



RESEARCH ARTICLE

REVISED **Healthcare Workers Bioresource: Study outline and baseline characteristics of a prospective healthcare worker cohort to study immune protection and pathogenesis in COVID-19 [version 2; peer review: 1 approved, 2 approved with reservations]**

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Abstract

Background: Most biomedical research has focused on sampling COVID-19 patients presenting to hospital with advanced disease, with less focus on the asymptomatic or paucisymptomatic. We established a bioresource with serial sampling of health care workers (HCWs) designed to obtain samples before and during mainly mild disease, with follow-up sampling to evaluate the quality and duration of immune memory.

Methods: We conducted a prospective study on HCWs from three hospital sites in London, initially at a single centre (recruited just prior to first peak community transmission in London), but then extended to multiple sites 3 weeks later (recruitment still ongoing, target n=1,000). Asymptomatic participants attending work complete a health questionnaire, and provide a nasal swab (for SARS-CoV-2 RNA by RT-PCR tests) and blood samples (mononuclear cells, serum, plasma, RNA and DNA are biobanked) at 16 weekly study visits, and at 6 and 12 months.

Results: Preliminary baseline results for the first 731 HCWs (400 single-centre, 331 multicentre extension) are presented. Mean age was 38±11 years; 67% are female, 31% nurses, 20% doctors, and 19% work in intensive care units. COVID-19-associated risk factors were: 37% black, Asian or minority ethnicities; 18% smokers; 13% obesity; 11% asthma; 7% hypertension and 2% diabetes mellitus. At baseline, 41% reported symptoms in the preceding 2 weeks. Preliminary test results from the initial cohort (n=400) are available: PCR at baseline for SARS-CoV-2 was positive in 28 of 396 (7.1%, 95% CI 4.9-10.0%) and 15 of 385 (3.9%, 2.4-6.3%) had circulating IgG antibodies.



Conclusions: This COVID-19 bioresource established just before the peak of infections in the UK will provide longitudinal assessments of incident infection and immune responses in HCWs through the natural time course of disease and convalescence. The samples and data from this bioresource are available to academic collaborators by application <https://covid-consortium.com/application-for-samples/>.

Keywords

COVID-19, healthcare workers, pandemic

Open Peer Review

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Any reports and responses or comments on the article can be found at the end of the article.			

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REVISED Amendments from Version 1

- A more detailed description of the healthcare workers (HCWs) roles is now provided in the results section. The characteristics here described are likely generalisable to HCWs in most institutions - participants recruited across all staff groups with broad baseline demographics. They are not, however, generalisable to the wider population given that all participants are of working age and in good general health. More granular data on exposure will be part of the study investigation and presented in subsequent publications
- We acknowledge a selection bias could be present as HCWs who felt at higher risk of exposure could have been more motivated to participate in the study than the rest of the hospital staff. However, it is worth highlighting that participants had to sign consent forms recognising that they would not receive results in real-time (particularly when access to tests was limited early in the pandemic), and therefore it should have minimised bias in recruitment. This has now been added to the limitations section.
- This is a cohort study. Thus we have removed the word "observational" as this was deemed redundant.
- We clarified the definition of ethnicity used in this study (see legend of Table 1).
- Typos in the last paragraph have been corrected.
- We avoided repetition of the link to the Covid Consortium application throughout the manuscript.
- A direct link to the UK COVID-19 surveillance reports was now added (reference 25).

Any further responses from the reviewers can be found at the end of the article

Introduction

The global pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to more than 6 million infections and 300,000 deaths worldwide at the time of writing¹. Healthcare workers (HCW) may be at greater infection risk compared to the general population²⁻⁵. Many infections are asymptomatic⁶, therefore surveillance of symptomatic coronavirus disease 2019 (COVID-19) underestimates the infection burden. This has led to calls for regular surveillance of asymptomatic HCWs⁷⁻¹⁰, to ensure that health care facilities do not become transmission hot-spots, to protect the workforce and vulnerable patients and to prevent community reseeded.

Most SARS-CoV-2 studies have focused on severe hospitalized COVID-19 cases¹¹⁻¹⁴. Data are lacking on the host response and biology of asymptomatic or pauci-symptomatic infection as well as the early (pre hospitalisation) stages of disease. This undermines efforts to understand the determinants of disease severity.

We sought to provide a resource to address these gaps by establishing a cohort of HCWs who are well and attending work across selected central London hospitals. We aimed to characterize and quantify the rates of HCW infection (particularly mild or asymptomatic) over the first

London COVID-19 pandemic wave, with moderate frequency longitudinal comprehensive sampling before infection and in the weeks to months afterwards. Accordingly, we established the COVID-consortium (<https://covid-consortium.com>) and the "COVID-19 Immune Protection and Pathogenesis in Healthcare Worker Bioresource" (NCT04318314). In this manuscript we: (1) provide a description of the study design, (2) present preliminary results of the baseline visit in the first 400 HCWs (single-centre, between March 23rd and 31st 2020) and subsequent 331 (multicentre, from mid-April 2020) – focusing on two different time-points in the epidemiologic curve (just before and after the peak of new daily cases in London), and (3) call for research collaborators wishing to access biological samples in participants across the spectrum of COVID-19 to contribute to a range of prespecified objectives, planned by the consortium <https://covid-consortium.com/application-for-samples/>.

Methods

Study approvals

The study was approved by a UK Research Ethics Committee (South Central - Oxford A Research Ethics Committee, reference 20/SC/0149). All participants provided written informed consent.

Study participants

Adult (>18 years) hospital HCWs who were fit and well to attend work in any role and across a range of clinical areas, were invited to participate via hospital email, posters, staff meetings, training sessions and participant information leaflets (see <https://covid-consortium.com>). No other inclusion or exclusion criteria were considered.

Study design

The "COVID-19 Immune Protection and Pathogenesis in Healthcare Worker Bioresource" (NCT04318314) uses a prospective cohort design (Figure 1). The study consists of questionnaires and biological samples (blood samples, nasal swabs ± saliva) performed at all visits: baseline, weekly follow-ups for 15 weeks, and visits at 6 and 12 months.

Recruitment was initially at St Bartholomew's Hospital, London, UK (400 HCWs recruited between 23rd and 31st March 2020, just before the peak of new daily cases in London, which happened on the 2nd April, with 1,022 new cases confirmed¹⁵), a secondary care hospital part of Barts and the Royal London NHS Trust to a local population of 3 million, with specialist cancer and cardiovascular services to a supra-regional population of 6 million. In response to the pandemic, the hospital expanded ventilated intensive care provision for COVID-19 patients to 122 beds across five units.

To improve statistical power for downstream analyses, we expanded the target sample size to n=1,000 and extended recruitment on 17th April 2020 (after peak transmission in London, recruitment still ongoing) to other local sites: Nightingale Hospital London (a temporary hospital providing intensive care, set up in response to COVID-19) and Royal Free NHS

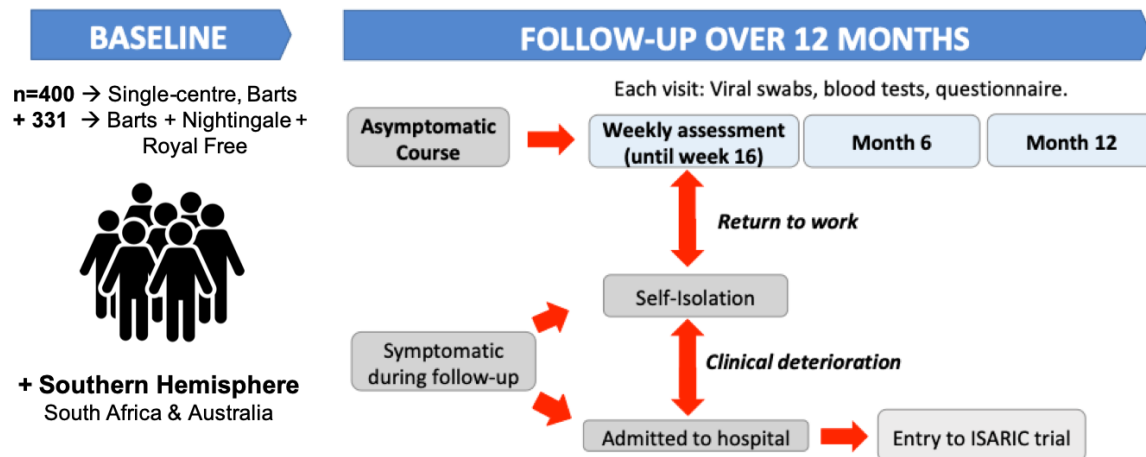


Figure 1. Study flow chart. HCW, healthcare workers.

Hospital Trust (large teaching hospital with specialist expertise in infectious diseases). Collaborations with Cape Town (South Africa) and Sydney (Australia) are also in place to explore the impact of different surge rates, ethnicity, vitamin D levels and the 6-month seasonal difference; unlike UK sites, follow-ups there are performed every fortnight. Our team was comprised of researchers and volunteers from outside of the clinical supply chains.

Baseline visit

Participants complete a baseline questionnaire (Table 1) including standard variables related to demographics and exposures. These included occupation, household details, smoking status, physical activity, anthropometry, medical history (including vaccination history, current medication and dietary supplements), occupational exposure (including specific clinical areas and access to/use of personal protective equipment [PPE]), travel history, previous COVID-19 symptoms, proven contact with SARS-CoV-2 infected individuals, and any prior testing for SARS-CoV-2 infection.

Follow-up

Following recruitment (baseline visit), if fit and well to attend work, participants would undertake in-person weekly questionnaires using research electronic data infrastructure (REDCap v8.5.22)¹⁶ to capture occupational metadata, new SARS-CoV-2 exposure, symptoms and test results, and biosample collection (blood sampling and nasopharyngeal swabs ± saliva). Following multi-site expansion, information on exercise, pregnancies/contraception, vitamin supplements, working hours and psychological wellbeing (General Health Questionnaire-12 and fatigue questions from the Burnout Assessment Tool)^{17,18} were added. The questionnaires used are summarized in Table 2.

Subjects who miss an attendance due to shift pattern, redeployment or self-isolation for any reason, resume follow-up on return

to work. Illness with suspected COVID-19 is self-reported to the study investigators. Following multisite expansion, participants were also allowed opt-in to a home nasopharyngeal swab and saliva test if self-isolating.

Sample collection

The schedule and quantity of biosample collection is summarized in Figure 2. All study personnel in contact with HCW participants were wearing appropriate PPE in accordance with Public Health England guidance. Nasopharyngeal RNA stabilising swabs are performed at baseline and weekly for 16 weeks. After appropriate training, participants were asked to self-swab both nostrils to minimise the risk to study staff. This strategy was later shown to be reliable when compared to swab collection by health care workers¹⁹. Blood samples were collected in Tempus™ tubes for whole blood RNA, clot activator tubes for serum, and EDTA tubes for plasma, peripheral blood mononuclear cells and DNA (Figure 2). Following multisite expansion in mid-April, a pool (2–3 mL) of saliva was collected into a dedicated saliva collection tube.

Initial sample processing

All samples were registered into a Laboratory Inventory Management system onsite and either frozen at -80°C or transferred to a containment level 3 facility. Key samples collected and planned laboratory procedures are described in Table 3.

Core analyses

The following experimental approaches will be implemented (Figure 3), including:

- Reverse transcription polymerase chain reaction (RT-PCR) of nasal swabs using Roche cobas® SARS-CoV-2 test²⁰.
- Pathogen sequencing with results via the COVID-19 Genomics UK (COG-UK) consortium²¹.

Table 1. Questionnaire and interview data at baseline assessment.

Questionnaire and interview	
Sociodemographic	Age; sex; ethnicity*; household size; children; postcode
Anthropometric measures	Height; weight
Family history	Family history of coronary artery disease
Health status	Medical history (respiratory, cardiovascular and other diseases); medications; flu vaccine; supplements; pregnancies, miscarriages and contraception; clinical frailty score
Active/ recent exposures/ diseases	Pregnancy; therapies; hospitalization; respiratory infections; symptoms (current and/or previous 14 days); known or perception of having had SARS-CoV-2 infection;
Lifestyle	Smoking; physical activity
Occupational factors	Recruiting centre; department; role; use and perceptions about personal protective equipment; contacts with confirmed COVID-19 patients and/or colleagues; aerosolization procedures; hours worked
Community exposure / environmental factors	Overseas travel; contacts with confirmed COVID-19 cases at home
Psychological factors	General health questionnaire-12; emotional and physical fatigue

* Ethnicity (with specification between brackets also recorded): white (Welsh / English / Scottish / Northern Irish / British Irish / Gypsy or Irish Traveler / any other white background), Asian / Asian British (Indian, Pakistani, Bangladeshi, Chinese, any other Asian background), black / African (African, Caribbean, any other black background), mixed / multiple ethnic groups (white and black Caribbean, white and black African, white and Asian, any other mixed / multiple ethnic background), other ethnic group (Arab, any other ethnic group).

Table 2. Questionnaire and interview at follow-up assessments.

Questionnaire and interview	
Active/ recent exposures/ diseases	New symptoms; new SARS-CoV-2 infection; new or discontinued medications
Occupational factors	Change in hospital or department/floor; new contacts with confirmed COVID-19 patients and/or colleagues; new contacts with aerosolization procedures; changes in use and perceptions about personal protective equipment; hours worked
Community exposure / environmental factors	New contacts at home with symptoms and/or confirmed COVID-19
Psychological factors	General health questionnaire-12; emotional and physical fatigue

Tube	Tube Volume (in mL)	Baseline	Week 2-3	Week 4	Week 5-7	Week 8	Week 9-11	Week 12	Week 13-15	Week 16	Month 6	Month 12	*Convalescence (replacing scheduled collection)
Nasal Swab		1	1	1	1	1	1	1	1	1	0	0	1
Saliva		1†	0	0	1†	†	†	†	†	†	1	1	1
Purple DNA	5	1	0	0	0	0	0	0	0	0	0	0	0
Purple PBMC/Plasma	5	2	0	1	0	1	0	1	0	1	1	1	1
Blue Pax RNA	2.5	1	1	1	1	1	1	1	1	1	1	1	1
Yellow Serum	6	2	1	1	1	1	1	1	1	1	1	1	2

Figure 2. Schedule of biosamples collection. Samples in red: added after ethics amendment on 17/04/2020. * Convalescence visit: first visit after self-isolation with symptoms. † In the first 400 healthcare workers cohort, saliva samples were taken at the first opportunity after week 5; the participants that followed had a saliva sample taken at baseline.

Table 3. List of key samples to be collected and planned laboratory procedures.

Biosample type [Time points]	Processing	Key analyte
Nasal swab [Baseline and follow-up until week 16]	Freeze -80°C	Molecular testing for SARS-CoV-2 ± other pathogens
Saliva sample [Baseline/from Week 5*, convalescence, months 6 and 12]	Freeze -80°C	Molecular testing for SARS-CoV-2 ± other pathogens
Yellow serum tube [Baseline, all follow-ups, convalescence]	Analyse and freeze -80°C	SARS-CoV-2 antibody testing
PAX RNA gene tube [Baseline, all follow-ups, convalescence]	Freeze -80°C	Transcriptomics
PAX DNA gene tube [Baseline]	Freeze -80°C	Genetics
Purple EDTA tube [Baseline, monthly follow-ups, convalescence]	Plasma: centrifuged and stored at -80°C PBMCs: separated by density gradient centrifugation and cryopreserved	Immunology

* In the first 400 healthcare workers cohort, saliva samples were taken at the first opportunity after week 5; the participants that followed had a saliva sample taken at baseline.

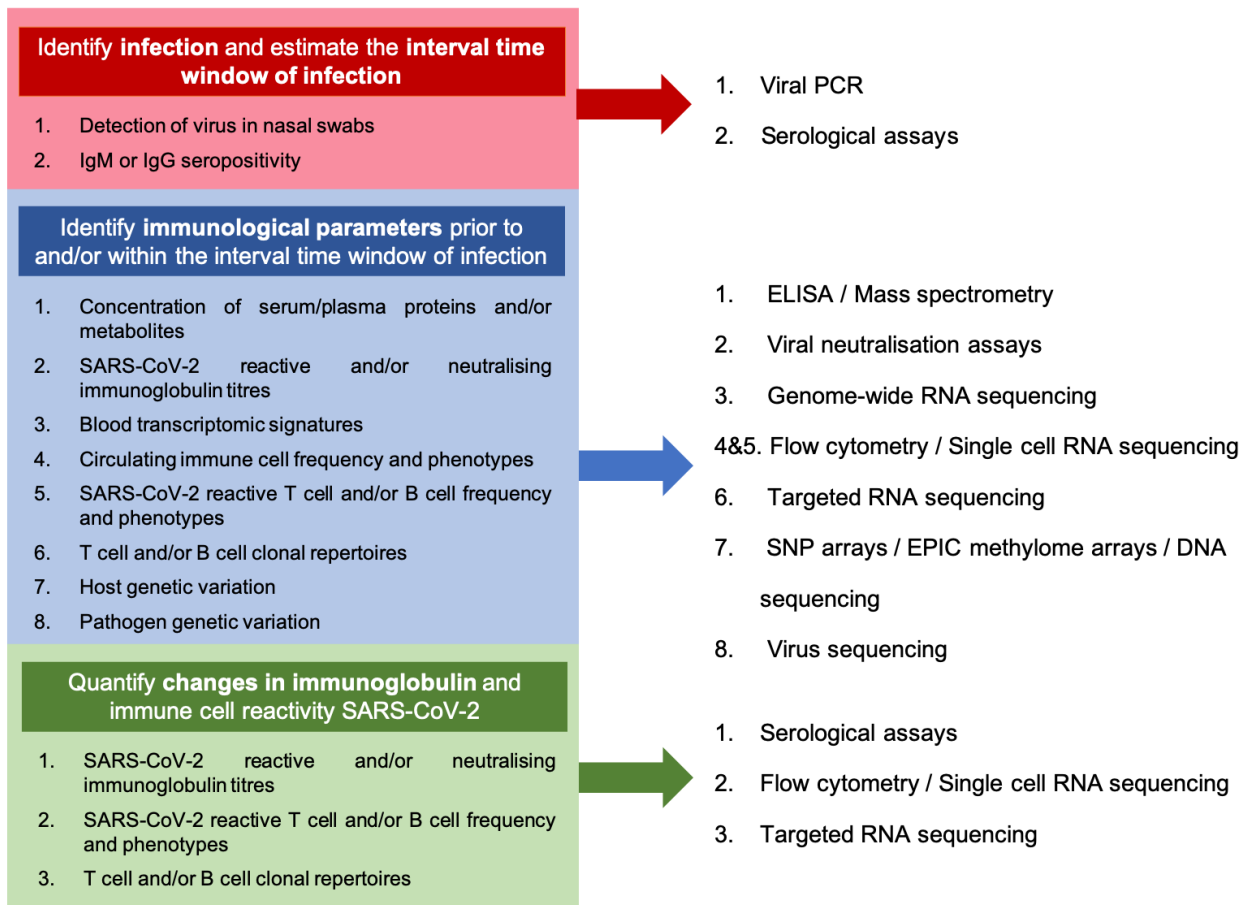


Figure 3. Specific research objectives and summary of experimental approaches.

- Host DNA extraction, quantification and SNP analysis via the Illumina Infinium® GlobalScreeningArray-24v1.0²².
- IgG antibodies assay to antigen S1, defining seroconversion (initially using the EUROIMMUN assay²³).
- Blood RNA extraction focusing on host transcriptomics;
- Peripheral blood mononuclear cells (PBMCs) are a scarce resource and discussions are ongoing about maximising yield;
- Saliva will be diluted and aliquots are available. Further aliquoting will be dependent on demand;
- Other antibody, antigen tests may also be made available should they emerge;
- Serum and plasma will be aliquoted into 100µL samples and divided into packs for individual research teams. Excess RNA (swab and blood) and host DNA will potentially also be available.

Access procedure

The COVID-19 consortium has developed access systems to facilitate the use of this bioresource by scientists for health-related research of public interest. Research teams can apply to use the bioresource via the study website (<https://covid-consortium.com/application-for-samples/>). The access principles are those standard to many bioresources: to maximise yield of timely science, to make results available to other researchers in a reasonable timeframe via a data lake, to reward researchers with appropriate levels of authorship and, where present, intellectual property in a fair, transparent and swift way. We encourage teams to apply and to link their analysis datasets of hospitalised patients with severe disease. We also encourage applications from commercial entities as long as the core principles above apply.

Statistical analysis

When designing the initial study, we aimed to sample the population prior to exposure. At the time of ethics submission, there was no data to provide precise estimates. The n=400 was pragmatic, aiming for rapid recruitment and limited by logistical challenges of conducting research within a pandemic environment. An initial n=400 was estimated conservatively in order to ensure sampling without compromising selection criteria. Following initial recruitment success, more formal sample size calculation was possible for study expansion and based on an expected average baseline frequency of SARS-CoV-2 infection of 5% in previously undiagnosed HCWs according to studies⁵. Accordingly, the estimated sample size was n=786 for a $\beta=0.20$ and two-sided $\alpha=0.05$. We targeted a sample size of 1,000 to account for a 20% drop-out rate. However, the specific responses we are seeking are emergent and unknown, and a wider strategy is to link with other studies.

This is a preliminary analysis of the key baseline characteristics of the data. We present discrete variables as absolute frequencies with percentages; continuous normally distributed variables as mean \pm standard deviation. Continuous data were checked

for normal distribution using Kolmogorov–Smirnov test and visual Q-Q plots assessment. Comparisons between groups were performed using Students' t-test, while categorical variables were compared using Fisher's exact test. Two-sided p-values <0.05 were considered significant. Statistical analysis was performed using SPSS (version 24.0, IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics for the first 400 HCWs (single-centre, recruited just before peak transmission, St Bartholomew's Hospital) and subsequent 331 multicentre study expansion participants (after peak transmission, n=101 in St Bartholomew's Hospital, n=10 in Nightingale Hospital and n=220 in Royal Free Hospital) are presented in [Table 4–Table 6](#). This reflects all baseline visits between March and May 2020 (total n=731).

Demographics

The mean age of all study participants was 38 ± 11 years (0.7% >65 years), 67% female, 37% were black, Asian or minority ethnicities. Demographics are further detailed in [Table 4](#).

Past medical history and medication

Co-morbidities and COVID-19 risk factors ([Table 4](#)) reported included: 18% smokers, 11% asthma, 7% hypertension, 4% dyslipidaemia, 2% diabetes mellitus; 1% rheumatological disease and one participant with coronary artery disease. Body mass index (BMI) was 25.1 ± 4.4 kg/m², 97 (13%) participants were obese (BMI >30 kg/m²). The proportion of sedentary participants (reported exercise <1.5 hours/week) was 17%.

Medications are detailed in [Table 5](#). These included short-acting β_2 agonist inhalers (5%), inhaled corticosteroids (6%), ACE inhibitors (3%), statins (4%) and paracetamol (7%); 18% of the participants reported having taken ibuprofen in the two weeks prior to recruitment. Over-the-counter supplements rates of usage were: 25% multivitamins, 22% vitamin D and 12% vitamin C.

Community/social exposure

The proportion of HCWs with a household size of at least three people was 48% (n=348), with a third of the participants reported having children at home ([Table 6](#)). Only eight participants (1%) had a proven contact with a confirmed COVID-19 case at home ([Table 6](#)). Overall, 41% percent (n=299) of HCWs reported having travelled overseas in 2020.

Occupational exposure

Roles of HCWs ([Table 6](#)) included nurses (n=228), allied health professionals (n=201, e.g. radiographers, cardiac physiologists), doctors (n=148), administrative staff (n=30) and other health-care roles (n=124, including managers, phlebotomists, laboratory and pharmacy staff, managers, porters, cleaners). HCWs worked in a range of departments ([Table 6](#)) – one-fifth worked in the intensive care unit. The multisite cohort (recruited later in the pandemic wave) reported significantly more contacts with

Table 4. Baseline demographics and past medical history.

	Single centre (n=400)	Multisite extension (n=331)	Total (n=731)
Age, years	36.7±10.4	39.5±11.4	38.0±10.9
Male, n (%)	157 (39.3)	84 (25.4)	241 (33.0)
BMI, kg/m ²	25.0±4.2	25.3±4.6	25.1±4.4
Non-white, n (%)	166 (41.5)	108 (32.6)	274 (37.5)
Household size ≥3 people, n (%)	170 (42.5)	178 (53.8)	348 (47.6)
Children at home, n (%)	147 (36.8)	91 (27.5)	238 (32.6)
Exercise <1.5 hours/week, n (%)	63 (15.8)	60 (18.1)	123 (16.8)
Past medical history			
Flu vaccine this season, n (%)	275 (68.8)	234 (70.7)	509 (69.6)
Pregnant in the last 3 months, n (%)	2 (0.5)	1 (0.3)	3 (0.4)
Recent respiratory tract infection, n (%)	73 (18.3)	70 (21.1)	143 (19.6)
Recent surgery, n (%)	6 (1.5)	5 (1.5)	11 (1.5)
Asthma, n (%)	41 (10.3)	37 (11.2)	78 (10.7)
Cancer, n (%)	4 (1.0)	2 (0.6)	6 (0.8)
HIV/Immunodeficiency, n (%)	1 (0.3)	0	1 (0.1)
Rheumatological disease, n (%)	8 (2.0)	1 (0.3)	9 (1.2)
Hypertension, n (%)	26 (6.5)	27 (8.2)	53 (7.3)
Dyslipidaemia, n (%)	18 (4.5)	8 (2.4)	26 (3.6)
Diabetes Mellitus, n (%)	8 (2.0)	7 (2.1)	15 (2.1)
Smoker, n (%)	67 (16.8)	65 (19.6)	132 (18.1)
Family history of CAD, n (%)	54 (13.5)	51 (15.4)	105 (14.4)
Obesity, n (%)	43 (10.8)	54 (16.3)	97 (12.6)

BMI, body mass index; CAD, coronary artery disease; HIV, human immunodeficiency virus. 'Recent' refers to the previous 3 months.

confirmed COVID-19 patients (59 vs 29%, $p<0.001$) and confirmed COVID-19-positive colleagues (49 vs 14%, $p<0.001$) at work. They also more frequently reported wearing PPE (84 vs 78%, $p=0.039$). Overall, 29% ($n=210$) wore long-sleeve gown, 54% ($n=398$) plastic aprons, 51% ($n=373$) surgical masks and 31% ($n=230$) FFP3 masks; 217 HCWs (30%) expressed concerns about PPE being insufficient or inadequate and 81 (11%) stated that PPE policy is either confusing or unclear.

Symptoms, infection and serology

The prevalence of COVID-related symptoms in the two weeks prior to recruitment was 34% ($n=249/731$), significantly higher in the early cohort recruited in March (41% vs late cohort 26%, $p<0.001$). More HCWs from the multisite cohort recruited at

the later time point thought that they had had prior COVID-19 (24 vs 7% in the initial cohort, $p<0.001$). Overall, the most prevalent symptom was nasal congestion (13%), followed by odynophagia (11%), dry cough (8%) and fatigue (8%). A recent (<3 months) respiratory tract infection was reported in 20% of the participants.

SARS-CoV-2 RT-PCR and serology were processed for the first cohort ($n=400$) and are described. PCR for SARS-CoV-2 was positive in 28 of 396 (7.1%, 95% confidence interval 4.9 – 10.0%, 4 swabs not available), of which 20 (71%) were symptomatic in the 14 days before (Figure 4A). In the same cohort, 15 of 385 (3.9%, 2.4 – 6.3%) had IgG positive serology to S1 spike protein, of which 11 (73%) reported

Table 5. Baseline use of medication and supplements.

Medication/supplement	Single centre (n=400)	Multisite extension (n=331)	Total (n=731)
Medication			
ACEI, n (%)	9 (2.3)	11 (3.3)	20 (2.7)
ARB, n (%)	8 (2.0)	4 (1.2)	12 (1.6)
Beta blockers, n (%)	17 (4.3)	4 (1.2)	21 (2.9)
MRAs, n (%)	2 (0.5)	0	2 (0.3)
Aspirin, n (%)	4 (1.0)	2 (0.6)	6 (0.8)
Statins, n (%)	16 (4.0)	11 (3.3)	27 (3.7)
Short-acting inhaled β 2 agonist p.r.n., n (%)	21 (5.3)	15 (4.5)	36 (4.9)
Long-acting inhaled β 2 agonist, n (%)	6 (1.5)	0	6 (0.8)
Inhaled corticosteroids, n (%)	22 (5.5)	19 (5.7)	41 (5.6)
Oral corticotherapy, n (%)	10 (2.5)	5 (1.5)	15 (2.1)
Use of ibuprofen \leq 3 months, n (%)	14 (3.5)	8 (2.4)	22 (3.0)
Ibuprofen use in the past 2 weeks, n (%)	78 (19.5)	54 (16.3)	132 (18.1)
Paracetamol, n (%)	39 (9.8)	14 (4.2)	53 (7.3)
Supplements			
Vitamin B complex, n (%)	12 (3.0)	21 (6.3)	33 (4.5)
Vitamin C, n (%)	44 (11.0)	43 (13.0)	87 (11.9)
Vitamin D, n (%)	72 (18.0)	86 (26.0)	158 (21.6)
Multivitamins, n (%)	108 (27.0)	73 (22.1)	181 (24.8)
Iron, n (%)	7 (1.8)	20 (6.0)	27 (3.7)
Zinc, n (%)	14 (3.5)	18 (5.4)	32 (4.4)
Fish oil / omega-3 fatty acids, n (%)	18 (4.5)	21 (6.3)	39 (5.3)

ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers; MRA, mineralocorticoid receptor antagonists.

prior symptoms (Figure 4B) and 3 (20%) were PCR positive. A total of 40 participants (10%) were PCR and/or IgG positive at baseline.

Discussion

This study is establishing a bioresource (COVID-consortium) derived from health care workers, with samples taken at the time of pre-symptomatic incident infection, linked to data on clinical outcomes, serology and follow-up sampling to evaluate the quality and duration of immune memory to the virus. Here we present preliminary baseline data on the first 731 participants, comprised of a single-centre cohort recruited in March 2020 just before the time of peak community transmission in London, and a subsequent expanded multicentre cohort recruited from mid-April 2020. This

resource should enable collaborative science and approved investigators can apply for sample access or access to the resultant data lake to address specific questions or for incorporation into larger COVID-19 datasets.

HCWs baseline characteristics

SARS-CoV-2 can rapidly spread to patients and HCWs in hospitals, and HCWs generally have been particularly hard hit with high reported rates of infection^{2,3,5,24}. Our cohort is representative of a multi-ethnic urban UK population of working age, and more specifically of the NHS workforce across different clinical roles and departments. Confirmed COVID-19 contacts were low in the community (1%), but much higher in-hospital (43% patients, 30% colleagues), particularly in the second cohort (recruited later). All participants were

Table 6. Baseline exposure to SARS-CoV-2 and symptoms.

Variable	Single centre (n=400)	Multisite extension (n=331)	Total (n=731)
Exposure			
Contact with confirmed COVID-19 patient, n (%)	116 (29.0)	196 (59.2)	312 (42.7)
Contact with confirmed COVID-19 colleague, n (%)	54 (13.5)	162 (48.9)	216 (29.5)
Confirmed COVID-19 household contact, n (%)	2 (0.5)	6 (1.8)	8 (1.1)
Think had COVID-19, n (%)	26 (6.5)	79 (23.9)	105 (14.4)
Does not wear any form of PPE, n (%)	89 (22.3)	54 (16.3)	143 (19.6)
Oversees COVID-19-care procedure prone to aerosolization, n (%)	94 (23.5)	93 (28.1)	187 (25.6)
Overseas travel in 2020, n (%)*	160 (40.0)	139 (42.0)	299 (40.9)
France, n (%)	25 (6.3)	15 (4.5)	40 (5.5)
Italy, n (%)	11 (2.8)	12 (3.6)	23 (3.1)
Spain, n (%)	24 (6.0)	17 (5.1)	41 (5.6)
HCW role			
Doctor, n (%)	83 (20.8)	65 (19.6)	148 (20.2)
Nurse, n (%)	126 (31.5)	102 (30.8)	228 (31.2)
Allied healthcare professional, n (%)	145 (36.3)	56 (16.9)	201 (27.5)
Other, n (%)	46 (11.5)	108 (32.6)	154 (21.1)
Working place			
ICU, n (%)	60 (15.0)	81 (24.5)	141 (19.3)
Anaesthesia department, n (%)	9 (2.3)	3 (0.9)	12 (1.6)
Emergency department, n (%)	0	24 (7.3)	24 (3.3)
COVID-19-like symptoms in the last 14 days, n (%)	163 (40.8)	86 (26.0)	249 (34.1)
Nasal congestion, n (%)	64 (16.0)	29 (8.8)	93 (12.7)
Odynophagia, n (%)	64 (16.0)	15 (4.5)	79 (10.8)
Productive cough, n (%)	25 (6.3)	3 (0.9)	28 (3.8)
Dry cough, n (%)	42 (10.5)	19 (5.7)	61 (8.3)
Fever, n (%)	24 (6.0)	1 (0.3)	25 (3.4)
Chills/rigors, n (%)	13 (3.3)	4 (1.2)	17 (2.3)
Chest pain, n (%)	13 (3.3)	6 (1.8)	19 (2.6)
Dyspnoea, n (%)	19 (4.8)	8 (2.4)	27 (3.7)
Myalgia, n (%)	21 (5.3)	8 (2.4)	29 (4.0)
Fatigue, n (%)	39 (9.8)	16 (4.8)	55 (7.5)
Diarrhoea, n (%)	14 (3.5)	4 (1.2)	18 (2.5)
Nausea/vomiting, n (%)	4 (1.0)	3 (0.9)	7 (1.0)
Anosmia, n (%)	17 (4.3)	11 (3.3)	28 (3.8)
Ageusia, n (%)	18 (4.5)	7 (2.1)	25 (3.4)

COVID-19, coronavirus disease 2019; HCW, healthcare workers; ICU, intensive care unit; PPE, personal protective equipment.

* No HCW reported having travelled to/from mainland China in 2020.

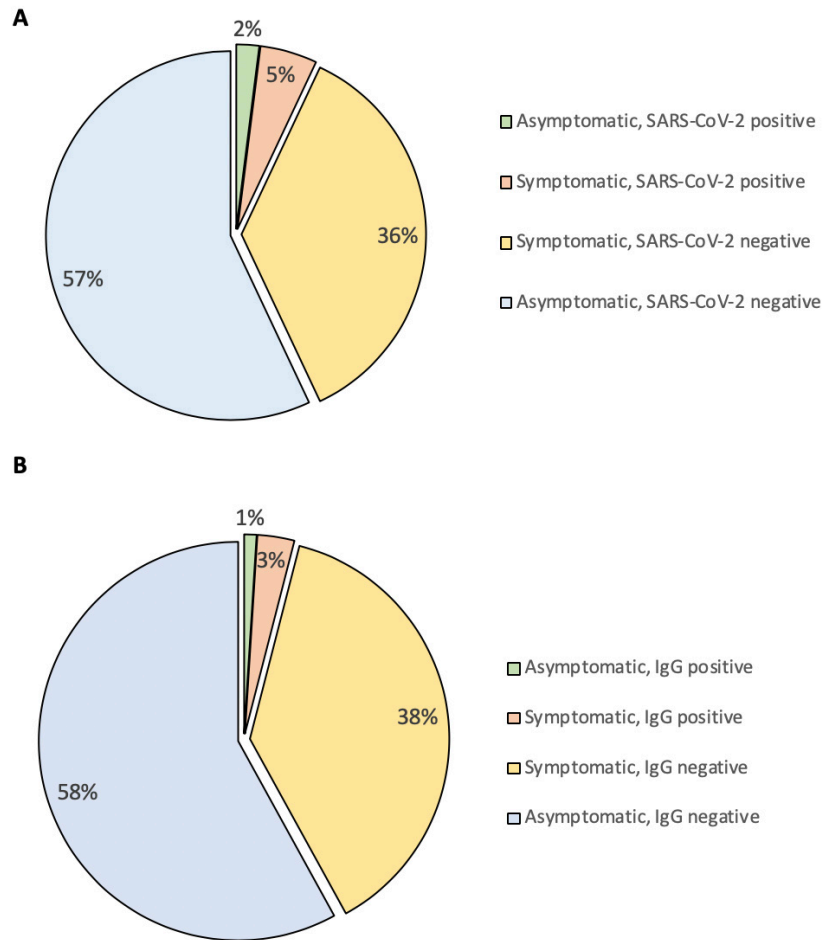


Figure 4. Symptoms in the 14 days before recruitment. (A) SARS-CoV-2 test results, and **(B)** serology results.

self-reported as fit to attend work on all clinical visits, and at baseline the majority of participants had been asymptomatic and did not think that they had been infected. Nevertheless, 1 out of 10 participants had a confirmed baseline SARS-CoV-2 infection confirmed by PCR and/or positive serology test that could represent current or previous infection, at the beginning of peak transmission in March.

Of interest, two different timepoints are presented here. As one would expect, the proportion of HCWs who reported prior symptoms was significantly higher in participants recruited just before peak community transmission²⁵, and those recruited a month later more often reported they suspected that they had already had COVID-19.

The COVID-19 bioresource

The scientific community has merged forces to tackle this unprecedented pandemic. Since the start of January 2020 (until 31st May 2020), 160 research projects on COVID-19 received a favourable opinion by the UK NHS Health Research Authority (last updated list on 3rd June 2020), the majority focused

on confirmed COVID-19 patients⁶. Emergent studies are now targeting mild and population disease, but almost all missed peak transmission. Larger-scale community surveillance studies typically also do not have temporal granularity to detect early disease changes and may be more focused on providing data to improve modelling rather than host:pathogen biology. Studying HCWs is a middle ground - subjects are deemed fit to work, but have higher exposure rates to confirmed COVID-19 cases, and can also be frequently assessed. COVID-19 bioresources in the general population and HCWs have already been established. Studies such as the COVID-19 Emergency Response Assessment (CERA)²⁶ and the Rapid European SARS-COV-2 Emergency research Response (RECOVER)²⁷ use qualitative instruments to assess the physical and psychological well-being of frontline doctors at different phases of the pandemic. The SARS-CoV-2 Acquisition in Frontline Health Care Workers – Evaluation to Inform Response (SAFER)²⁸ study will perform qualitative interviews and collect nose and throat swabs twice weekly and serum samples monthly from healthcare staff. Preliminary results from the SAFER study revealed a higher PCR positive rate of 21%

among HCWs (42/200), but during the whole first month of observation (starting between 26th March and 8th April 2020)²⁹. The COVID-19 Staff Testing of Antibody Responses Study (CO-STARS) follows a similar design, with serologies performed monthly for 6 months and then 6-monthly for a total of 6 years³⁰.

The comprehensive (questionnaires and biosamples) serial assessment of asymptomatic participants starting just before peak community transmission of SARS-CoV-2 makes our bioresource a precious dataset for the scientific community. We expect that the data sampled from HCWs facilitates understanding of mild disease and subclinical infection at a more rapid rate than the general population allowing comparison with those more severely affected or hospitalised for COVID-19. The COVID-19 consortium (<https://covid-consortium.com>) and the “COVID-19 Immune Protection and Pathogenesis in Healthcare Worker Bioresource” (NCT04318314) thus encourages research teams to apply and even potentially link their own datasets to ours (with results expected to be returned to the data lake for collaborative science). Some of the fields worth exploring include immune responses during the subclinical phases of infection, properties of the immunoglobulins and immune cellular reactivity (correlations between viral RNA PCR and subsequent serology, persistence of neutralizing antibodies, immune decay and longevity of serological responses), host and viral genetic variation, and other environmental or acquired risk factors.

Limitations

The three centres initially included reflect the epidemiological curve of a single city (London). The COVID-19 bioresource started at peak community transmission with prevalent asymptomatic infection in 7.1% and seropositivity of 3.8% at baseline. In data from the subsequent four weeks, we have already reported that the incident asymptomatic infections fell in line with reductions in the London wide incidence³¹. Nationwide data are accruing to assess the generalisability of our findings,

but there are also opportunities to expand geographical coverage of our bioresource through collaborations with other studies that include serial sampling of HCWs. Although our cohort is ethnically diverse (37% non-white), the frequency of comorbidities is relatively low, there are no children and elderly subjects are under-represented. In addition, our cohort of hospital HCWs is unlikely to be generalisable to other institutional settings such as care homes, or to the wider population given that all participants are of working age and in good general health. A selection bias could also be present as HCWs who felt at higher risk of exposure could have been more motivated to participate in the study than the rest of the hospital staff. However, it is worth highlighting that participants had to sign consent forms recognising that they would not receive results in real-time (particularly when access to tests was limited early in the pandemic), and therefore it should have minimised bias in recruitment.

Conclusions

Just before the peak of COVID-19 infections in the UK we established a rich and granular bioresource of healthcare workers with the aim of gathering insights into early disease / asymptomatic SARS-CoV-2 infection. Combining exposure with multi-qualitative and quantitative assessments, we envision a more complete picture of immune response in this context. The samples and data securely curated this bioresource are now accessible to the wider scientific community by application.

Data availability

The COVID-19 consortium has developed access systems to facilitate the use of this bioresource and the data underlying this article by scientists for health-related research of public interest. However, although participants are pseudoanonymised, there is data regarding home addresses, household characteristics, and other details that could potentially lead to identification. Research teams can therefore apply to use the bioresource via the application form that can be found on the study website (<https://covid-consortium.com/application-for-samples/>).

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Open Peer Review

Current Peer Review Status: ? ✓ ?

Version 2

Reviewer Report 22 January 2021

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Berta Grau-Pujol 

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The study is clearly described, as well as the changes occurred in study procedures. The emerging COVID-19 pandemic and availability of tests and materials during this period justifies these changes. Although it provides baseline information, it is worth sharing it, and thus indexing it.

Few comments on Methodology:

- It is not described which statistical power they had.
- Study design and procedures in Cape Town and Sydney should be further described.
- In core analysis, the authors use future tense, not sure that is correct.
- Further statistical analysis could be conducted, such as regression analysis. Participants' site could be also considered.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology of infectious diseases.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Version 1

Reviewer Report 24 September 2020

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Aodhan Breathnach

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This is obviously a very preliminary description of a just-started observational study, with no results reported other than the baseline characteristics of the patients. The stated purpose - to prospectively study a cohort of HCWs, thereby including milder and earlier COVID19 infections that would not necessarily be hospitalised - is worthwhile. The main value of reporting at this stage seems to be to publicise the study and to invite collaborators.

The paper is clear and well-organised. The limitations are acknowledged, the main one being that the cohort of HCWs is of necessity a working-age population, with few elderly workers, and no children.

There is a typo in the last paragraph, and the last sentence of the paper does not make complete sense.

The link to the Covid Consortium application form is given three times in the last page - is this repetition necessary?

The paper is well referenced, though I was unable to find Ref 25 online.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am a clinical microbiology consultant in a combined Infection Department. As such, my academic work is limited to observational and epidemiological research, with an interest in bacteraemia, endocarditis, infection control and OPAT services. I have recently become involved in analysing COVID infections and seroconversions in our hospital staff.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 05 Oct 2020

João Augusto, University College London, London, UK

We thank the reviewer for the pertinent comments.

We provide below a point-by-point response.

There is a typo in the last paragraph, and the last sentence of the paper does not make complete sense.

Thank you. This has now been corrected.

The link to the Covid Consortium application form is given three times in the last page - is this repetition necessary?

Thank you. We agree and have now amended this.

The paper is well referenced, though I was unable to find Ref 25 online.

We have now added a direct link to the UK COVID-19 surveillance reports.

Competing Interests: No competing interests were disclosed.

Reviewer Report 01 September 2020

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David Murdoch 

Department of Pathology and Biomedical Science, University of Otago, Christchurch, New Zealand

This paper presents the design and baseline characteristics of a prospective cohort study of healthcare workers (HCWs) for use as a "bioresource" for research on COVID-19. The study population has a high prevalence of exposure to COVID-19 and evidence of recent SARS-CoV-2 infection.

Specific comments:

1. The study population is a relatively select group of healthcare workers. It is essential that this group is described in greater detail in order to best understand the generalisability of any study findings. As such, it is unclear whether any of the HCWs do not have direct patient contact (e.g. laboratory staff). It would also be helpful to have a commentary on whether there is any selection bias among those volunteering to be study participants, beyond the baseline data presented. This is critical in order to understand any study population-level analyses.
2. A cohort study is an observational study by definition. Therefore "observational" is an unnecessary adjective in several places.
3. What definition of ethnicity is being used? Is the same definition being used for different countries?

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious diseases, microbiology, epidemiology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 05 Oct 2020

João Augusto, University College London, London, UK

We thank the reviewer for the time taken to review our manuscript and for the pertinent comments. We provide below a point-by-point response.

1. The study population is a relatively select group of healthcare workers. It is essential that this group is described in greater detail in order to best understand the generalisability of any study findings. As such, it is unclear whether any of the HCWs do not have direct patient contact (e.g. laboratory staff). It would also be helpful to have a commentary on whether there is any selection bias among those volunteering to be study participants, beyond the baseline data presented. This is critical in order to understand any study population-level analyses.

Thank you. This cohort represents a heterogeneous group with different degrees of patient contact and consequently different degrees of exposure – from nurses/doctors to laboratory/pharmacy staff and managers. We, however, believe that this can prove advantageous to understand risk factors. A more detailed description of the HCWs' roles is now provided in the results section. The characteristics here described are likely generalisable to HCWs in most institutions – participants recruited across all staff groups with broad baseline demographics. They are not, however, generalisable to the wider population given that all participants are of working age and in good general health. More granular data on exposure will be part of the study investigation and presented in subsequent publications. Of note, the factor “patient contact” was taken into account in our questionnaire (with details of the healthcare role, hospital department/unit, and COVID-care procedure – if any).

We acknowledge a selection bias could be present as HCWs who felt at higher risk of exposure could have been more motivated to participate in the study than the rest of the hospital staff. However, it is worth highlighting that participants had to sign consent forms recognising that they would not receive results in real-time (particularly when access to tests was limited early in the pandemic), and therefore it should have minimised bias in recruitment. This has now been added to the limitations section.

2. A cohort study is an observational study by definition. Therefore "observational" is an unnecessary adjective in several places.

Thank you. We agree and have now corrected this.

3. What definition of ethnicity is being used? Is the same definition being used for different countries?

We have now clarified this – see legend of table 1.

Competing Interests: No competing interests were disclosed.

