Study Protocol

Title: Facilitating A SARS CoV-2 TEst for Rapid triage (FASTER)

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Abstract
This project will evaluate point-of-need (PON) tests for the detection of the novel strain of coronavirus SARS-COV-2 (COVID-19) causing the rapidly growing deadly outbreak and will study the association between COVID-19 and *S. pneumoniae* colonisation and clinical outcome.

We are working with industrial partners who have developed a low cost, lateral flow assay (LFA) to detect viral circulating antigens and IgM/G against COVID-19 in less than 15 minutes. These PON tests are intended for the rapid triage of patients with fever and/or cough. Furthermore, the PON tests will be formatted as self-tests, offering the additional benefit of deploying widely in the home and community settings. In addition, we will evaluate ELISA assays to detect IgG, IgA and IgM against COVID-19.

Aims and Objectives

- Evaluate lateral flow tests and ELISAs in patients with presumptive COVID-19 attending the Liverpool University Hospital NHS Foundation Trust (LUHFT).
- To evaluate other molecular point-of-need diagnostic tests
- To investigate the association between 1) pneumococcal colonisation and COVID-19 infection among hospitalised persons tested for COVID-19 infection, and 2) pneumococcal colonisation and the severity of clinical outcome among hospitalised COVID-19 infected persons.
- To measure inflammatory responses at mucosal sites in participants by following up at day 2, 7 and 28post baseline samples (Day 0).
- To investigate blood immune cell activation and transcriptome in participants by following up at day 2, 7 and 28 post baseline samples (Day 0).
- To assess if frequency and density of pneumococcal carriage differs for those with COVID-19 infection compared to those without
- To assess the association between COVID-19 infection and pneumococcal pneumonia and the severity of outcomes associated with pneumococcal LRTI among hospitalized COVID-19 infected persons
- To develop a serum antibody assay for assessing vaccine response with the Pfizer-BioNGen vaccine

Background
In December 2019 a cluster of cases of pneumonia from a novel coronavirus called SARS-CoV-2 (COVID-19), was reported in Wuhan, China (1,2). This outbreak has spread rapidly, with over 160,000 reported Coronavirus disease (COVID-19) cases and 6,600 deaths as of March 16th, 2020 (3). The World Health Organisation (WHO) declared on the 12th of March the COVID-19 outbreak a pandemic (4). Currently, Europe has become the epicentre of the pandemic and in the UK, cases are increasing. Due to the rise of the number of samples to diagnose, tests are taking longer than expected. Among the foremost priorities to facilitate public health interventions is a reliable laboratory diagnosis. Prompt case confirmation is necessary to ensure rapid and effective contact tracing, implementation of infection prevention and control measures according to WHO recommendations, and collection of relevant epidemiological and clinical information. The ultimate diagnosis of COVID-19 is performed by laboratory testing as the clinical features are non-disease specific. Diagnostic testing for COVID-19 is currently undertaken using real-time reverse transcriptase PCR (RT-PCR) to detect the viral ribonucleic acid (RNA). These assays are sensitive but require sending the samples to reference laboratories and thus results are obtained with a delay. In the UK, results are reported with a delay of 2-4 days (5) impeding the correct triage of patients, correct isolation measures and therefore putting the community and healthcare workers at risk.
A fast and reliable diagnostic assay that could be used at the point-of-need (PON) is yet to be

developed. We have been working closely with our commercial partners in 2020 on the development of highly sensitive PON tests to facilitate diagnosis at the point of need and to reduce the consequences of diagnostic delay.

We will use dual antigen and antibody test prototype lateral flow tests and ELISA that are ready for preliminary evaluation, and subsequently use the lateral flow tests on-site to evaluate the test at the point of need. Left over and anonymised samples will be used to evaluate other diagnostic tests if appropriate.

Additionally, it is currently unknown why some patients develop severe COVID-19, while others have mild symptoms by the same SARS-CoV-2 infection. Although general predisposing factors, such as hypertension, kidney disease and diabetes are well established, immunopathogenesis data of severe infections involve hyper-inflammatory responses and cytokine storm but are less characterised. Colonisation of the nasopharynx results in micro-aspiration of pneumococci and promotes activation of alveolar macrophages with an inflammatory phenotype (6). Further activation by COVID-19 may lead to overwhelming inflammatory responses.
Previous studies have demonstrated that the presence of virus can increase pneumococcal colonisation facilitated by a pro-inflammatory response resulting in a secondary infection and increased disease severity. It is important, therefore, to investigate the relationship between COVID-19 and *S. pneumoniae* colonisation/lower respiratory tract infection (LRTI)as well as *S. pneumoniae* colonisation/LRTI and COVID-19 related disease severity among those that are COVID-19 positive.

The information from our study will add significantly to the understanding of COVID-19 diagnostics and control and will improve the evidence-base for the protection of patients, healthcare workers and the community from outbreaks of COVID-19. The acquired knowledge of this project will also inform current pneumococcal vaccination strategies that could potentially reduce cases of severe COVID-19 infection or prevent disease exaggerations due to a secondary pneumococcal infection in the seniors.

Method

Study design
This will be an observational study taking samples and collecting data from patients admitted with suspected COVID-19 at hospitals across the North West Coast region. Residents at nursing/care homes and patients at GP practices may also be approached to participate.

Participants and enrolment
All individuals fulfilling the inclusion criteria will be invited to take part in the study. Participation will be voluntary and there will be no payment. It is expected patients will appreciate the potential benefits of the study and be willing to participate.

Members of the research team will attend the clinical areas to invite eligible individuals to enroll. Verbal and written information, including a patient information leaflet (PIL) will be provided to eligible candidates

Due to the minimal burden of the study and the emergency condition of the patient, witnessed verbal consent will be sought in order to commence taking samples and data collection. Verbal consent will be witnessed by a member of the clinical team and documented for evidence. A copy of the participant information leaflet will be given to the participant for their records.

If a participant loses capacity during the study due to a deterioration in their condition, a member of the clinical team will be approached to act as a nominated consultee. It is not practical to approach a family member as they will be restricted from visiting the hospital to reduce transmission. The member of the clinical team will be asked if they consider it appropriate for the participant to continue in the study. They will be given written and verbal information to consider and asked to complete the consultee declaration form if they think it is appropriate. If they decline or think that it is not appropriate, the participant will be removed from the study and only previously collected samples and data will be used. If the consultee thinks it is appropriate for the participant to remain in the study, samples and data will continue to be collected. Participation is considered minimally intrusive with data collection and minimally invasive samples collected only. Due to the nature of the disease, it is considered that a large number of participants may require ventilation, thereby, losing capacity to consent. In order to gain scientific merit from such studies, we need to validate the use of the PON tests with a variety of patients experiencing varied severity of disease. Removing all of these participants would negatively affect the validation of the test. In normal circumstances, we would ask for a family member to act as a nominated consultee on behalf of the participant, however, family members are prohibited from entering the hospital to reduce the spread of the pandemic.

The research team (nurses/doctors) will screen patients that are admitted to LUHFT with respiratory symptoms and symptoms typical of COVID-19. These patients will be given a participation information leaflet (PIL) and verbal information. They will be given adequate time to decide if they wish to participate in the study. If they are happy to participate in the study, they will be asked to give verbal consent that will be witnessed and documented by a member of the clinical team. The research team will provide the patient information sheet and request consent from the participant. The baseline samples will be taken on the same day as the participant consent/ witnessed verbal consent

Participants will be able to take part in multiple research studies relating to COVID-19 in order to increase the knowledge of pandemics. We are collecting samples at different timepoints deliberately so there is minimal daily burden on patients for samples.

Inclusion criteria

- **Adults 18 years old**
- **Presenting with any of the following COVID-19 symptoms**
    - fever ≥37.8^{0}C +/-
    - shortness of breath +/-
    - new/ persistent cough

OR

    - Clinical or radiological evidence of pneumonia
- **Fluent spoken English** - to ensure a comprehensive understanding of the research project and their proposed involvement
- **Capacity to give informed verbal consent**

Exclusion criteria

- Children under 18 years old
- No symptoms of COVID-19

- Lack of capacity or unable to perform verbal consent

Participants will be free to withdraw from the study at any point without giving any reason. Data and samples taken up to the point of withdrawal will be used, however no further samples or data will be collected.

The enrolment questionnaire will collect demographic and comorbidity data as well as baseline symptoms. Each subsequent sampling will include a very brief symptom questionnaire. All data will be entered onto LSTM's protected servers.
We will collect some medical, medication, vaccination history and pneumococcal risk factors from the participant's GP. This will be completed retrospectively by sending a GP questionnaire. To avoid unnecessary burden during the pandemic, the GP can send a printout of the Participant medical, medication and vaccination history from the primary care records using EMIS or relevant IT system. Participation into the study is not dependent upon completion of the GP questionnaire.

Study period

The study period will start as soon as possible after ethical approval is granted and will continue for a period of up to 12 months.

Endpoints

Cross sectional

- Prevalence of COVID-19 positive tests among all study participants at time 0 (enrolment point) and at follow up (2, 7, and 28 days post enrolment) among COVID-19 positive hospitalised patients
- Absence of COVID-19 in study participants at time 0 (enrolment point) and at follow up (28 days post enrolment) for negative patients
- Sensitivity and specificity of the PON tests (LFA assay) in comparison with the ELISA
- test developed by Mologic and the reference test used in the NHS
- To evaluate the potential of the PON tests and identify barriers to clinical implementation.

Percentage of participants with pneumococcal LRTI identified by any means (eg, UAD, Binax, blood or high-quality lower respiratory culture) among participants with a positive COVID-19 test compared to participants with a negative COVID-19 test, overall and stratified by age group

- During hospitalization, pneumococcal carriage prevalence and density among participants with versus without a positive COVID-19 test, overall and stratified by age group.

- Among COVID-19 positive persons, the percent of participants with pneumococcal LRTI or carriage among participants with versus without severe outcomes (severity will be defined as described below)

Serum COVID-19 antibody levels as determined at Pfizer.

- The rate of SARS-CoV-2 shedding as defined by exhaled detection facemask at day 0 (presence and density (CFU/ml).
- Detection of other respiratory viruses and *S. pneumoniae* carriage as defined by the exhaled detection facemask and nasopharyngeal swabs at D0

Longitudinal

- Proportion of tested persons with COVID-19 determined by seroconversion, antigen detection and viral RNA
- Comparison of host immune responses (IgG, IgA and IgM levels) in participants with

infection who develop severe COVID-19 disease versus COVID-19 positive participants without severe disease

- To evaluate the kinetics of host inflammatory responses during different stages of theCOVID-19 disease, among all patients and stratified by different measures of pneumococcal carriage (frequency, density, duration) as well as stratified by those who did and did not have evidence of pneumococcal LRTI

- Frequency, density and duration of pneumococcal carriage among participants with COVID-19 infection compared to frequency, density and duration of pneumococcal carriage among participants without COVID-19 infection, overall and by age group

Pneumococcal-related LRTI Case Definition. Enrolled participants with following test results will be considered to have a pneumococcal lower respiratory tract infection (LRTI): positive UAD1/UAD2, BinaxNow, or pneumococcus isolated from relevant bacterial cultures including standard of care specimens (ie, blood, pleural fluid, and high-quality lower respiratory specimens). Use of a more restrictive definitions will also be explored that also require: 1) lower respiratory tract disease diagnosis (eg, pneumonia or LRTI) or LRTI sign/symptoms (at least 1 of the following conditions: abnormal breath sounds, documented tachypnea, cough, sputum production, or dyspnea) and/or 2) radiologic confirmation of pneumonia.

Severe COVID-19 disease. Severe COVID-19 will be defined as requiring mechanical ventilation. Additional measures of severity involving length of stay, level of hypoxia, and mortality will also be explored.

Sample size

The proportion of patients with symptomatic COVID-19 who will attend the LUHFT is not known, thus sample size calculations are challenging. Current testing (early March 2020) indicates ~20% of suspects are COVID-19 positive. The R0 is expected to be between 2 and 3 but the number of patients who will be admitted, as well as the effectiveness of the recruitment process is not known.

We expect to recruit at least 400 participants. Enrolling 400 participants would allow a precision of +/- 0.03 with 95% of confidence if the prevalence of positives was around 10%.

For the objective of determining whether COVID-19 is associated with the presence of pneumococcal carriage, we modeled carriage prevalence of 7% (baseline culture positive), 15%, and 40% (baseline PCR positive); 2x and 3x increase in carriage among those COVID-19 positive vs. COVID-19 negative; a 1:1 and 3:1 ratio of COVID-19 negative to positive patients. For all scenarios except 7% carriage, 2x increase, and 3:1 ratio, the 400 planned participants will provide an adequate sample size assuming 10% drop-out.

If there was a strong desire to participate in the study, the enrolled number could be increased, pending additional funding. We may also consider enrolling additional participants for some objectives. For example, depending on the proportion of pneumonias due to pneumococcus we may need to enroll additional participants to assess the objectives related to this outcome.

The study may be stopped for reasons of futility or if the study becomes unviable.

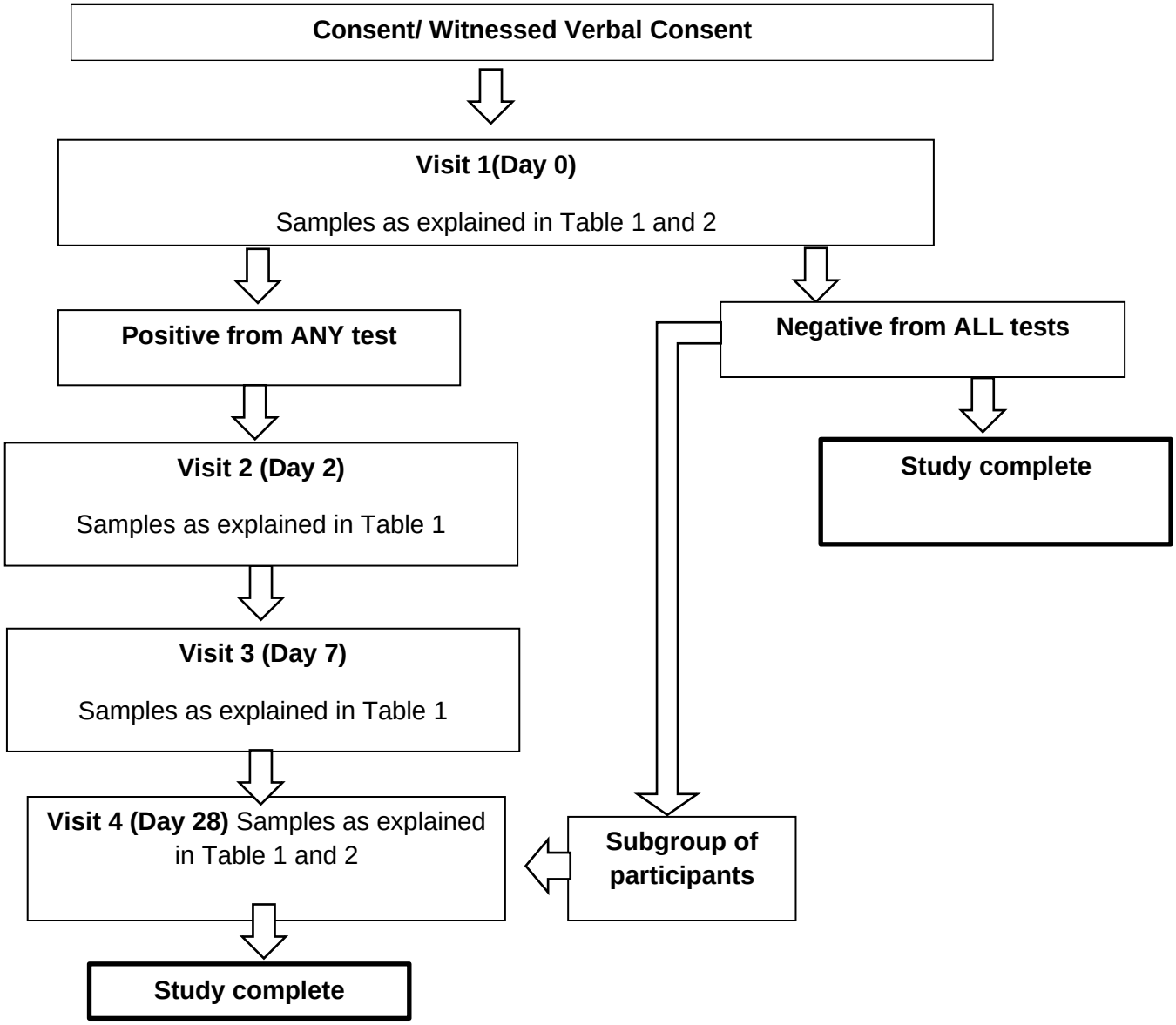
Participant enrolment and follow up

The study will run for 12 months. Preparations for running the study have started, pending ethical approval.

Participants who have provided verbal consent, will complete a brief baseline questionnaire, providing demographic information and information on baseline health status which will be submitted to the research team on the day of recruitment. The research team will perform the sample collection. They are trained and experienced in the sampling methods and will work according to GCP guidelines.

Participants will be requested to record any known COVID-19 contact, without personal identifiers. Participants who test positive (enrolment point using any of the COVID-19 tests) will continue to follow up if admitted to hospital. A selection of those testing negative will also continue with follow up samples at day 28 only. They will be asked to submit further information on their illness including, change in symptomatology, number of days they remain away from work. During their illness, they will be advised to follow national guidelines and will be assessed and treated by routine clinical services, as required. Samples from negative participants will be taken at LSTMs ARC facility, Well-Travelled Clinic or Clinical Research Facility within the hospital. Participants testing positive will be followed up at day 2, 7 and 28 post baseline samples. If discharged from hospital, they will be invited to attend the clinic for day 28 samples. If the participant is unable to attend a clinic visit but is willing to have day 28 samples taken, a research nurse may visit the participant at their home address to allow the samples to be taken. All staff in the clinic or visiting the participant at home will wear PPE when sampling from both the previously negative and positive participants.
The NHS health care team will be advised if the results from the qPCR test within this study are positive and the NHS qPCR test is negative where possible. The results from the investigational testing will not be made readily available to the NHS healthcare team. All samples will be taken by trained and experienced research nurses/ doctors at each timepoint as per Figure 1 and Table 1 and 2.

Figure 1: Participant Flow Chart



Nasal & throat combined swabs: Two nasal & throat combined swabs will be collected. The swab will be inserted into the mouth to swab the palatopharyngeal arches and then into the media. The same swab is then inserted into the nose and rotated. The swab will be taken according to the NHS guidelines. This process will be repeated for a second sample. It is important that the NP swab for the reference test is taken at the same time as other project samples as viral dynamics are not well understood (i.e. not reliant on the outcome of the NHS swab). The participants will be asked to answer a brief questionnaire accompanied with the swabs.

Throat swab: A swab will be inserted into the mouth and wiped over the palatopharyngeal arches and then inserted into media. This will be repeated at each visit.

Saliva: this involves the participant providing a 1ml saliva sample by using a saliva funnel to directly spit into a saliva tube.

Blood samples: Up to 40ml (~7 teaspoons) of blood will be taken.

Nasosorption: An absorbent material will be inserted into the nostril for up to 3 minutes to collect nasal secretions. This will be repeated in each nostril per visit (2 samples).

Urine samples: 20mls of urine will be collected for testing by BinaxNOW, a commercially

available *S. pneumoniae* antigen test, and Pfizer's serotype specific urinary antigen detection (UAD) tests: UAD1 (the 13 serotypes in PCV13) and UAD2 (the serotypes in Pneumococcal polysaccharide vaccine [PPSV23] that are not in PCV13),which are the most sensitive diagnostic tests available for non-bacteremic pneumococcal pneumonia.

Exhaled detection facemask: Some participants (those not requiring oxygen) will be asked to breathe into an exhaled detection mask. They will wear the face mask so it covers both nose and mouth for a duration of 30-60 minutes. There are no restrictions on talking or coughing while the mask is in situ. After sampling the face masks are removed and immediately placed in a double grip seal bag then stored at 4°C. The gelinate filer is then removed and cultured.

The initial phase of the study will recruit suspected and positive participants into the study as described above to validate the LFA within the lab. Once this phase is complete, the LFA will move to the bedside and subsequent participants will be sampled as described above and have the LFA perfomed at the bedside. For the purpose of the protocol and PIL we have referred to this as the oral test.

Oral test: Some participants will be required to use an oral test to take some liquid and cells from their mouth, inside their cheek to test for COVID-19. This will occur at the bedside to validate the LFA test.

Samples and accompanying questionnaires will be collected from a designated collection point by the research team and handed in to the designated research staff within the same sampling shift. Depending on the number of participants recruited, samples will be processed within the same day in LSTM laboratories or stored at -80^{0}C until processed.

Participants positive for COVID-19 with any of the tests will be retested on day 2, 7 and 28 post baseline samples. In this stage, saliva, nasal/throat swabs, nasosorption, blood and urine samples will be taken at each timepoint. A subgroup of participants testing negative will also be tested at day 28 post enrolment only. They may be required to attend a clinic appointment or have a research nurse to their home to complete this visit. If a participant is discharged from hospital, they may be invited to attend clinic or a home visit arranged for day 28 visit only.

Once the study is completed, participants may be invited to take part in further studies (specifically research bronchoscopy in recovered participants) this will involve a separate PIL from a separate research protocol.

Table 1. Participant sample schedule COVID-19 positive at baseline

	Baseline	**Follow up**		
Visit	**Day 0**	**Day 2**	**Day 7**	**Day 28**
Window (days)	NA	+/- 1	+/- 2	+/- 15
Consent/ Witnessed Verbal Consent	X			
Blood	X	X	X	X
Nose & throat combined swab x2	X	X	X	X
Throat swab	X	X	X	X
Saliva	X	X	X	X
Nasosorption x2	X	X	X	X
Urine	X	X	X	X
Oral test	X$^{\$}$	X	X$^{\$}$	X$^{\$}$
Exhaled detection facemask	X*$^{\$}$			

X$^{\$}$ Only in a select group of participants

Table 2. Participant sample schedule COVID-19 negative at baseline

	Baseline	Follow up
Visit	**Day 0**	**Day 28**
Window (days)	NA	+/- 15
Consent/ Witnessed Verbal Consent/legal representative consent	X	
Blood	X	X*
Nose & throat combined swab x2	X	X*
Throat swab	X	X*
Saliva	X	X*
Nasosorption x2	X	X*
Urine	X	X*
Oral test	X*$	X*$
Exhaled detection facemask	X*$	

X* Only in a subgroup of participants

X*$ / X$ Only in a select group of participants

Laboratory procedures

The table provides an example of the laboratory test that may be performed however this may be limited or expanded upon.

Table 2. Details of laboratory procedures to be performed on each sample type.

Sample type	Key analyte	Additional analytes that may be measured
Blood (up to 40mls)	COVID-19 antibody testing i.e IgG, IgM Immune cell phenotyping and activation Serum antibody assay	Molecular testing for COVID-19 by qPCR Immunological markers including CRP & PCT
Nasal/throat swabs (x2)	Molecular testing for COVID-19 and influenza by qPCR Pneumococcal DNA by molecular methods	Viral load
Saliva	COVID-19 antibody and antigen testing by LFA Pneumococcal DNA by molecular methods	COVID-19 antibody testing (IgG, IgA) by ELISA
Nasosorption	30 cytokines and chemokines	
Urine	Pneumococcal antigen testing, overall and serotype specific	

Exhaled Detection facemask	Molecular testing for SARS-CoV-2 by qPCR	Molecular testing for other respiratory viruses and *S. pneumoniae* by qPCR

Ethics
Ethical approval for the study will be sought from the NHS Health Research Authority

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 during the pandemic which may help diagnostics and future patient care. There will be no payment made to the participants.

Potential harms or risks to participants:
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 & combined throat swabs: participants may find this causes temporary discomfort or bleeding, the throat swab may make them gag a little.
Saliva, nasosorption and urine collection: these pose no risk
Exhaled Detection Facemask: participants may feel claustrophobic while wearing the facemask

Potential harms or risks to researchers:

Risk to researchers: possible risk to researchers include:

1) Needle stick injury during venepuncture
2) Infection from contact with positive participants
3) Biological and chemical hazards within the laboratory

The research team competencies in each role are assessed and delegated by the Chief or Principal Investigator. Procedures undertaken are consistent with LSTM and NHS SOPs and GCP guidelines. Appropriate risk and COSHH assessments are in place for all laboratory procedures. All laboratory work will be conducted in line with health and safety regulations for research with human tissues / infectious agents. All Personal Protective Equipment (PPE) will be used by research staff in contact with participants as recommended by Public Health England (PHE).

Sample storage and Data management

Professor Daniela Ferreira will act as the custodian of the samples. All samples and data collected during the study will be anonymized. As part of recommended practice (MRC tissue and biological samples for use in research) participants will be asked to consent to gift their samples for use in future studies and shared with collaborators internationally. A continuous consent approach will be used throughout the study as participants will be asked at each visit if they are willing to continue in the study.

The study site will ensure that samples are appropriately labelled in accordance with procedures to comply with the 1998 Data Protection Act. Biological samples collected from

participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act. Samples will be stored at LSTM.

All documents will be stored safely under strict confidentiality and with restricted access. The participant will be referred to by a unique study participant number/code on study-specific documents. Participant details and screening log located on a password protected shared network drive.

Participant data including the case report form, colonisation, clinical and laboratory results and safety reports will be anonymised prior to archiving or use outside of the direct research team. Data will be recorded and stored on a password protected database hosted on LSTM servers. Data will be kept for as long as the samples are stored and for a minimum of ten years post-study closure.

The samples will be processed and stored at the LSTM. Samples may be transferred to national and international collaborators for their expertise. Samples will be gifted for future research related to COVID-19 and pandemic research. Urine samples will be shipped to Pfizer laboratory in the United States, these samples will be anonymous and will be retained by Pfizer Ltd for up to 15 years.

Recording and reporting of Serious Adverse Events (SAE) and Adverse Events (AE)
No serious adverse events (SAE) are anticipated to be attributed to this study.
In the event of a SAE or an unexpected adverse event (AE) potentially attributed to the study, the site principal investigator will ensure this is investigated, recorded and reported to the sponsor and Pfizer within 24 hours of becoming aware of the event and use medical judgement in assigning the SAEs seriousness and causality. SAE will be reported using the HRA form
(https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/)
to the main NRES within 15 days of the Chief Investigator (CI) becoming aware of the event where in the opinion of the CI the event was:

- Related – that is, it resulted from administration of any of the research procedures (also known as research-related injury), and
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

If possibly related the research will be stopped temporarily for investigation and any further work referred back to the REC for consideration (within 7 days). Of note, as COVID-19 disease is a study endpoint, COVID-19 disease and related morbidity will not be reported as an SAE unless it is considered to be potentially attributed to the study in some way.
Adverse events will be self-reported by the participant, the contact details will be in the Participant Information Leaflet.

Potential applications/benefit from this study
Overall the data will help strengthen diagnostic efficacy, infection control, pandemic response and preparedness.

Direct access to anonymised data will be granted to authorised representatives from the Sponsor, host institutions and collaborators in line with participant consent.

LSTM as sponsor will be responsible for archiving data including the essential documents, case report forms and trial database for a minimum of ten years. Destruction of essential documents will require authorisation from the Sponsor.

Publication policy
We will follow 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 (U. Liverpool, Pfizer) will participate. Each organization will determine members that meet authorship criteria.

Dissemination of results
At completion of the study, findings will be disseminated to the hospital management and relevant groups (for example, infection control), and to all hospital staff at arranged open meetings. No individuals who test positive for COVID-19 will be identifiable at any time. Pfizer will also receive study results.

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