The long-term sequelae of COVID-19

International research priorities to address the long-term effects of COVID-19 in airways diseases

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Abstract

The recently described persistent ill health after acute COVID-19, so called “long COVID” has emerged as a major concern. We conducted a prioritisation exercise to identify research priorities for the long term effects of COVID-19 in airways diseases. A total of 202 international experts were invited to submit a minimum of three research ideas. Following a two-phase internal review process, a final list of 98 research questions was scored by 48 experts. The top ranked research question proposed investigating the relationship between an admission prognostic score and post-discharge morbidity at 3- and 12-months in groups of patients with and without pre-existing airways diseases. High scores were also assigned to comparing those two groups of patients in prevalence and severity of post-COVID-19 fatigue, sarcopenia, anxiety, depression and risk of future cardiovascular complications. Our approach has allowed development of a priority list that may inform future research studies and funding decisions. This prioritisation process can be adapted to other areas in long COVID.

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Key messages

Rationale

- Patients with pre-existing airways diseases are thought to be at higher risk of developing serious outcomes from acute COVID-19 and new incident cases of airways diseases have been reported after acute COVID-19 illness. Given the emergence of this new entity, we sought to identify airways related research priorities for “long COVID”.

Approach

- Using the Child Health and Nutrition Research Initiative (CHNRI) prioritisation methodology, 300 proposed research ideas were proposed from participants (including international experts in airways diseases and clinicians tackling long COVID). Following a two-phase internal review process, a final list of 98 research questions was scored by 48 participants according to five pre-defined criteria: answerability, feasibility, timeliness, impact on burden reduction and equity. Weighted scores were adjusted using input from patients with chronic airways diseases.

Top priorities

- A list of the top 20 research questions was developed using the experts’ scores and the patients’ input. The top priority suggested exploring the relationship between the admission ISARIC 4C prognostic score (a risk stratification score that predicts in-hospital mortality for hospitalised COVID-19 patients) and the post-discharge morbidity at 3- and 12-months in groups of patients with and without pre-existing airways diseases.
- High scores were also assigned to research questions investigating the difference between patients with and without airways diseases in relation to: the prevalence and severity of post-COVID-19 fatigue, sarcopenia, anxiety, depression and the risk of future cardiovascular complications; understanding predictors of hospital re-admission; validating tools for remote monitoring of symptoms; determining the incidence and risk factors of new-onset airways diseases using lung function and diagnostic imaging; studying cost-effectiveness of exercise rehabilitation; and investigating risk of venous thrombotic events.

Implications

- Understanding research priorities for the long-term effects of COVID-19 in airways diseases is important at a time when resources are limited and rapid answers are needed
- The CHNRI process can be readily adapted to help develop prioritisation in other disease areas relevant to COVID-19 care.

Introduction

The emergence and rapid spread of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has led to over 100 million confirmed cases and over two million deaths worldwide at the time of writing this paper.[1] The acute phase of SARS-CoV-2 infection may result in a range of clinical presentations, from asymptomatic infection to severe illness requiring hospitalisation and intensive care.[2]

Acute COVID-19 infection is characterised by a wide range of patterns. Certain factors have emerged as increasing both the risk of infection and more severe disease presentation. These include, but are not limited to, age, sex, ethnicity and socio-economic status.[3,4] Major risk factors also include pre-existing comorbidities, with pre-existing respiratory disease among the leading risk factors.[5]

There is already a high burden of existing airways diseases in the population. For example, between 300-400 million people globally are living with chronic obstructive pulmonary disease (COPD).[6] This number is broadly comparable with asthma, which has an increasing global prevalence and affects about 10% of the population in economically developed countries.[7] Furthermore, the ongoing COVID-19 pandemic highlighted COPD as a condition that predisposes an increased risk of hospitalisation and death.[8] Studies in mild and moderate asthma have generally not associated asthma with increased risk of hospitalisation and mortality,[9] though individuals with asthma who have required oral steroids in the past year have been associated with increased mortality risk in acute COVID-19.[3,5]

In addition to acute illness, COVID-19 can result in a prolonged morbidity and recovery period.[10] This post-acute phase of COVID-19 (or "long COVID" as it is now widely known) has been reported in post-hospitalisation survivors,[10] as well as among those who initially experienced mild disease,[11] both children and adults.[10,12,13] In the UK, it has been estimated that approximately one in five people have COVID-19 symptoms beyond five weeks, while one in 10 report symptoms persisting for 12 weeks or more.[14] As a disease that affects multiple body systems, long COVID can result in wide ranging symptoms including breathlessness, chest pain, fatigue, muscle weakness, impaired cognition, anxiety and depression.[10] Yet, there remain numerous uncertainties around the mechanisms of these chronic health sequelae of COVID-19, particularly in relation to those with pre-existing and newly developed airways diseases.[10,15]

To address these uncertainties and improve long-term health outcomes related to COVID-19, the post-hospitalisation COVID-19 (PHOSP-COVID) consortium (https://www.phosp.org/) was established. PHOSP-COVID is a UK national consortium of a multi-disciplinary team of clinicians, data and basic scientists, aiming to create an integrated research and clinical platform to investigate the multi-dimensional long-term impact of COVID-19 on the health outcomes of hospitalised COVID-19 patients. Within this consortium, expert sub-groups were established including an airways diseases, bronchiolitis and bronchiectasis working group who commissioned this study. We sought to identify research priorities for the long-term consequences of COVID-19, with a focus on airways diseases, to guide researchers, clinicians, policy makers and funding organisations to address the burden of long COVID globally.

Methods

Overview of the CHNRI method

We adapted the Child Health and Nutrition Research Initiative (CHNRI) method to set research priorities for airways diseases in the context of long COVID-19. The CHNRI method employs the principle of crowdsourcing to independently generate research ideas from a large group of experts, and score these against a predefined set of criteria. It is a systematic, transparent, and democratic approach that has been used in over 100 exercises led by national governments (e.g. China, India,

South Africa), funders (e.g. The Bill and Melinda Gates Foundation), and multilateral organisations, including the World Health Organisation (WHO) and United Nations Children's Fund (UNICEF). The aim of those exercises was to set research priorities in areas ranging from the reduction of global child mortality, non-communicable diseases or disability, to the efficient execution of national health plans.[16-19] The main advantages of the CHNRI method include: (i) its systematic nature; (ii) transparency and replicability; (iii) clearly defined context and criteria; (iv) involvement of the funders, stakeholders and policymakers; (v) a structured way of obtaining information; (vi) informative and intuitive quantitative outputs; (vii) studying the level of agreement over each proposed research idea; and (viii) independent scoring of many experts, thus limiting the influence of individuals on the rest of the group.[18-25] As a result of this process, clinicians, academics, funders and policymakers are able to clearly visualise the strengths, weaknesses, and relative ranking of each proposed research question. The quantitative output of the CHNRI method is based on the collective optimism of a large group of experts in airways diseases.

Expert Management Group

In September 2020, an Expert Management Group (EMG), consisting of members (LGH, ADS, AS, IR, OE, LD, KP and DA) of the PHOSP-COVID project and the Centre for Global Health at the Usher Institute, University of Edinburgh, was established. The EMG defined the aims of the exercise and context and drafted the guidelines for the application of the CHNRI method in the context of airways diseases in long COVID-19. This included defining the final criteria, approach to scoring, invitation of experts, timelines and coordinating the steps of the priority setting exercise. Revised guidelines for the CHNRI method, based on the experience of its use, have recently been published.[19-25]

Search strategy and selection criteria

We conducted a PubMed search up to 14 January 2021 with no language restrictions using combination of search terms: “health priorities OR priority setting OR resource allocation” AND “research” AND “COVID-19 OR SARS-CoV-2 OR coronavirus disease 2019 OR 2019-nCoV” AND “survivor* OR recover* OR persistent OR follow up OR discharge* OR long term OR sequelae”.

The CHNRI approach is largely based on selecting experts based on their impact on the research field in previous years. However, as studies on COVID-19 were only emerging in the world literature at the time the EMG was established, we employed two main approaches to identify international experts. Firstly, experts that contributed to recently completed CHNRI-based prioritisation exercises on asthma and COPD were invited. Their opinion was relevant because their research already focused on chronic airways diseases. They were identified in the respective CHNRI exercises through searching the Web of Science for the most productive authors in the preceding five-year period, or those who were lead authors (first, last or corresponding) of the top 1% most cited research articles.

Secondly, experts were invited from other established research groups working on airways diseases and COVID-19, including the PHOSP-COVID consortium, Airways Diseases Working Group, Severe Asthma Registry (SAR) Network, The UK Bronchiectasis Network and Biobank (BRONCH-UK), Asthma UK and British Lung Foundation (AUK-BLF), and the International Primary Care Respiratory Group (IPCRG). After excluding duplicate names, a total of 202 experts were identified and invited. Each expert was invited to submit a minimum of three priority research questions in relation to COVID-19 and airways diseases.

Scoring

In the first phase of internal review by the EMG, submitted research questions were checked for meeting the purpose of the study and for clarity. The final list of research questions was

consolidated through the second review which involved refining the submitted research questions to clearly identify the new knowledge that each question proposed to generate through research. Research questions with a high degree of overlap were merged. Research sub-themes were identified from the consolidated list. Then, the experts were re-invited to systematically rank the final list of research questions using the five pre-defined criteria – answerability, feasibility, timeliness, burden and equity (see Panel 1 for details). Experts were offered four response options for scoring: 0 (unlikely to meet the criterion); 0·5 (informed, but not sure if it can meet the criterion); 1 (likely to meet the criterion); or left blank if the expert felt insufficiently informed to make a judgment.

Panel 1. Pre-defined context for prioritisation and criteria for scoring.

The context:

1. **Population of interest:** patients hospitalised for COVID-19 who had pre-existing airways disease OR developed airways disease post-COVID.
2. **Disease, disability or death burden**: long-term consequences of airways diseases in COVID-19 survivors with a severe form of the disease that required hospital admission.
3. **Geographic limits**: the results of this exercise should be relevant globally.
4. **Time scale**: the results of the proposed research should produce an impact within 3 years.
5. **The preferred style of investing**: the results should guide investment strategy in health research with respect to different levels of risks, benefits and preferences identified from the research options.

The criteria for scoring:

1. **Answerability**: is the research idea likely to be answerable, using the proposed study design?
2. **Feasibility**: is the research idea feasible, given the required inputs, facilities, equipment and personnel?
3. **Timeliness**: is the research idea likely to be answered within the time frame specified in the context?
4. **Burden**: is the research idea likely to lead to a substantial reduction of the burden specified in the context)?
5. **Equity**: is the research idea likely to lead to interventions or changes in practices that will favour patients equally?

The context and the criteria for scoring were defined in line with recommendations from the previous exercises and guidelines.[24,25]

Data analysis

Each completed scoresheet from the experts was collated into a separate final worksheet. First, we checked all entries for consistency and errors. We then computed intermediate scores for each criterion as the sum of the scores (i.e., “1”, “0·5” or “0”) across the criterion divided by total number of answers received. The answers that were left blank were not included in the denominator. The overall research priority score (RPS) for each question was computed as the mean of the scores for the five criteria. Thus, the RPS that could theoretically range between 0 and 100% for each scored research question. Previous experiences and statistical simulations have found considerable convergence of collective expert opinion when the number of scoring experts is 40 or greater, leading to stable and replicable results.[20]

To give insight into the level of agreement among all the scorers, we computed the Average Expert Agreement (AEA). This is an indicator of the average proportion of scorers who gave the most common answer while scoring a particular research question, expressed as:

$$AEA = \frac{1}{5} \times \sum_{q=1}^{5} \frac{N\,(Scorers\ that\ provided\ most\ frequent\ response)}{N\,(Scorers)}$$

Where "*5*" represents the five criteria, and "*N*" is the total number of experts.

Patients' input and weighting

In addition to the experts' scoring, we extended aspects of the exercise to patients with airways diseases (including individuals with pre-existing airways diseases, and individuals who developed a new airways disease after treatment for COVID-19). To account for patient views, we developed weights for the selected criteria using a method already established by the CHNRI for involving stakeholders.[23] We contacted patients through Asthma UK and the British Lung Foundation. This UK-based national charity is focused on ensuring significant improvements in outcomes for persons affected by lung diseases. The purpose, context and criteria specific for this exercise was explained to the patients, who then answered the question: "Which of the criteria (i.e., answerability, feasibility, timeliness, burden, equity) do you consider most important to set research priorities for COVID-19 in airways diseases?" The resulting weights were expressed as a percentage and applied to each criterion. This resulted in a weighted RPS (wRPS).

$$wRPS = \frac{1}{\sum_{n=1}^{5} (w_n)} \times \sum_{n=1}^{5} (RPS_n \times w_n)$$

Where "RPS_n" and "w_n" are the research priority score and weights from each of the five criteria, respectively.

Weighted priority scores are available in the supplementary material.

Role of funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. DA, KP, OE, LD, IR, AS, ADS, and LGH had full access to all the data in the study and had final responsibility for the decision to submit the article for publication.

Results

Research ideas, themes and scoring

Among the 202 experts contacted, 88 (44%) accepted the invitation and 59 (29%) contributed research questions after the CHNRI process had been explained to them. Over a four-week period, we received 300 research ideas from experts. After a two-phase internal review by the EMG, 165 duplicate or unclear research questions were removed and 27 were merged. 10 research questions were excluded because they were considered out of scope or unanswerable within the context of PHOSP-COVID research (see supplementary material for merged and excluded research questions). The final list of 98 research questions was organised into five sub-themes and sent back to the contributing experts for scoring. The sub-themes were:

I. Studying associations or risk factors for developing or having worsening airways diseases in COVID-19 survivors (36 research ideas).
II. Understanding the role of interventions in the short- and long-term outcomes of those with chronic airways diseases (22 research ideas).
III. Investigating long-term effects of COVID-19 in patients with chronic airways diseases – physiological and disease burden (21 research ideas).

IV. Investigating long-term effects of COVID-19 in patients with chronic airways diseases – quality of life, mental health and social characteristics (6 research ideas).
V. Innovative approaches to healthcare and policymaking initiatives targeting patients with chronic airways diseases (13 research ideas).

A total of 48 experts (55% of those who accepted the invitation) returned completed scoresheets within four-weeks. Receiving over 40 responses ensured the stability and replicability of final rankings according to the CHNRI methodology.[18,20] Figure 1 summarises the process of the CHNRI prioritisation exercise.

Overall Research Priority Score

The overall RPS for the 98 research ideas ranged from 0·339 to 0·864. The AEA ranged from 41.7% to 84·6%, with a median of 68·3%. Consistent with previous CHNRI exercises, there was a high degree of agreement among experts on the top ranked research ideas, with the AEA decreasing with decreasing RPS (Spearman's rho (ρ) = 0·9334, $P<0·001$). See the supplementary material for RPS and AEA for all 98 research ideas.

Of the top 20 research ideas, half (with 5 in the top 10 research ideas) were on sub-theme I, which focused on studying risk factors for developing or worsening airways diseases in COVID-19 survivors (Table 1). The top 3 ranked research questions sought to compare post-discharge morbidity between COVID-19 patients with pre-existing airways diseases and those without, with the first (RPS 0·864, AEA 83·8%) exploring correlation between admission prognostic score and post-discharge morbidity at 3 and 12 months in the two groups. The second highest-ranked research question (RPS 0·852, AEA 84·6%) was to determine the extent of post COVID-19 fatigue, sarcopenia, anxiety and depression. The third (RPS 0·849, AEA 81·7%) was to investigate the risk of future cardiovascular complications in patients treated for severe COVID-19. The top 10 included research questions on hospitalisation and symptoms in patients with pre-existing airways diseases, including understanding predictors of hospital re-admission in patients, and validating tools for remote monitoring of symptoms. Other top 10 research questions were specific for obstructive airways diseases in COVID-19 patients including determining the incidence and risk factors for new-onset disease, recovery of current smokers with COPD, and cost effectiveness of exercise rehabilitation. Research questions exploring the risk of venous thromboembolic events in COVID-19 patients, including estimating incidence of pulmonary embolism and studying the effects of long-term anticoagulants on outcomes of acute hospitalisation with COVID-19 were in the top 20.

Table 2 presents the 20 research questions that had the lowest RPS scores. Of note, 14 of the research ideas were from sub-themes II and V (seven from each sub-theme). They focused on understanding the role of interventions and approaches to health policy-making initiatives for chronic airways diseases. The three lowest ranked research questions recommended an evaluation of the role of the private sector in pandemic management (RPS 0·339, AEA 63·8%), alternative medicine in COVID-19 patients with pre-existing airways diseases (RPS 0·362, AEA 60·8%), and the risk of developing lung cancer from acute or long COVID-19 (RPS 0·446, AEA 58·8%). Other lower ranked research questions included determining priority for vaccination among COVID-19 survivors, exploring the opportunities for artificial intelligence and advanced technologies like Xenon MRI in the treatment of COVID-19 patients, investigating the risk of developing pulmonary aspergillosis in COVID-19 survivors, and studying the perceptions of general practitioners during the COVID-19 pandemic.

Scores received for each of the priority-setting criteria

Across three of the criteria (answerability, feasibility and timeliness), the research question that scored highest sought to explore correlation between admission prognostic score and post-

discharge morbidity at 3 and 12 months between patients with pre-existing airways diseases and those without (see Table 3). Another research question that was ranked second for both feasibility and timeliness proposed to estimate the incidence of pulmonary embolism up to one year after acute COVID-19. Table 3 shows that, most of the research questions that were ranked among the top three for some priority-setting criteria were also included in the top 20 questions by their overall RPS. A notable exception was the research question "determining if patients at risk of persisting disability following COVID-19 can be identified and targeted for rehabilitation and/or nutritional interventions". This question was ranked highest for both "burden" and "equity" criteria, but it eventually ranked 21st in the overall list. Similarly, the research question "investigating long-term effects of surviving COVID-19 on the mental health of people with COPD" ranked third for "answerability", while "developing scores to predict long-term respiratory disease severity and risk of mortality in survivors from severe COVID-19" ranked third for "equity", but they eventually ranked 25th and 28th in the overall list, respectively (Table 3). The top 10 research ideas for each of the five criteria are provided in the supplementary material.

Patients' weighting

The patients' contributions offered insights into the overall ranking of the research ideas, providing additional perspectives for clinicians, researchers and policymakers. From the 61 patients that responded to the weighting question, 32·8% considered burden most important to set research priorities for COVID-19 in airways diseases, 21·3% selected answerability and equity each, 18% chose feasibility, and 6·6% opted for timeliness (supplementary material)

Applying those weights to generate weighted ranks (wRPS) led to four research questions moving up into the weighted top 20. Of note were "investigating long-term effects of surviving COVID-19 on the mental health of people with COPD", and "developing scores to predict long-term respiratory disease severity and risk of mortality in survivors from severe COVID-19" - both already identified in the top three research ideas under burden and equity criteria. The two other research ideas that moved into the weighted top 20 focused on "assessing effectiveness of counselling services in addressing long-term psychological and cognitive effects of COVID-19 in patients with pre-existing airways diseases" and "exploring whether patients with pre-existing asthma develop an accelerated loss of lung function following severe COVID-19". In summary, applying the wRPS and the individual RPS showed that the top 20 overall research priorities were largely overlapping, although their rankings changed slightly (supplementary material).

Discussion

As the COVID-19 pandemic progresses into a second year, there is an increasing requirement to understand the burden of emerging or worsening pre-existing comorbidities. This paper reports on the findings of a CHNRI research priority-setting exercise aimed at addressing this burden in relation to airways diseases in those who survived an acute illness due to COVID-19. While we had an airways diseases' focus, many of the priorities emerging would be broadly applicable to the study of long COVID and its' management in non-hospitalised patients and/or those with other comorbidities. We observed a considerable diversity in the top ranked questions. This can be explained by the nature of the wide range of concerns around the burden of long-term sequelae of COVID-19, ranging from identifying associated risk factors, measuring incidence of events, to investigating the impact of interventions both in the acute setting and post discharge.

Main findings

The top four ranked research priority questions proposed to compare the healthcare outcomes of the COVID-19 survivors with pre-existing airways diseases against those with none. This included

exploring how the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) 4C score[26] correlates with post discharge morbidity at 3 and 12 months and to investigate the potential risk of developing comorbidities in the COVID-19 survivors. These comorbidities include fatigue, sarcopenia, depression, cardiovascular complications and hospital readmission. Investigating the incidence and risk factors (e.g. smoking and ethnicity) associated with developing new symptomatic airways disease or structural airways abnormalities in radiological images also featured in the top 20 questions. Additionally, investigating the correlation between the imaging findings identified during acute COVID-19 illness and the subsequent long-term symptoms and outcomes also ranked highly.

The importance of the increased incidence of venous thromboembolic disease in COVID-19 patients was reflected with 3 of the top 20 questions addressing this issue, ranging from the incidence of pulmonary embolism to the role of anticoagulants - both newly administered, or previously prescribed. Other ideas that generated interest from the experts included the role of interventions like exercise-based rehabilitation programmes, nutritional intervention and the usage of acute non-invasive ventilation (NIV) in patients with pre-existing airways diseases. Research questions from the sub-categories of innovative initiatives and long-term effects on mental health and quality of life were less common among the top 20, featuring one question each.

Questions regarded as less important by the experts in this exercise were those that proposed basic science research, the role of advanced technologies like Xenon MRI, artificial intelligence and suggestions to amend international guidelines. Other questions with low scores included understanding the perception of the private sector and primary care providers during the pandemic, and the number of patients that suffered from less observed conditions like invasive aspergillosis post severe pneumonia. These likely reflected concerns over deliverability in a pandemic situation (e.g. MRI based studies) and/or the perceived burden of disease (e.g. aspergillosis complicating COVID).

Strengths and limitations

The utilisation of a standardised tool like the CHNRI method enabled a systematic, transparent and democratic approach to identifying research priorities for long COVID in the setting of airways diseases. Despite the pressures associated with the pandemic on clinicians and researchers, we achieved a return rate of over 40% which is comparable to previous CHNRI exercises.[16,17] Consequently, we were able to include opinions from a range of experts with both clinical and academic expertise including some from low- and middle-income countries (LMICs). Though individuals from 36 nations were invited, we had no response from experts in South America, and few participants from Africa and Asia, meaning that the identified research priorities may not be directly relevant to these regions. Similarly, whilst general practitioners with respiratory expertise, and IPCRG members were invited, only a few experts from primary care took part in the study which may have contributed to the research priorities specific to primary care having a lower RPS. The relative lack of primary care focused research priorities is likely to reflect the targeted population of hospitalised COVID-19 survivors but may also have been due to fewer primary care experts being involved. As the burden of COVID-19 shifts from acute to chronic care more primary care input in priority setting will be mandatory. Reflecting the symptoms seen in long COVID, additional expertise should be sought such as neurological, psychological, renal and cardiac fields to capture diversity in questions to then feed into the priority setting exercise.

The incorporation of patients' priorities offers additional benefits in the future direction of research by ensuring that researchers, policy makers and stakeholders are engaging in research that meets the needs of those affected individuals. We conducted a rapid, online patient survey which helped

us to achieve a good number of respondents, though it is likely that views of certain patient groups were missed.

A limitation of this exercise is the large number of ideas that were unclear or out of scope of the PHOSP-COVID study, which were removed during internal review (see supplementary material). Interestingly, few of the proposed research priorities focussed on non-respiratory co-morbidities, which most likely reflects the focus of this study on airways diseases. Despite the respiratory focus, the lack of research ideas relating to cystic fibrosis or sleep-related disorders is important to acknowledge.

Although we endeavoured to carefully rephrase research ideas to reflect the new knowledge they propose to generate, some were potentially poorly worded which may have contributed to some questions being considered at lower priority.

Interpretation in the context of wider literature

Clinicians and policymakers already recognise the need to follow up post-acute COVID-19. However, understanding which sub-groups of patients need follow-up the most, will be generated through answering the top-ranked questions. The development of the ISARIC 4C score has helped to identify those at high risk of in-patient adverse outcomes.[26] The ISARIC 4C score is readily available and increasingly adopted in clinical practice.[26] If subsequent studies show that this acute severity score also helps identify those with the greatest risk of more severe long COVID-19, it will help service provision and treatment algorithms. Conversely, if there is limited correlation with acute illness score, as suggested by some early data,[2] then long COVID clinics may need a much larger service provision to provide follow up to long COVID sufferers who were not hospitalised. This is highly relevant as COVID-19 has undoubtedly affected outpatient follow-up for long-term conditions across most medical specialties. Respiratory and infectious diseases are likely further disadvantaged, reflecting the key roles of these specialties in providing acute COVID-19 services.

Patients with airways diseases have a recognised complex of comorbidities and (pre-COVID-19) clinical patterns which are relevant to COVID-19 and its multisystem disease manifestations. For example, acute COPD exacerbations are associated with a high readmission rate - up to 40% at three months - and a long-term increased risk of vascular events, such as myocardial infarction and pulmonary embolism.[27] This is highly relevant in the COVID era, where the complex multisystem nature of acute COVID-19, with acute extra-pulmonary disease and widely reported thrombotic events, may confer post-discharge disease. Understanding the frequency and severity of complications in post-acute COVID-19 and identifying patient sub-groups at highest risk of those complications should lead to testing of different intervention strategies, for example anticoagulant treatment post discharge, which could minimise early and late thromboembolism.

As the COVID-19 pandemic has progressed, it has become clear that - unlike many other respiratory viruses - SARS-CoV-2 does not cause typical exacerbations of airways diseases.[28] Observational data has suggested that patients with COPD and selected sub groups of asthma have poorer outcomes.[3,5,8,9]

Reports suggest that inhaled steroid treatment may be protective (research into the role of inhaled steroids was ranked 12th).[29] The available observational studies on inhaled steroids are potentially confounded by the effects of behavioural factors such as better adherence to treatments, “shielding” programmes and a wider reduction of exposure to other factors related to exacerbation events (e.g. other infections and air pollution). Thus, the effect of COVID-19 on patients with pre-existing airways disease, or with *de novo* airways disease, needs to be studied prospectively in large cohorts of patients. These studies will need to have an appropriately matched control group, with

linked retrospective healthcare data to ensure robust assessment of pre-COVID health status. This priority setting exercise provides a framework to answer the key questions in this important patient group.

Implications for policy, practice and research

This exercise showed an excellent level of similarity in the top 20 questions when the novel aspect of the method was included – i.e., weighting of the criteria according to the patients' input. We do not have extensive data on the demographics on the patient survey respondents but nearly half reported a pre-COVID airways disease. The weighting led to some differences in the top five ranked questions, but it was satisfactory to note that the experts' ranks, in general, reflected patients' expectations. As a result, we expect that there will be positive engagement in research participation to answer the questions identified.

Many of the top research questions are answerable within a short time frame, particularly with national and international coordination. Investigating the factors suggested in the research priorities (for example, socio-economic status, co-morbidities, ethnicity, nutritional status and medication use), could help to identify which patients are at the highest risk of long COVID, which in turn will inform service development during a time of resource constraint and large backlogs in clinical follow up. The predictors and causes of readmissions post-COVID-19 may allow targeted interventions to minimise readmission and reduce the strain on hospital capacity. Care bundles to minimise COPD readmissions have been widely adopted and could form the basis to inform post-acute COVID-19 care. Development of multidisciplinary post COVID-19 clinics is already encouraged by policy makers and patient advocacy groups.[30] These clinics can form the basis for multi-site international studies and testing interventions to either prevent additional morbidity (e.g. anticoagulation studies) or enhance return to baseline (e.g. rehabilitation studies to tackle sarcopenia).[30]

In summary, we have undertaken a robust exercise to identify research priorities in long COVID in relation to airways diseases, based on a large group of international experts and also seeking patients' views. The identified research priorities reflect the rankings of the experts included in this exercise, together with patient responses. The research priorities are therefore likely to have been influenced by the current stage of the pandemic, status of vaccine development and roll-out, as well as the knowledge base and backgrounds of the experts and patients. Involving a different group of participants (for instance with expertise in neurology, psychiatry, cardiovascular or digital health) in a future exercise as the burden and symptom complex of long COVID becomes more recognised should be considered in future priority exercises. With the COVID-19 pandemic set to continue for the foreseeable future, we recommend that such prioritisation exercises be repeated once the initial priority areas are addressed and the knowledge base grows.

Contributors: AS, IR & DA conceptualised the research priority exercise. The Expert Management Group (EMG), consisting of members (LGH, ADS, AS, IR, OE, LD, KP and DA) defined the aims of the exercise and context, identified and contacted the experts, collected and analysed the results. KP & SW designed and organised the patients' survey. DA, LD & OE wrote the initial draft of the manuscript. The PHOSP-COVID Airways Working Group (listed in the supplementary material) oversaw the exercise, contributed to the proposed research questions, completed the scoresheets, reviewed and edited the manuscript. The rest of the authors were the international experts, they proposed research questions, completed the scoresheets, reviewed, edited and approved the manuscript.

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Data sharing: All data for this study were linked, stored, and analysed within a secure online platform. All data have been de-identified where necessary and are available in the supplementary material.

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