table 3. Schedule of Events –Controls without Acute LRTD

Study Visit	Enrolment
Study Day Windows	1
STUDY PROCEDURES	
Obtain Informed Consent	X
Review Eligibility Criteria	X
Patient Interview, including review of cardiovascular events in prior 2 months[a]	X
Review of Medical Record	X
SPECIMEN COLLECTION	
Urine specimen	X
Obtain respiratory swab	X
Obtain blood specimen (optional)	X

[a]Collect cardiovascular events per Protocol Section 6.2 in past 2 months.

UAD 1 and UAD 2. The Pfizer UAD is a multiplex immunoassay, based on the Luminex xMAP bead technology, with the ability to combine multiple spectrally distinct microspheres, each conjugated to a different serotype-specific monoclonal antibody in a single well to allow the detection of all antigens simultaneously using only a small volume of urine sample. The 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V,

14, 18C, 19A, 19F, 23F) covered in the validated UAD 1 assay are the 13 polysaccharide antigens used in Pfizer's 13vPnC vaccine. The UAD 2 assay, using the same Luminex xMAP bead technology detects 11 additional serotypes (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F).

BinaxNOW® is a commercially available, Food and Drug Administration (FDA) approved assay for the detection of S. *pneumoniae* in the urine and cerebrospinal fluid (CSF) from patients with pneumonia or meningitis. The BinaxNOW® S. *pneumoniae* test is an *in vitro* rapid immunochromatographic test intended to be used in conjunction with culture and other methods, to aid in the diagnosis of pneumococcal pneumonia.

Aliquots for urine samples for testing conducted by Pfizer Inc will be processed and kept frozen in an appropriate local laboratory and will be shipped in bulk for analysis at the Pfizer Vaccines Research and Development (VRD) laboratory, Pearl River, New York, USA. Details regarding sample processing and shipping are provided in a separate laboratory manual. Residual samples from urine aliquots sent for UAD/BinaxNOW testing may be stored for future testing at Pfizer laboratories and may be kept for up to 15 years after the study ends, at which time they will be destroyed. In addition to testing for this study, any residual urine from these aliquots left over after the study is complete may be used for additional research related to the development of products. Pfizer will not perform any testing of genetic material. Residual urine samples at Pfizer may be shared with other researchers as long as confidentiality is maintained, and no testing of the participant's genetic material is performed.

6.3.5 Serology testing for serology subset participants

All participants enrolled in the Serology subset will have a blood sample collected for acute and convalescent serologic testing, including for RSV infection. If a blood sample is drawn for standard care, an aliquot of this specimen may be scavenged and used for serologic testing in lieu of a separate specimen collection if it meets the requirements outlined in the Laboratory Manual. If a participant has another enrolment qualifying acute LRTD event(s) prior to their convalescent visit, they will have acute serology specimen taken at each enrolment and only one convalescent serology visit will be completed 42 days after last acute specimen was taken. Control participants may also have a blood specimen taken, and serologic testing may be conducted on those specimens.

6.3.6 Additional testing for respiratory infection

This study anticipates that novel diagnostic and prognostic tests for respiratory infection may emerge throughout the study period, including against COVID-19. Any biological specimens (urine, serum or blood derivatives and respiratory samples) collected as primary research or salvage samples in this study, which are surplus to study requirements following testing as outlined in the protocol above, may be used for novel and emergent assays to detect, quantify and/or characterize the respiratory infection and the immune system response to pathogens such as SARS-CoV-2.

6.3.7 Biological samples

The participant may request that their samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. All anonymized biological samples not required for this protocol may be deposited in the Bristol Biobank to be used in future research and shared with other researchers, as long as appropriate approvals are obtained.

7 Study procedures and clinical data – Consented arm

Total duration of participation per participant will be approximately one month from date of admission. One visit is in person if possible (V1), and one may involve record abstraction and/or phone contact (V2). For the Serology subset, participation will extend to approximately 6 weeks and involve an additional in person visit.

7.1 Consented arm, Visit 1: Screening/Enrolment (Day 1)

Screening all potential participants (adult patients with respiratory symptoms and/or suspected COVID-19) for eligibility for the disease surveillance and consented parts of the study. Every effort will be made to approach, discuss, and enrol participants in the consented arm and seek their consent for collection and use of data. Participants should be enrolled as soon as feasible after admission (no later than 48 hours after admission if at all possible). Screening while administrative admission process is occurring is encouraged. The enrolment visit will be conducted in person and include the following activities:

- Screen patients against the inclusion/exclusion criteria of this protocol
- Provision of enhanced testing information to LRTD patient, answer any questions with particular attention to the study schedule and sample collection.
- Obtain signed and dated written informed consent from participant for LRTD patients who want to participate in enhanced diagnostic testing. In the event that a potential participant lacks capacity to consent to participation, study staff will follow protocols for patients unable to provide informed consent.
- If the participant has been enrolled in the study during a previous hospitalisation, a declaration of ongoing consent may be used (to avoid completing the consent form in its entirety again and inconvenience to the participant)
- Enter standard of care data into eCRF for LRTD events
- For consented participants, collect and process urine, blood and respiratory specimens as detailed in Laboratory Manual (unless refused at time of collection or the patient's clinical status prevents collection, e.g. an anuric participant cannot provide urine).
- For consented participants, salvage standard of care respiratory specimens for respiratory pathogen and pneumococcal testing. See laboratory manual for details.
- For consented participants, interview participant if possible, for past medical history and eCRF elements not in medical chart, COVID risk behaviours questionnaire

- For consented participants, record any serious adverse events associated with sample collection and RRIs.
- If participating in Serology subset, obtain a blood specimen for serology per specification in laboratory manual. Salvaged SOC specimens may be used if meet specifications outlined in the Laboratory Manual.

Non-consented arm

- Screen patients against the inclusion/exclusion criteria of this protocol
- Enter standard of care data into eCRF for LRTD events

7.1.1 V1 data collection

Patients meeting screening criteria will have basic demographic and clinical data collected on an e-CRF after consent. This will involve collection of the following data at visit 1:

- Patient details
- Eligibility checks – inclusion/ exclusion criteria components
- Date of hospitalization, length of stay in hospital
- Demographics (age, gender, race/ethnicity, socioeconomic status estimated by postcode, vaccination [e.g. influenza/ PCV13/PPV23/COVID-19 and date of relevant administration], smoking status, alcohol/drug use)
- Details of present illness (symptoms, date of onset, vital signs on admission to hospital)
    - Used antibiotics/antivirals in the 14 days prior to admission
- Standard-of-care test results
    - Routine biochemistry and haematology test results on admission, including C-reactive protein and NT-proBNP
    - Blood cultures
    - Respiratory microbiology testing, including bacterial (eg, PCR and culture) and viral testing (eg, COVID19, RSV and influenza)
    - Pneumococcal testing (eg, BinaxNOW urine test),
    - Antibiotic resistance results for pneumococcal isolates
    - Sputum Gram stain results
    - COVID-19 testing data collection will include tests from up to 14 days prior to hospitalisation based on patient self-report and medical records
- Hospitalization data:

  - Admission hospital
  - Dates and time of admission/discharge
  - ICU stay (yes/no)
  - Number of days in ICU
  - Mechanical ventilation and days of ventilator use
  - Requirement for new/increased haemofiltration
  - Non-invasive ventilation requirement and days of usage
- New York Heart Association (NYHA) Heart Failure Classification, Pneumonia Severity (CRB65 and PSI scores)
- Relevant Medical History and Major Comorbidities
- Rockwood Frailty Score and Charlson Comorbidity Index
- COVID risk behaviours questionnaire, which may include occupation, household structure, inclusion in social bubble and mask wearing

7.2 Consented arm, Visit 2: Final diagnosis/Vital status assessment (Day 30)

The assessment may be completed 30 to 45 days after enrolment by phone call, medical record review, during a follow-up standard care visit and/or other means.

At day 30 after admission, the following will be assessed and recorded in the CRF:

- Record final clinical/standard-of-care diagnosis for qualifying acute LRTD illness
- Vital status (alive or deceased) at Day 30 after enrolment
- Cardiac complications through Day 30 after enrolment

The Principal Investigator or designee should make an assessment of final standard -of-care LRTD-related diagnosis if any discrepancy exists in the record. The Investigator is to also confirm, based on any existing or new information, if the participant had clinically and radiographically confirmed pneumonia.

7.2.1 Data collection at V2:

- Record RRIs
- Hospital-related adverse events (e.g., falls in hospital and hospital-acquired infections)
- Final standard of care/ clinical diagnosis of acute LRTD illness
- Vital status at Day 30
- Occurrence of cardiovascular events within 30 days of illness onset (pneumonia only):

- non-ST elevation myocardial infarction (NSTEMI)
- ST-elevation myocardial infarction (STEMI)
- cerebrovascular accident
- new episode of atrial fibrillation or other clinically significant arrhythmia
- deep venous thrombosis or pulmonary embolism
- new or worsening congestive heart failure
- cardiovascular-related death

7.3 Consented arm, Visit 3 [serology subset only]: Convalescent serology assessment on Day 45

For those enrolled in the Serology subset who have signed the related ICD Annex, a follow-up visit will be conducted approximately 45 days after enrolment (visit window: Day 22 – 60). If there is a low patient return rate for this follow-up visit, the study will consider whether home visits may be more convenient and better suited to patients in this study. If home visits are undertaken, they will be offered to participants as a visit option, and an appropriate time will be arranged after liaison between the participant and research team. The procedures undertaken during home visits will ensure that both study participants and research staff are appropriately protected in line with any Health and Safety regulations (e.g. PPI, sharps bins, etc.).

- Blood specimen for respiratory pathogen serology including RSV will be obtained. An upper respiratory swab will be obtained if intercurrent acute respiratory illness has occurred
- Record RRIs.

7.4 Consented arm, Visit 4: One-year mortality assessment on Day 365

The assessment may be completed 365 to 390 days after enrolment by medical record review, during a follow-up standard care visit and/or other means.

At day 365 after admission, the following will be assessed and recorded in the CRF:

- Vital status (alive or deceased) at Day 365 after enrolment
- If the participant is deceased, total survival days following enrolment

7.5 Consented arm, Patient outcome:

The follow-up information should be collected 1 month after enrolment or when the patient is discharged from hospital (whichever occurs later). At day 30 after admission, the following will be assessed and recorded in the CRF:

- Record final clinical/standard-of-care diagnosis for qualifying acute LRTD illness:
    - CAP – radiologically or clinically confirmed, acute bronchitis/LRTI, exacerbation of underlying chronic respiratory disease, LRTI not otherwise specified, congestive cardiac failure, empyema/lung abscess, non-infective process, and non-respiratory infection-related diagnosis.
- Vital status at Day 30 after enrolment:
    - deceased, not recovered, recovered, recovered with sequelae, recovery ongoing, unknown
- Cardiac complications through Day 30 after enrolment:
    - ST- and non-ST elevation myocardial infarction, cerebrovascular accident, new episode of atrial fibrillation or other arrythmia, venous thromboembolism, cardiovascular-related death

The Principal Investigator or designee will assess final standard -of-care LRTD/COVID-related diagnosis if any discrepancy exists in the record. The Investigator is to also confirm, based on any existing or new information, if the participant had clinically and radiographically confirmed pneumonia.

7.6 Ongoing clinical care

This is an observational epidemiological study collating and recording standard-of-care investigations and patient details in a consented study with enhanced diagnostic tests. As such, Avon CAP should not impact on any aspect of clinical care or other interventional trial in which the patient may be participating.

7.6 Safety Reporting

This is a minimal-risk, low-interventional study; however, certain safety reporting obligations must be met. Some of these reporting requirements are reported into the clinical study database via the CRF and others must be reported directly to Pfizer as well. A summary is below, and more detail is provided in sections 7.6.1 and in the Safety Reporting Reference Manual.

1. During the 15 minutes after the study-required sample collection, all adverse events (AE)/ serious adverse events (SAE)s that occur in that 15 minutes will be recorded in the study database. This is called the "active collection period".

2. Medically important research related injuries (RRIs) (SAEs related to study participation) will be recorded in the study database only. These do not need to be reported to the Pfizer Drug Safety Unit (DSU), but should be reported to the Pfizer clinical/medical team upon awareness and may also need to be reported to other oversight entities as required by local or institutional regulations.

3. This study does not involve the administration of vaccines or other drugs. However, any SAE that is related to receipt of the Pfizer-BioNTech COVID-19 vaccine, BNT162b2, that the PI/site becomes aware of will be reported to Pfizer DSU within 24 hours of awareness, or immediately if life threatening.

4. Exposures to BNT162b2 during pregnancy will not be reported to the Pfizer DSU as individual case reports unless there is an associated SAE.

5. Lack of Effectiveness (LOE) of BNT162b2 will not be reported as individual SAE reports, since this is a study endpoint and will be tabulated in the clinical study report (CSR).

6. Any reporting requirements described above are not intended to replace reporting obligations to other institutional, local, or regional entities. The reporting required by Pfizer or this study protocol does not take the place of these other obligations.

7.6.1 Events Reported in the CRF/Study Database

Study staff will actively elicit and collect information about the occurrence of adverse events in a non-leading manner during the active collection period (as defined above), covering the time period beginning when the first protocol-required procedure is performed at Visit 1 and concluding 15 minutes after the procedure is performed. AEs identified as occurring during the active collection period may be based on symptoms or other complaints reported to the Investigator (or designee) by the participant, or may be based on clinical findings made by the Investigator (or designee).

The Investigator is required to assess whether these events are serious or non-serious, and whether or not they are related to study participation. All AEs that occur during the active collection period will

be collected in the clinical study database only via the CRF. These procedure-related events do not need to be sent to the Pfizer DSU.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

7.6.2 Medically Important RRIs

Given this study only involves specimen collection using methods routinely used in clinical care (i.e., collection of urine, nasal swabs, and blood samples), no SAEs are anticipated. However, should a participant, in the investigator's opinion, suffer a medically important research related injury (RRI) caused by their participation in the study, the sponsor and designated Pfizer clinician or medical monitor must be notified immediately. A medically important RRI is any untoward medical occurrence that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the
- ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an injury is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as a medically important RRI.

7.6.3 Vaccine-Related SAEs and Other Special Exposure Scenarios

AvonCAP study staff will also record SAEs related to the Pfizer-BioNTech COVID-19 vaccine, BNT1672b2, should the investigator (or designee) become aware of any such event during the course of the study.

SAEs that are explicitly related to receipt of BNT1672b2 vaccine will be reported to the Pfizer Drug Safety Unit (DSU) within 24 hours of awareness via the provided Pfizer SAE report form, if the investigator becomes aware of such an event at any time during the study.

This study recognizes that, although active solicitation of safety reports related to receipt of BNT162b2 vaccine is not required as part of this study, the sponsor/investigator/research team may incidentally become aware of reportable events, as described in this section, through **unsolicited** patient report. Examples of how this might occur included, but are not limited to:

- the study participant reports an event during enrollment, contacts the investigator or study staff **outside** of the active collection period

- the Investigator becomes aware of events explicitly related to BNT162b2 through medical record review performed for the purposes of study data collection.

The awareness date for the purpose of reporting an event to the Pfizer drug safety unit is the date that the Investigator (or designee) becomes aware of the presence of all 4 minimum reporting criteria (i.e. an identifiable subject, an identifiable reporter, an event meeting SAE or special exposure definition, and history of vaccination with BNT162b2 vaccine). If the Investigator becomes aware of additional information about the event following initial reporting, this additional information must also be reported in a follow up report within 24 hours of awareness. The Investigator may also be requested by the Pfizer DSU to obtain specific follow-up information in an expedited fashion. Furthermore, the research team will encourage study participants to report their vaccine-related AE or SAE to the MHRA via the Yellow Card system.

Special exposure scenarios, including Exposure During Breastfeeding [EDB], Occupational/Environmental exposure, medication errors and overdose related to BNT162b2, will be reported to the Pfizer DSU within 24 hours of awareness. Definitions and reporting instructions are included in the Safety Reporting Reference Manual.

Exposure during pregnancy (EDP) to the COVID-19 vaccines including BNT162b2 is not reportable as an individual safety report, unless there is an associated SAE. Since vaccine effectiveness by pregnancy status is an endpoint in the study, these exposures will be summarized in the clinical study report (CSR). No clinical data on the pregnancy will be collected as part of this study, but follow-up information may be requested by the Pfizer DSU if the case is also associated with an SAE.

BNT162b2 vaccine effectiveness is an AvonCAP study endpoint, so individual SAE reports for lack of efficacy will not be submitted to the Pfizer DSU as vaccine-related AEs. Vaccine effectiveness will be summarized in the CSR.

The definitions of an AE, SAE, RRI, LOE and special exposure scenarios can be found in the Safety Reporting Reference Manual.

8 Study procedures and clinical data – Non-Consented arm

Total duration of participation per participant will be approximately one month from date of admission.

8.1 Non-consented, Surveillance Admission Data Collection (Day 1)

Screening all potential participants (adult patients with respiratory symptoms and/or suspected COVID-19) for eligibility for the disease surveillance study. Every effort will be made to approach, discuss, and enrol participants in the consented study arm and seek their consent for collection and use of data. However, in patients in whom it is not practicable to do so, surveillance activity will be undertaken as outlined below. Participants should be enrolled as soon as feasible after admission (no later than 48 hours after admission if at all possible). Data collection will include the following activities:

- Screen patients against the inclusion/exclusion criteria of this protocol
- Enter standard of care data into eCRF for LRTD events

8.1.1 Admission data collection

Patients meeting screening criteria will have basic demographic and clinical data collected on an e-CRF. This will involve collection of the following data at admission:

- Patient details
- Eligibility checks – inclusion/ exclusion criteria components
- Date of hospitalization
- Demographics (age, gender, race/ethnicity, socioeconomic status estimated by postcode, vaccination [influenza/ PCV13/PPV23/COVID-19 and date of relevant administration], smoking status, alcohol/drug use)
- Details of present illness (symptoms, date of onset, vital signs on admission to hospital)
    - Used antibiotics/antivirals in the 14 days prior to admission
- Standard-of-care test results
    - Routine biochemistry and haematology test results on admission, including C-reactive protein and NT-proBNP, and blood group
- Hospitalization data:
    - Admission hospital
    - Dates and time of admission

- New York Heart Association (NYHA) Heart Failure Classification, Pneumonia Severity (CRB65 and PSI scores)
- Relevant Medical History and Major Comorbidities
- Rockwell Frailty Score and Charlson Comorbidity Index

8.2 Non-consented Patient Outcome measures

The follow-up information should be collected 1 month after enrolment or when the patient is discharged from hospital (whichever occurs later). At day 30 after admission, the following will be assessed and recorded in the CRF:

- Microbiological investigation results
    - Blood cultures.
    - Respiratory microbiology testing, including bacterial (eg, PCR and culture) and viral testing (eg, COVID19, RSV and influenza),
    - Pneumococcal testing (eg, BinaxNOW urine test),
    - Antibiotic resistance results for pneumococcal isolates
    - Sputum Gram stain results
- Hospitalization data:
    - Dates of discharge
    - ICU stay (yes/no)
    - Number of days in ICU
    - Mechanical ventilation and days of ventilator use
    - Requirement for new/increased haemofiltration
    - Non-invasive ventilation requirement and days of usage
- Vital status at Day 30 after enrolment:
    - Deceased, not recovered, recovered, recovered with sequelae, recovery ongoing, unknown
    - Date of death if under 30 days from admission
- Record final clinical/standard-of-care diagnosis for qualifying acute LRTD illness:
    - CAP – radiologically or clinically confirmed, acute bronchitis/LRTI, exacerbation of underlying chronic respiratory disease, LRTI not otherwise specified, congestive cardiac failure, empyema/lung abscess, non-infective process, and non-respiratory infection-related diagnosis.
- Cardiac complications through Day 30 after enrolment:

  - ST- and non-ST elevation myocardial infarction, cerebrovascular accident, new episode of atrial fibrillation or other arrythmia, venous thromboembolism, cardiovascular-related death
- Hospital related adverse events (e.g., falls in hospital and hospital-acquired infections)

The Principal Investigator or designee should make an assessment of final standard -of-care LRTD-related diagnosis if any discrepancy exists in the record. The Investigator is to also confirm, based on any existing or new information, if the participant had clinically and radiographically confirmed pneumonia.

8.3 Non-Consented arms Patient Outcomes: One-year mortality assessment on Day 365

The assessment may be completed 365 to 390 days after enrolment by medical record review, during a follow-up standard care visit and/or other means.

At day 365 after admission, the following will be assessed and recorded in the CRF:

- Vital status (alive or deceased) at Day 365 after enrolment
- If the participant is deceased, total survival days following enrolment

8.4 Ongoing clinical care

This is an observational epidemiological study collating and recording standard-of-care investigations and patient details in a consented study with enhanced diagnostic tests. As such, Avon CAP should not impact on any aspect of clinical care or other interventional trial in which the patient may be participating.

8.5 Research-related injury reporting

Given that this study is non-interventional and covers a period during which participants are under clinical care, Adverse Event data will not be recorded - except that which is pertinent to study data collection - and Serious Adverse Events will not be reported unless they are related to the patient's involvement in this study.

Any event that;

- Results in death;

- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions); OR,
- Results in congenital anomaly/birth defect.

and is judged by an Investigator to be possibly, probably or definitely related to the patient's participation in this study (i.e. the collection of their data) will be reported to the Sponsor within 24 hours and to the approving REC within 15 days of the study team becoming aware of it.

9 Study size and data analytics

9.1 Study size

Expected study size was calculated using both a retrospective coding data from 2018-2019, and a 21-day prospective audit of adult patients admitted to the Acute Medical Unit at NBT. It should be noted that both methods used to calculate estimated patient numbers were conducted in a time period before the COVID-19 pandemic. Both methods calculated an Avon CAP patient cohort approximately 7,000 adult patients per annum at NBT, and assuming all 2 hospital sites have similar patient numbers, the envisaged patient cohort before COVID-19 was 14,000 patients per annum. However, given the COVID-19 pandemic we expect a significantly large sample size, which is likely to approximate 23,000 patients per annum across the 2 sites. Number of adults in surveillance population is approximately 630,000, yielding expected LRTD incidence of >3,600 per 100,000 population annually (3.65 per 100 person years; 95% CI: 3.60 to 3.70).

9.2 Pneumonia and LRTD group classifications

LRTD participants will be classified by standard-of-care diagnoses extracted from the medical chart and using standardized case definitions (e.g., for radiologically confirmed CAP). Standardized case definitions not specifically referenced in the study objectives will be included in the Statistical Analysis Plan (SAP). Events with a final diagnosis of pneumonia by the treating clinician will be considered to have standard-of-care pneumonia diagnosis. A case of RSV is considered any patient with positive molecular test from any specimen type and/or RSV seroconversion defined as 4-fold rise in RSV antibody titers between acute/convalescent samples. Participants with pneumococcus identified through standard of care testing (aside from colonization specimens) and UAD1/2 and BinaxNOW will be considered to have pneumococcal infection. COVID-19 infection will be defined as any patient who has current infection confirmed via laboratory diagnostic testing (molecular, serological or other future test deemed clinically appropriate to determine current SARS-CoV-A infection). Alternatively, any individual who meets any future diagnostic criteria which are determined sufficient to confirm current SARS-CoV-A infection will also be deemed to have COVID-19.

9.2.1 Radiologically confirmed pneumonia

Radiologically confirmed pneumonia will be defined as patients in whom the treating physician clinically suspected pneumonia who meet the following 2 criteria:

1. Has a radiologic finding that is consistent with pneumonia (e.g., pleural effusion, increased pulmonary density due to infection, the presence of alveolar infiltrates [multilobar, lobar or segmental] containing air bronchograms); **AND**
2. Illness involves ≥2 of the following signs or symptoms:
   a. fever (>38.0°C) within 24 hours before enrolment
   b. hypothermia (<35.5°C) within 24 hours of enrolment
   c. chills or rigors
   d. pleuritic chest pain
   e. new or worsening cough
   f. sputum production
   g. dyspnea (shortness of breath)
   h. tachypnea (respiratory rate >20/min) documented by healthcare professional
   i. malaise
   j. abnormal auscultatory findings suggestive of pneumonia (crepitations/rales or evidence of pulmonary consolidation including dullness on percussion, bronchial breath sounds, or egophony).

9.2.2 Lower respiratory tract infection

Lower respiratory tract Infection will be defined as enrolled subject with one of the following:

1. Final clinical diagnosis consistent with LRTI (ie, pneumonia or other LRTI); **OR**
2. Positive laboratory test for pneumococcus, RSV, SARS-CoV-2 or any other infectious respiratory pathogen; **OR**
3. Evidence of both:
   a. Active infection, ie at least 1 of the following conditions: reported fever, reported chills, measured temperature of >38.2°C or <35°C, or an abnormal white blood cell count or differential) **AND**
   b. Lower respiratory tract disease (at least 1 of the following conditions: abnormal breath sounds, documented tachypnea, cough, sputum production, or dyspnea)

9.2.3 Cardiovascular events following pneumonia

The rates of cardiovascular events at 30 days following pneumonia will be compared to rates among controls without acute LRTD in the 2 months prior to their enrollment. In addition, a group of comparable persons based on age, Charlson co-morbidity index and underlying disease will be assembled through analysis of anonymized health data to assess the rate of these outcomes in this population with pneumonia. Full details will be provided in the SAP.

9.2.4 Acute Respiratory Illness (ARI)

The WHO definition of ARI will be used: An acute respiratory infection with: history of fever or measured fever of ≥ 38 C°; and cough; with onset within the last 10 days; and requires hospitalization. (https://www.who.int/influenza/surveillance_monitoring/ili_sari_surveillance_case_definition/en/)

9.3 Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the investigators. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.4 Limitations of the research methods

As with any study in humans there is potential for limitations. The methodology used here in recruiting participants, data collection and analyses will seek to minimize these, as listed below.

9.4.1 Denominator

The two hospitals included in the study serve much of the Bristol population. However, there is likely some cross over at the geographical borders, for example with Bath Hospital. It is expected that this may be directional towards Bristol, as both hospitals are tertiary referral centres so individuals may preferentially attend in Bristol rather than Bath, which is a district general hospital. The team will have assessed the degree of such cross over by the analysis phase so that a correction can be factored into the denominator, but this will be by estimation.

9.4.2 Representativeness

Hospitalized individuals admitted with LRTD who meet the eligibility criteria will be invited to participate in the enhanced diagnostic testing portion of the study. It is possible there could be bias in the refusals being different from those who do take part, for example those with most severe disease. Further, if recruitment for enhanced diagnostic testing cannot be performed at all times (eg, weekends, overnights, and holidays), some patients with acute LRTD may not be able to participate in the enhanced diagnostic testing portion of the study on that basis. The representativeness of enhanced diagnostic testing participants will be established by comparing the groups that have accepted and declined using eCRF data.

9.4.3 Recruitment completeness

It is possible patients may be missed by virtue of their pathway through the hospital being atypical, the time of admission or a human error factor. This would be a random error so should not bias the study. Every effort will be made to identify such patients through ongoing audits for surveillance completeness (e.g., via radiological records, ICD discharge codes, or microbiology tests ordered). A second factor may be the inability to collect samples from all consented participants, possibly through their refusal or inability to provide them. This will be addressed through appropriate training of staff in the importance of and methods to obtain as comprehensive a set as possible, while respecting patient choice and well-being.

9.4.4 Data completeness

Collection of information will mainly come from medical notes, which may not always be complete. However, the fields selected for this study would come from the basic registration information and from details that would be required in order to treat the individual so should be completed reliably.

10 Regulatory issues

10.1 Research governance

This study will be conducted in accordance with:

- The International conference for harmonisation of good clinical practice (ICH GCP)
- The UK Policy Framework for Health and Social Care Research, and
- The Declaration of Helsinki

10.2 Ethics approval

The Health Research Authority (including review by an NHS research ethics committee) will review the study prior to recruitment commencing. The HRA/NHS REC will be asked to approve the study protocol, as well as any "public-facing" or "participant-facing" documentation (e.g. patient information sheet and consent form). All the above will be approved by the Sponsor prior to submission.

10.3 Risks and anticipated benefits for participants and society

10.3.1 Potential benefits for participants:

There are no direct benefits to taking part in this study, however, the participant may feel that they are contributing to the scientific knowledge about COVID-19 and vaccine preventable infections during the pandemic which may help diagnostics, vaccine development, and future patient care.

10.3.2 Potential harms or risks to participants:

Biological Samples:

The collection of nasal/throat swabs, saliva, nasosorption, blood and urine samples are considered to be minimally arduous for participants. Potential harms:

- Venepuncture: taking blood samples may cause some discomfort and occasionally result in a bruise.
- Nasal swabs: participants may find this causes temporary discomfort or bleeding.
- Urine collection: this poses no risk

Data collection and protection:

There are risks to study participants concerning the collection and use of data, namely potential identification of study participants, inappropriate access to participants' data, and inappropriate transfer of participants' data.

In order to ensure that data protection requirements concerning identifiable data collected through this study, and the right to privacy and confidentiality are maintained, the study will:

- Apply to the Clinical Advisory Group for Section 251 of the NHS Act,
- Complete and adhere to Data Protection Impact Assessments
- Ensure that appropriate Data Security Protection Toolkit Assessments are undertaken by participating organisations
- That participating organisations adhere to GDPR compliance.

Further study protocols to mitigate these risks are outlined in Section 11 of this protocol.

10.3.3 Anticipated benefits for society

Data analysis will be conducted at interim intervals, which may allow for initial results for the primary and secondary outcome measures at a time-point before end date. This would allow for potential publication of important data which impacts on the clinical care of patients with COVID-19 and may impact vaccination strategies to prevent adult respiratory disease and associated morbidity and mortality. Further, this information is also intended to improve the understanding of how much LRTD is vaccine preventable, either with approved vaccines (e.g., pneumococcal vaccines) or investigational vaccines (e.g., RSV and COVID-19 vaccines), which would help inform vaccine recommendations in the future which allow for prevention of LRTIs in this population.

10.4 Sponsor approval

All study documents will be approved by the Sponsor prior to submission for regulatory approval. Any amendments following a favourable ethical opinion, will be approved by the Sponsor prior to submission.

10.5 NHS approval

Confirmation of capacity and capability from the local NHS Trust (NBT and UHBW) is required prior to recruitment. Any amendments to the study documents will be approved by all necessary parties prior to implementation.

10.6 Investigator responsibilities

This is a multisite observational epidemiology study. The Chief Investigator (Prof Adam Finn) will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participants. The CI will also be required to allow access to study documentation or source data, on the request, for monitoring visits and audits performed by the Sponsor or any regulatory authority.

10.7 Consent

Consented arm

In line with applicable regulations, consent will be obtained (as specified above) for access to patient data and to obtain clinical specimens.

Non-Consented arm

In line with applicable regulations, Confidentiality Advisory Group approval under Section 251 of the NHS Act 2006 will be sought to obtain patient records without consent. This will only apply to individuals who are eligible for the study but who could not be approached to discuss or seek consent to participate in the consented study. Therefore, Section 251 of the NHS Act will only apply to those individuals in whom it is not practicable to obtain consent e.g. those who died or were discharged before the research team could approach them. For participants enrolled in the embedded enhanced diagnostic study arm, consent will be obtained for access to patient data. Individuals approached by the research team to discuss and seek consent for the embedded enhanced diagnostic study will subsequently fall into three categories:

- Those who provide full consent to the study, including access to medical data
- Those who provide consent to access to medical data only (and not biological samples)
- Those who decline consent and are not enrolled in the study, and are only noted in the screening log

10.8 Confidentiality

The Chief Investigator (Prof Adam Finn), Principal Investigator (Dr Catherine Hyams) and Sponsor (University of Bristol) will preserve the confidentiality of participants taking part in the study in accordance with the Data Protection Act 2018 and any other local requirements. Study documentation and the study database will be anonymised using a unique identification number, generated during enrolment. No individual participant will be identified in any publications which may arise from this study.

10.9 Indemnity

The University of Bristol has arranged Public Liability insurance to cover the legal liability of the University as Research Sponsor in the eventuality of harm to a research participant arising from management of the research by the University.

The University of Bristol holds Professional Negligence insurance to cover the legal liability of the University, for harm to participants arising from the design of the research, where the research protocol was designed by the University.

The University of Bristol's Public Liability insurance policy provides an indemnity to our employees for their potential liability for harm to participants during the conduct of the research.

Equivalent appropriate cover will be in place at all study sites. In addition, investigators have the protection of medical malpractice indemnity with the Medical Protection Society or Medical Defence Union.

10.10 Sponsor

University of Bristol will act as the Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

10.11 Monitoring

The study may be subject to inspection and audit by University of Bristol (under their remit as Sponsor) and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research.

Monitoring is provided on behalf of University of Bristol by University Hospitals Bristol and Weston NHS Trust, who are contracted to monitor a sample of 10% of ongoing studies annually.

10.12 Patient expenses

No incentive payment will be made to patients involved in the Avon CAP study.

11 Data management

11.1 Data recording, storage and access

Accurate source data will be kept for all study participants. This will typically comprise the standard demographic information, past medical history, and baseline biochemistry results.

All data will be stored securely in line with the Data Protection Act 2018 and the principles of GCP. Electronic data will be stored on encrypted and password-protected severs. Physical records, including consent forms, will be stored in secured and lockable cabinets. In line with local policy for non-CTIMPs, data from this study will be retained for at least 5 years.

Appropriate Data Protection Impact Assessments will be undertaken as required for the surveillance study and will be submitted alongside the protocol for review by the HRA and other regulators. All necessary agreements, including Data Transfer Agreements, will be agreed between the respective NHS Trusts and University of Bristol. All study sites and the University of Bristol will ensure an accurate and updated Data Security and Protection Toolkit is available.

11.2 NHS Databases

A site-specific study database will be built within the NHS IT domain at each participating NHS site, using the REDCap database management software. Study data will be entered by the study team. The study database will only be accessible to named personnel within the study team using the password-protected REDCap website. User access privileges will be defined within the REDCap software to ensure that study staff are assigned an appropriate level of data access, with the minimum amount of data access required as the default access setting. The REDCap database will be programmed to mark identifiable fields (and therefore restrict their access or download), and to calculate fields such as length of hospital admission, survival (up to 30 days following admission), age at admission. These fields will be exported in the pseudonymised dataset as opposed to the specific date, thereby removing identifiers and aggregating data.

Before transfer of data to the University IT domain, the study CI, PI or senior research team member (such as research database manager) will undertake the following activity:

- Removal of name from any NHS database
- Removal of other potentially identifying fields from pseudonymised database (e.g. date of death, hospital discharge date)
- Splitting of the data, resulting in the production of two databases:

  - Pseudonymised database containing pseudonymising surveillance number and clinical data, with calculate fields
  - Identifiable data including NHS number, sector level postcode, ethnicity, date of birth and admission date
- Encryption of data and/or other data protection measures before transfer of data to the University IT domain, for example use of Open Pseudonymiser.

11.3 University of Bristol Data

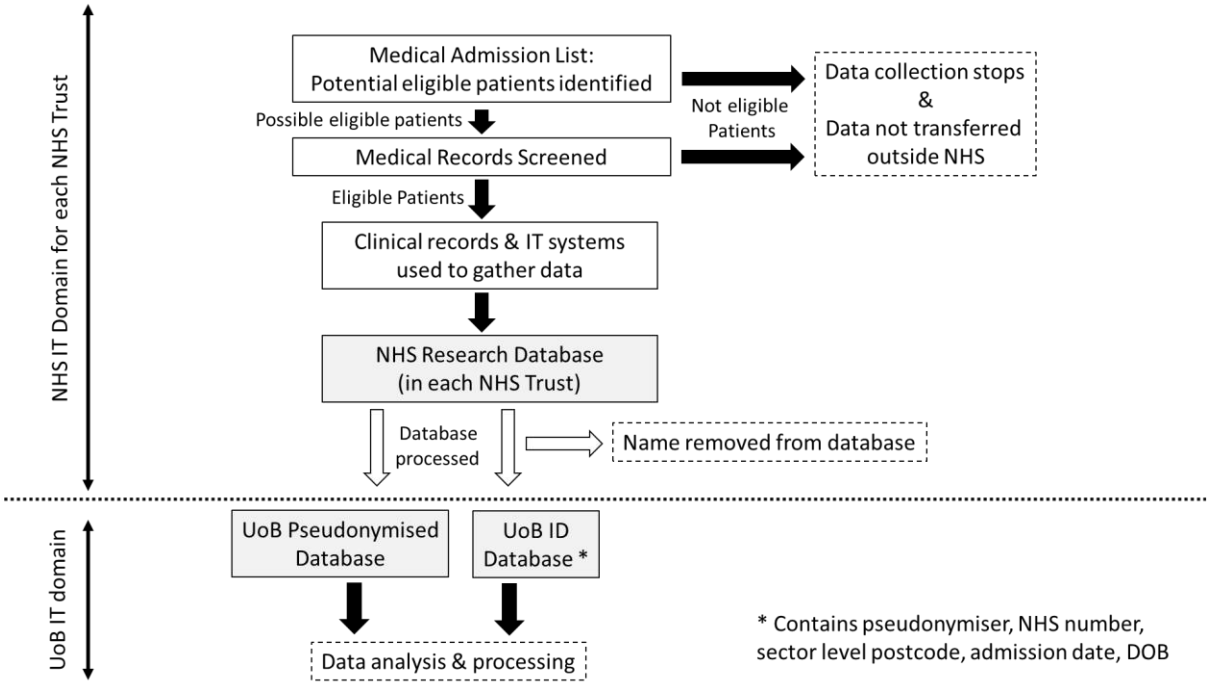
Data from each participating NHS Trust will be imported and held in two separate databases:

1. A REDCap database within a secure University IT domain, which contains only pseudonymised data
2. A password protected database containing identifiable data, with restricted user access on a bespoke server

This will create a single unifying research dataset, allowing for analysis of data to meet the study objectives, whilst enabling data security measures to protect data and participants.

Once the data has been pseudonymised, the identifying data will not be utilised unless there is a specific reason for this being needed (e.g. geotemporal analysis, identifying individuals across multiple NHS sites). Furthermore, wherever possible data will be processed to the least specific possible in order to address the research question being investigated – for example, patients will be aggregated by admission year, month or week of the year, or selected using a random number generator if this is possible. Ethnicity will be aggregated wherever possible (e.g. BAME, etc.).

11.4 Data Flow Diagram



11.5 Data monitoring

The study may be monitored by the Sponsor or other regulatory bodies. For the purposes of audit and compliance monitoring, clinical study data will be available to delegated members of the local study teams, as well as to representatives of the Sponsor, relevant regulatory authorities, and the study co-ordinating team. Participants in the consented arm will be consented to their study data being released for this purpose. Pfizer or its agent may conduct visits to the study sites during study conduct or after study completion to ensure that the protocol and Good Clinical Practices (GCPs) and/or Good Pharmacoepidemiology Practices (GPP), as relevant, are being followed.

11.6 Data Sharing

11.6.1 Data linkage

We plan to share data with our “sister” study AvonCAP GP2 (IRAS Reference: 305956), which aims to determine the incidence of aLRTD within the same defined geographical area but for patients presenting to primary care. Combining data from the studies will allow us to calculate the total aLRTD incidence for patients presenting to primary and/or secondary care within the Bristol area over a defined period. To facilitate this, participant identifiers (including NHS number and date of birth) will be securely shared by the AvonCAP GP2 study team, allowing identification of duplicate records. A list

of duplicate records will be produced, allowing data to be combined for these participants across primary and secondary care settings.

Due to the richness of the Avon CAP study dataset, and the unique period during which data will be collected (across the COVID-19 pandemic), it is anticipated that it will be of great value to other studies and organisations. In order to link with other datasets, we will ask to securely receive identifiable information from other studies and organisations. These data will be used to link to our retained participant identifiers. Pseudonymised data (i.e. study ID only) will be shared with these studies and organisations, and the amount of data items shared will be minimised. Appendix 2 will be used to record studies and organisations where data sharing has been requested.

11.6.2 **Sharing for secondary research**

Pseudonymised study data will be made available for sharing outside the AvonCAP study group following publication of the main results. Data will be made available for secondary research, conditional on assurance that the proposed use of the data is compliant with the MRC Policy on Data Sharing. A minimum requirement for sharing will be a publicly available protocol describing the purpose, methods and analysis of the research.

11.7 Publication policy

The Chief Investigator will have primary responsibility for the expedient preparation, review and submission of any manuscripts, abstracts, press releases or other publications detailing the study's procedures or findings. We will follow the International Committee of Medical Journal Editors (ICMJE) criteria to determine authors, and all authors who meet these criteria will be offered authorship. We anticipate that as a collaborative project, members of each of the study organizations (University of Bristol and Pfizer) will participate. Each organization will determine members that meet authorship criteria. Any publication will include a list of investigators, with authors being determined in line with the ICMJE guidelines, as well as an acknowledgement of roles of the study Sponsor and Funder(s).

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APPENDIX 1 – Description of COVID-19 vaccine effectiveness assessment

1. Analysis design

A test negative design will be used, with patients identified using a clinical case definition (e.g. acute respiratory infection (ARI)). Patients are then tested for a vaccine aetiologic agent, and VE is estimated by comparing the odds of vaccination among patients testing positive versus negative for vaccine-type aetiology. Adjusting can be undertaken for potential confounding factors that may exist in the absence of randomized participation and blinded follow-up. TND studies are considered a robust type of observational study for evaluating VE against infectious respiratory diseases (De Serres et al 2013, Jackson et al 2013, Lipsitch et al 2016, Sullivan et al 2014, Foppa et al 2016, Orenstein et al 2007). The main advantages of the TND are that it helps avoid bias due to (unmeasured) healthcare-seeking behavior and its ease of access to a series of controls that are representative of the source population. Previous research has shown that this simplicity does not necessarily come at the cost of validity (De Serres et al 2013, Jackson et al 2013, Lipsitch et al 2016, Sullivan et al 2014, Foppa et al 2016, Orenstein et al 2007, Schwartz et al 2017). Full details of these analyses will be outlined in the statistical analysis plan (SAP), which will include statistical adjustment to control confounding due to age and risk-based vaccination schemas.

2. Defining Cases and Test-Negative Controls

Both cases and controls will only include subjects that meet WHO ARI case definition in Protocol Section 9.2.4.

2.1 Detection of cases

SARS-CoV-2 will be detected by molecular techniques (i.e. nucleic acid amplification tests, NAAT) from biological specimens collected from the naso- or oropharynx. This will be undertaken via collection of results of routine standard-of-care testing or from research specimen (if not undertaken by standard-of-care testing).

Cases will be defined as patients who meet these analysis selection criteria and:

1. Test positive for SARS-CoV-2 via NAAT performed at hospital admission or study enrollment, OR
2. Tested positive by NAAT from samples collection ≤14 days prior to hospital admission or study enrollment.

2.2 Definition of Test-Negative Controls

All other patients who met study inclusion criteria (e.g., at least one NP or nasal swab that was tested for SARS-CoV-2 using NAAT) but for whom SARS-CoV-2 is not identified from NAAT will serve as test-negative controls. This approach mimics the definition of test-negative controls that is commonly used in TND studies of influenza and pneumococcal vaccines.

3. Primary exposure of interest

The primary exposure of interest is history of vaccination with COVID-19 vaccine. As an observational study design, COVID-19 vaccination is not part of the study procedures, rather it would be given as part of the national vaccination campaign. The dates of administration and which vaccine was given, by manufacturer or product, taken from medical records, will be included in the study CRF data.

COVID-19 vaccination status will be also captured as part of the patient interview and will be analyzed in sensitivity analyses.

For the primary objective, patients will be considered vaccinated if they have documented evidence of receiving the second dose of COVID-19 vaccine ≥7 days before symptom onset. When evaluating the effectiveness of one dose of COVID-19 vaccine, patients will be considered vaccinated if they have documented evidence of receiving the first dose of COVID-19 vaccine ≥14 days before ARI symptom onset.

Multiple levels of the primary exposure variable will be assessed, including:

1. **Fully vaccinated** defined as 2 doses of the same COVID-19 vaccine received with ≥7 days between ARI symptom onset and receipt of the 2nd dose. This group will serve as the 'exposed' group evaluated in the primary objective. Patients who received 2 doses of COVID-19 vaccine with <7 days between ARI symptom onset and receipt of the 2nd dose will be excluded from this analysis.
2. **Partially vaccinated** defined as 1 dose (only) of COVID-19 vaccine received with ≥14 days between ARI symptom onset and receipt of the 1st dose. This group will serve as the 'exposed' group as a secondary endpoint. Patients who received 1 dose of COVID-19 vaccine with <14 days between ARI symptom onset and receipt of the 1st dose will be excluded from this analysis.
3. **Ever vaccinated** defined as 1 or 2 doses of the same COVID-19 vaccine received with ≥14 days between ARI symptom onset and receipt of the 1st dose. Patients who received 1 dose of COVID-19 vaccine received with <14 days between ARI symptom onset and receipt of the

1st dose will be excluded from this analysis. This group will serve as the 'exposed' group as a secondary endpoint.

4. **Never vaccinated** defined as never received COVID-19 vaccine. This group will serve as the reference exposure group (i.e., 'unexposed' group) in all VE analyses.

TABLE 1. DEFINITIONS OF STUDY POPULATION, EXPOSURE, CASES, AND TEST-NEGATIVE CONTROLS FOR PRIMARY AND SECONDARY STUDY OBJECTIVES

Objective	**Study Population**	**Exposure***	**Case**	**Test-negative Control**
Primary Objective (1)	patients ≥18 years of age hospitalized for ARI	**Fully vaccinated** defined as 2 doses of the same COVID-19 vaccine received with ≥7 days between ARI symptom onset and receipt of the 2nd dose.	SARS-CoV-2 identified by NAAT	SARS-CoV-2 NOT identified by NAAT
Secondary Objectives				
2	patients ≥18 years of age hospitalized for ARI	**Partially vaccinated** defined as 1 dose (only) of COVID-19 vaccine received with ≥14 days between ARI symptom onset and receipt of the 1st dose.	SARS-CoV-2 identified by NAAT	SARS-CoV-2 NOT identified by NAAT
3	patients ≥18 years of age hospitalized for ARI	**Ever vaccinated** defined as 1 or 2 doses of COVID-19 vaccine received with ≥14 days between ARI symptom onset and receipt of the 1st dose.		

NAAT= nucleic acid amplification test; SARS-CoV-2= severe acute respiratory syndrome coronavirus 2.

** Patients who never received COVID-19 vaccine will serve as the reference exposure group (i.e., 'unexposed' group) in all VE analyses. For the primary objective, patients will be considered vaccinated if they have documented evidence of receiving the second dose of COVID-19 vaccine ≥7 days before ARI symptom onset. When evaluating the effectiveness of one dose of COVID-19 vaccine, patients will be considered vaccinated if they have documented evidence of receiving the first dose of COVID-19 vaccine ≥14 days before ARI symptom onset.*

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APPENDIX 2 – Data Sharing Requests

Study Short Title / Organisation Name	IRAS Number (if applicable)	Reason for data sharing
AvonCAP GP2	305956	To calculate the total aLRTD incidence for patients presenting to primary and/or secondary care within the Bristol area over a defined period
ALSPAC (Avon Longitudinal Study of Parents and Children)		Identify overlap between the studies, provide ALSPAC with additional COVID-19 related data on their participants