Expert Report for the Scottish COVID-19 Public Inquiry

POST-ACUTE INFECTION SYNDROMES AND IMPLICATIONS FOR PANDEMIC PREPAREDNESS PRE- AND POST- THE COVID-19 PANDEMIC.

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Background

This report should be read in conjunction with our reports on Long COVID for Module 2 and Module 3 for the UK Covid Inquiry.

Definition of Long COVID:

Long COVID was initially described in spring 2020 by people with lived experience and rapidly formed patient support groups: Long Covid SOS, Long Covid Support and Long Covid Kids. People were reporting ongoing challenging symptoms commonly fatigue, breathlessness, brain fog, and headaches with reduced physical function after COVID-19.

The National Institute for Health and Care Excellence (NICE) issued a living review and clinical knowledge summary on Long COVID including clinical case definitions to identify and diagnose the long-term effects of COVID-19 in December 2020 [NICE 2020], which remains active to date [NICE 2022]. Acute COVID-19 is defined as signs and symptoms of infection consistent with COVID-19 for up to four weeks. Ongoing symptomatic COVID-19 is defined by signs and symptoms of COVID-19 infection from four weeks up to 12 weeks. Post-COVID-19 syndrome is defined as signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks, and are not explained by an alternative diagnosis. Long COVID usually presents with clusters of symptoms that may overlap, fluctuate, change over time, and affect any body system. The World Health Organisation has subsequently defined Post-COVID condition by a Delphi consensus as the continuation or development of new symptoms three months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least two months with no other explanation [WHO 2021].

Further information about Long COVID can be found in our modules for the UK Covid-19 Inquiry.

1. How the lessons from previous viral infections informed the scientific community's understanding about how long-term sequelae typically present in populations pre-COVID-19

1.1. At the start of the Coronavirus Disease 2019 (COVID-19) pandemic, understanding of the potential long-term sequelae from Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was extrapolated from existing knowledge of Severe Acute Respiratory Syndrome Coronavirus-1 ('SARS-CoV-1' or 'SARS'), Middle East Respiratory Syndrome-Coronavirus (MERS-CoV) other causes of acute respiratory distress syndrome (ARDS) and its consequences, and other post-viral syndromes.

Severe Acute Respiratory Syndrome Coronavirus-1 Epidemic

1.2. Almost 20 years before the COVID-19 pandemic, an epidemic was caused by the SARS-CoV-1 virus [Drosten C 2003, Ksiazek TG 2003]. Akin to the SARS-CoV-2 pandemic, SARS-CoV-1 caused a global epidemic thought to originate in China in November 2002. It involved 29 countries across Asia, North America and Europe, but was shorter than the COVID-19 pandemic with the World Health Organisation declaring the end of the epidemic by July 2003 [WHO Health topic SARS, Mackensie JS 2004]. Prior to the SARS-CoV-1 epidemic, the human coronaviruses were considered relatively harmless viruses causing illnesses such as the common cold, but with over 8000 people infected globally with SARS-CoV-1 and 774 recorded deaths due to 'SARS', this novel virus marked coronaviruses as a new threat to health and life [Benitez MA 2003, Pyrc K 2007]. An important multicentre collaboration was formed early to investigate and describe the causal pathogen [World Health Organization Multicentre Collaborative Network for Severe Acute Respiratory Syndrome Diagnosis established in March 2003], but similar networks were not employed to investigate the longer-term consequences.

1.3. The SARS-CoV-1 virus was thought to originate from small mammals ingested by humans, with the infection spreading by respiratory droplets. It spread by close contact such as in hospitals, hotels, and aeroplanes. The eventual containment was thought to be achieved due to strict quarantine, isolation, contact tracing and travel restriction measures. SARS-CoV-1 appeared to only transmit in symptomatic cases. The acute illness involved a combination of respiratory symptoms and those of acute infection i.e., dry cough, shortness of breath, myalgia and fever, and commonly resulted in pneumonia and critical illness. In a small cohort [Booth CM 2003], 20% (29/144) of patients were admitted to intensive care and (8/144) 6.5% died. Pre-existing health conditions were associated with worse outcomes. In other studies, lymphopenia was noted during the acute SARS-CoV-1 illness [He Z 2005], this phenomenon was also noted early in the SARS-CoV-2 pandemic and used clinically as an indicator of likely COVID-19 prior to the introduction of rapid testing.

1.4. Compared to the co-ordinated global approach to identify the virus causing the 'SARS epidemic' and to develop and implement diagnostic testing, there were relatively few longer-term follow-up cohorts, and most were opportunistic clinical cohorts assessed by clinical teams and therefore biased by clinical need. Pulmonary health assessed by CT scans of the chest was noted to improve in 10/12 patients by day 90, in a retrospective report from Taiwan, but not to fully resolve [Wang CH 2005]. Data from two studies showed post-SARS diffusion capacity, indicated by a breathing test, was abnormal. This suggested possible underlying lung scarring in over 25% of people who had been hospitalised for the acute infection [Hui DS 2005; Ngai JC 2010]. One of these studies from a single hospital site in Hong Kong, highlighted considerable morbidity two years after hospital discharge with a lower walking performance and health-related quality of life compared with population norms (although pre-illness values are unknown), and nearly 3 in 10 healthcare workers and nearly 1 in 13 other workers had not returned to work two years after the hospital admission with SARS [Ngai HC

2010]. Psychiatric complications were investigated, also in Hong Kong but in a different hospital site (n=90 participants), and highlighted significant prevalence of post-traumatic stress disorder (PTSD) (33%) and depression (15.6%) 30 months after the hospital admission [Mak IW 2009].

1.5. For context, it is important to note that the United Kingdom only had four confirmed cases of SARS-CoV-1 during 2002-3 and all were linked to travel to affected areas with no sustained community transmission. The Health Protection Agency (HPA) England stated lessons learned included: "the importance of international collaboration; formation of a UK-wide, multidisciplinary Task Force; flexible case reporting mechanisms; integration of surveillance and laboratory data; generation of prompt and web-accessible guidance and advice; availability of surge capacity; and contingency planning. Lessons learned are being incorporated into the HPA's preparedness to prevent and control future newly emerging infectious disease threats" [Goddard NL 2005].

1.6. In summary, although there were only a few prospective studies, and these were single site and mostly without control groups, it was clear after the SARS-CoV-1 epidemic that significant life-altering complications could be expected after future similar coronavirus pandemics. These complications were likely to be multi-system (i.e., involves multiple parts of the body), affect both physical and mental health, and negatively affect both quality of life and occupational status. It was also clear that the severity of the acute illness was associated with the likelihood of developing longer term sequelae and for some people these could last years. The other main lesson from the SARS-CoV-1 epidemic for future pandemic planning was that dedicated clinical research cohort studies were going to be needed at scale to understand incidence of post-infectious sequelae, the type and severity of sequelae, and the

underpinning mechanisms to enable new treatments and adequate clinical care to support survivors.

Middle Eastern Respiratory Syndrome (MERS)

1.7. The Middle Eastern Respiratory Syndrome (MERS) was first identified in Saudia Arabia in 2012 and subsequently known to be caused by a coronavirus (MERS-CoV) [CDC 2024]. Similar to SARS-CoV-1, it is transmitted from animals to humans i.e., a zoonotic virus. Compared with SARS-CoV-1 and SARS-CoV-2, MERS has a low human to human transmission rate but a high fatality rate of approximately one third of cases [WHO MERS key facts 2022]. Unlike SARS, MERS has never become a global pandemic but there are ongoing outbreaks and sporadic clusters particularly in the Middle East. Cases of MERS have been reported in 27 countries and by early 2024 approximately 2600 cases were reported with 940 deaths. Adults with pre-existing health conditions such as diabetes, chronic heart, lung, or kidney disease, and cancer are at a higher risk of dying from MERS.

1.8. The MERS coronavirus was described in November 2012 [Zaki AM 2012] and diagnostic tests such as polymerase chain reaction (PCR) based tests were quickly available [Lu X 2014]. The acute effects of MERS include fever, shortness of breath and cough, with pneumonia being common [Naeem Z 2013]. Gastrointestinal symptoms particularly diarrhoea have also been reported commonly. Similar to SARS, patients with pneumonia can deteriorate further requiring intensive care unit support and mechanical ventilations. There are no specific treatments other than organ support during recovery.

1.9. There is rather a paucity of evidence on the longer-term effects of MERS, and similar to SARS rely on clinical cohort reporting with inherent biases around clinical need and lack of control groups. One cohort followed up 83/355 MERS survivors and 78 participated. MERS survivors

were compared to a sample of survivors from other non-MERS severe acute respiratory infection survivors. Health-related quality of life was worse in MERS than non-MERS, and within the MERS group impairments in mental and physical health were described at one year after hospitalisation. A large systematic review was conducted in 2020 describing outcomes of MERS and SARS coronavirus infections beyond six months after hospital discharge and included 28 studies [Ahmed H 2020]. Over 1 in 4 participants had impaired lung function, exercise capacity was overall reduced, PTSD, anxiety and depression were all present in a least a third of survivors, and reduced health-related quality of life was reported. The authors concluded that similar outcomes should be anticipated for COVID-19 survivors.

1.10. There is some interest into whether 'Gulf War Illness' a condition described in veterans (30-40% of 700 000 veterans) deployed to Operation Desert Shield/Storm/Sabre between Aug 1990 and 1991 was MERS [Bast E 2025]. Gulf War Illness is characterised by multiple symptoms including fatigue, mood disturbance, cognitive impairment, chronic pain and gastrointestinal upset. The assertion is supported by MERS being present in camels in Saudi Arabia since 1983, but no firm conclusions are able to be made at the current time.

1.11. Similar to the SARS-CoV-1 epidemic, the UK saw very few cases of MERS with only five cases being reported since 2012. These cases were primarily linked to travel from the Middle East with no evidence of community transmission in the UK (although human to human transmission particularly in healthcare settings has been described in other countries). There have been no cases of MERS reported in Scotland [Public Health Scotland 2025]. The low number of cases seen in the UK potentially limited the vision and priority for pandemic preparedness.

1.12. Lastly, an important aspect for SARS-CoV-1 and MERS is that very few non-hospitalised cases were/are reported and even fewer with longer-term sequelae in stark contrast with what is now known for COVID-19 and Long COVID. This may have led to an assumption at the start of the SARS-CoV-2 pandemic that most infected people were hospitalised missing the rapid community transmission including asymptomatic cases. Research and any clinical care for longer term sequelae were therefore also focused on the hospitalised population. For future pandemics, preparation should involve a level of community surveillance for the infection and for any longer-term sequelae so that research and clinical care can be escalated at scale and pace as needed.

Lessons learned about potential underlying mechanisms of longer-term sequelae from acute respiratory illnesses from SARS and MERS

1.13. As there were few long-term (even one-year post-infection) studies for SARS-CoV-1 or MERS, unsurprisingly there were even fewer mechanistic studies investigating the cause of any longer-term sequelae. However, there is some evidence of immune system dysregulation, autoantibody formation particularly endothelial and epithelial, and some limited studies demonstrating viral persistence is some patients [Jiang Y 2005, Yang YH 2005, Mizutani T 2006].

Adult Respiratory Distress Syndrome and longer-term sequelae

1.14. For respiratory viruses causing pneumonia, some patients will develop acute lung injury and Adult Respiratory Distress Syndrome (ARDS). ARDS was first described in a case series in 1967 with viral infections identified as one of the recognised causes [Ashbaugh DG 1967]. The lungs in ARDS are very badly damaged and cause respiratory failure. ARDS is defined where there are bilateral lung opacities on imaging such as a chest x-ray, and low oxygen levels despite a given amount of oxygen (high flow nasal oxygen >30L/min, $Pa_{O2}:Fi_{O2} \leqslant 300$ mm Hg) [Matthay MA 2024]. Patients with ARDS will require further respiratory support beyond oxygen supplementation called mechanical ventilation. Mechanical ventilation can either be provided via a facemask where ventilation remains spontaneous (patient is breathing for themselves) or in very severe cases invasive mechanical ventilation is needed, and a patient will need to be supported on an intensive care unit. Patients requiring invasive mechanical ventilation are put into a medically induced coma and the machine supports their breathing while the lungs recover ("life support"). There are many different causes of ARDS. Independent of the original cause, survivors commonly have persisting deficits. In one cohort

of 109 participants, survivors had persistent physical function and psychological impairment five years after the original intensive care unit admission [Herridge MS 2011].

1.15. Early in 2020 at the start of the COVID-19 pandemic, it was quickly apparent in other countries that SARS-CoV-2 was causing severe pneumonia and ARDS with the need for life-support for a significant proportion of patients and therefore longer-term sequelae were anticipated.

Post-viral syndromes

1.16. There are known post-viral syndromes from other viruses, for example Epstein-Barr virus causing glandular fever particularly in teenagers; Coxsackie viruses and Bornholm disease (the latter presents with flu-like symptoms); Coxsackie viruses and inflammation of the heart muscle (myocarditis) and lining of the heart (pericarditis); and enteroviruses such as Ebola [Calder B 1987, Jenkins R 1991, Lorusso L 2008]. Post-viral syndromes are typically multi-system and can affect both physical and mental health. Of note, many of the acute illnesses due to these viruses can be relatively mild and not require hospital admission for organ impairment or failure, in contrast with SARS and MERS. Debilitating fatigue is a common feature of the post-viral syndrome, and some adults will subsequently develop Chronic Fatigue Syndrome (CFS) / Myalgic Encephalomyelitis (ME) [Hicki I 2006].

1.17. There are multiple definitions of ME/CFS from different organisations and countries. The National Institute for Health and Care Excellence [NICE 2021] defines ME/CFS as persistent symptoms for three months, other causes should be considered and excluded, and a ME/CFS specialist team should confirm the diagnosis. All the following symptoms should be present:

- Debilitating fatigue that is worsened by activity, is not caused by excessive cognitive, physical, emotional or social exertion, and is not significantly relieved by rest.

- Post-exertional malaise after activity in which the worsening of symptoms:
    - is often delayed in onset by hours or days
    - is disproportionate to the activity
    - has a prolonged recovery time that may last hours, days, weeks or longer.
- Unrefreshing sleep or sleep disturbance (or both), which may include:
    - feeling exhausted, feeling flu-like and stiff on waking
    - broken or shallow sleep, altered sleep pattern or hypersomnia.
- Cognitive difficulties (sometimes described as 'brain fog'), which may include problems finding words or numbers, difficulty in speaking, slowed responsiveness, short-term memory problems, and difficulty concentrating or multitasking.

1.18. Multiple viruses have been shown to be associated with ME/CFS shown in Table 1. In addition, survivors of the severe enterovirus Ebola are particularly prone to ongoing fatigue, post-exertional symptom exacerbation (where exercise can worsen symptoms for a few days to weeks), and other features of ME/CFS. In one cross-sectional study conducted in Liberia, 90% (242/268) of survivors had symptoms of Post-Ebola Syndrome [Wilson HW 2018]. Following the West African outbreak of Ebola Virus Disease (EVD) in 2013-2016, a prospective study of longer-term sequelae, risks of reactivation, and viral persistence was conducted. 78% of adults and 64% of children had at least one persistent symptom on average one year after the viral infection. 5% of men demonstrated viral persistence in their semen. However, many men had ongoing symptoms without viral persistence highlighting that this is an unlikely universal underpinning mechanism of post-viral sequelae.

1.19. Whilst infection with Human Immunodeficiency Virus (HIV) is now treatable and associated with a good prognosis overall, fatigue is also a common symptom at presentation and a post-viral syndrome is described [Perazzo JD 2017].

Table 1. Incidence of ME/CFS following different acute infections

Infectious pathogen	Type	Study	Findings (diagnosis of ME/CFS)
SARS-CoV-2 (COVID-19)	RNA virus	279 people with COVID-19 infection history assessed at 3 months; used 1994 Fuduka, 2015 IOM and 2003 Canadian consensus criteria for ME/CFS [Tokumasu K 2022]	16.5% met all the three criteria for ME/CFS
		130 people with COVID-19 infection history assessed at 6 months; used 2015 IOM criteria for ME/CFS [Gonzalez-Hermosillo JA 2021]	13% met the criteria for ME/CFS
		42 people with COVID-19 infection history and persistent fatigue at 6 months; used 2003 Canadian consensus criteria [Kedor C 2022]	45.2% met the criteria for ME/CFS
West Nile virus	RNA virus	140 people with West Nile Viral infection followed for 5 years; used CDC criteria for ME/CFS [Garcia MN 2014]	64% those with fatigue (20% overall) met the criteria for ME/CFS
Epstein-Barr virus, Coxiella Burnetti, Ross River virus	Herpes virus, bacteria, RNA virus	253 IgM positive individuals with any of these infections followed for 6 months; used DSM IV criteria for ME/ CFS [Hickie I 2006]	11% met the criteria for ME/CFS
Giardia duodenalis	Protozoa	53 people after Giardia infection followed for 5 years; used Fukuda criteria for ME/ CFS [Mørch K 2013]	41.5% met the criteria for ME/CFS
SARS	RNA	233 SARS survivors followed for 4 years: used 1994 CDC criteria for ME/ CFS [Lam MH 2009]	27.1% met the criteria for ME/CFS

Table adapted from original by Professor Manoj Sivan for an NIHR grant application – with thanks.

1.20. In summary, there should have been an expectation that SARS-CoV-2 would involve longer term sequelae, but the scale and severity would have been unknown. Future pandemic preparedness should include an assumption that acute infections will result in a long tail of recovery lasting years and will add to the burden of ME/CFS both for individuals and healthcare systems. The exact scale and severity of the ongoing symptoms and organ damage will vary according to the pathogen. Pandemic preparedness could involve plans for early small scale, detailed surveillance of the incidence/prevalence and severity of longer-term sequelae to inform escalation plans for research / clinical care accordingly.

2. Further commentary on the typical post-infectious sequelae of other potential pandemic-causing pathogens, such as bacteria, fungi or parasites.

2.1. Multiple bacterial, fungal and parasitic infections result in longer term complications. Many of these are very specific. Examples of specific sequelae resulting from bacterial infections include: streptococcus throat infection resulting in inflammation of the kidneys causing long-term kidney damage (Post-streptococcus Glomerulonephritis); salmonella infection causing a reactive arthritis (Reiter's Syndrome); and Neisseria Meningitidis (a cause of meningitis) can result in longer term brain damage and other brain sequelae. Specific examples of sequelae of fungal infections include: Histoplasma Capsulatum causing lung nodules and scarring in the tissue of the centre of the chest (fibrosing mediastinitis); and valley fever by Coccidioides which can cause chronic fatigue, joint ache (arthralgia) and lung nodules (small scars in the lungs). One of the most common parasitic infections worldwide remains Malaria which can result in chronic anaemia, an enlarged spleen and brain complications. Other tropical diseases include Chagas Disease, which can cause long-term heart damage, and Schistosomiasis which can cause long-term liver damage. These examples illustrate the wide range of post-infectious sequelae that can occur.

2.2. However, post-infectious syndromes can be very similar to the post-viral syndromes described including ME/CFS. In the UK, probably one of the most common causes of a post-infectious syndrome from a bacterium is from Borrelia Burgdorferi which is transmitted by ticks. Treatment is with specific antibiotics. Although most people make a full recovery with early treatment, some patients develop Post-Treatment Lyme Disease Syndrome which has commonalities with ME/CFS.

3. Your views on whether learning from previous outbreaks where the pathogen is viral and the route of transmission is respiratory, can be used to foresee the long-term sequelae of a future pathogen of unknown origin or one that may not be viral.

3.1. . Broad lessons learned from the SARS-CoV-1 and SARS-CoV-2 pandemics, and from MERS outbreaks of the 21st century, can be applied to future pandemics caused by unknown pathogens, irrespective of whether viral or otherwise. Long-term health and societal sequelae should be assumed and planned for regarding any future pathogen pandemic. The exact sequelae including those resulting from the primary organ affected will differ depending on the type of acute infection for example lung disease from acute respiratory viruses versus liver damage from hepatitis. However, many long-term sequelae including recognised post-infectious syndromes are multi-system and affect both physical and mental health. Return to work is often complex and needs to be specifically managed and monitored, with societal economic activity also quantified. Research and clinical care for post-infectious sequelae should be founded on a person-centred, multi-system approach.

3.2. A proportion of post-infectious sequelae will include syndromes that meet the criteria for ME/CFS. Symptoms such as fatigue, post-exertional symptom exacerbation, postural orthostatic tachycardia syndrome (where the heart rate disproportionately increases with standing giving rise to debilitating symptoms) should be expected in some people, and recovery and rehabilitation programmes adapted accordingly. ME/CFS services will likely need expanding for future pandemics and therefore planned for.

3.3. Rather than waiting for the 'next pandemic', research and clinical care should be co-ordinated and research the underlying mechanisms of these phenomena to enable better treatment for current and future patients.

4. **Any evidence to suggest that different groups experience different outcomes in relation to the prevalence of long-term sequelae, particularly groups from ethnic minority backgrounds.**

4.1. SARS and MERS were not on the same scale as the COVID-19 pandemic and there were no co-ordinated national or global epidemiological studies at scale conducted; limiting the learning about the risk factors for post-infectious sequelae. Furthermore, commonly the cohorts involved in these studies were predominantly people of single ethnic backgrounds [Leung GM 2003]. For MERS, people at risk of severe disease are people over the age of 65 years, children, pregnant women, people with pre-existing health conditions or with weakened immune systems and in survivors, it is likely these are shared risk factors for longer term complications. If cohort studies only include survivors, then risk factors for long-term complications may be biased (survivor bias) i.e., a risk factor for dying from an acute illness may not be seen in the longer-term outcomes as it will be underrepresented in survivors.

4.2. The risk factors for survivors not feeling fully recovered after a hospital admission with COVID-19 were identified early by the PHOSP-COVID study, and included female sex, obesity, middle age, presence of pre-existing health conditions, acute illness severity, and white ethnicity [Evans RA 2021]. At one-year post-hospital discharge, only female sex, obesity and having received invasive mechanical ventilation remained associated with not feeling fully recovered [Evans RA 2022]. Other larger studies in non-hospitalised infections highlighted the following as risk factors for Long COVID: female sex, worse social deprivation, pre-existing health conditions particularly asthma, and increased age [Sudre CH 2021, Whitaker M 2022, Subramanian A 2022, Wang HI 2024].

4.3. However, there were sections of our community where there was a paucity of data during the pandemic either due to the population being small or 'hard to reach'. The latter can be due to the way potential participants are invited for research studies, survey targets such as the office of national statistics survey being only available for private households, and electronic health data capturing people who seek healthcare. An exemplar population missing from the literature is people who are homeless: they are less likely to be invited to participate in research studies and less likely to seek medical attention other than for emergencies. Individuals who are immunosuppressed have remained at high risk of severe disease from COVID-19 throughout the pandemic [Evans RA 2023, Quint J 2025], but it remains unclear whether they are also at higher risk of post-infectious sequelae such as Long COVID. Similarly, in pregnancy there are studies reporting the effects of contracting COVID-19 during pregnancy on babies, but there is very little evidence about the risks of post-infectious sequelae in the mother.

4.4. Whether and how ethnic background is a risk factor for Long COVID and other post-infectious sequelae remains uncertain [Khunti K 2024]. In epidemiological studies the results have been inconsistent, in some being of non-white ethnicity was associated with Long COVID [Subramanian A 2022, Wang HI 2024] whilst others have shown the opposite [Evans RA 2021, Whitaker M 2024]. Intersectionality is common with ethnicity i.e., there are other drivers such as social deprivation associated with ethnic background that are the drivers of worse outcome rather than a genetic predisposition and depending how far intersectionality has been considered within a study may in part explain some of the inconsistencies.

4.5. Taken together, there are some common themes learned from the longer-term effects of the SARS and MERS coronaviruses and other pathogens: post-infectious sequelae are more

commonly associated with acute illness severity, aging, pre-existing health conditions, but importantly can occur in anyone who is infected.

5. **Further commentary regarding the protocols, guidance and other strategic arrangements relative to the identification and monitoring of long-term sequelae that were known to the scientific community before the pandemic and throughout and based on previous exercises/ viruses/ studies/ best practices.**

5.1. Despite the recognition of long-term sequelae in some individuals following some infections described above, we are not aware of any protocols or other strategic arrangements that were in place for rapid implementation at the beginning of the COVID-19 pandemic to identify and monitor long-term sequelae. This contrasts with the observational 'hibernating' study led by the ISARIC consortium [Drake TM 2021, isaric.org] that was activated at the beginning of the pandemic and enabled rapid analysis of the incidence of hospitalisation and associated risk factors. This study provided critical early disease understanding and informed public preventative care and acute healthcare. Throughout the pandemic numerous studies were initiated to identify and monitor long-term sequelae. Studies in the UK initially focussed on people that were hospitalised for acute COVID-19 e.g. PHOSP-COVID and later included those people that were managed in the community [Routen A 2022]. From these studies strategies were developed to identify and monitor the long-term sequelae. Some data collection protocols are now available e.g. ISARIC (isaric.org).

6. **Any information on what, if any, hibernation protocols had been/were being developed in the wider community in relation to long-term sequelae that could have been considered and if these were widely accepted**.

6.1. Study protocols for long-term sequelae needed to be created *de novo* at the beginning of the COVID-19 pandemic. For example, PHOSP-COVID was the first study across the UK to study long-term sequelae of people hospitalised with acute COVID-19. This study recognised that the long-term consequences would likely affect mental and physical health including multiple body systems. The consortium brought together patient groups,

charities and experts across multiple disciplines at pace and scale to develop new protocols for the study.

6.2. In future, hibernating studies could enable almost immediate set up and data collection, enabling resources to focus on delivery rather than designing, writing, and approving studies under pandemic conditions.

7. Further commentary on what additional mechanisms or structures may need to be put in place to ensure post-infectious sequelae are effectively considered by governments and included in future pandemic preparedness plans.

Summary and Conclusions

- Pandemic preparedness is currently focussed on reducing the impact of future pandemics by making diagnostics, therapeutics, and vaccines available early - such as the 100 days mission. However, there is minimal focus on preparedness for long-term consequences.

- Data from pandemics repeatedly highlight the negative impact of post-infectious sequelae on individuals, health-care systems, and the economy, all shown at scale by the COVID-19 pandemic - highlighting the need for post-infectious sequelae to be front and centre of future pandemic preparedness plans.

- The minimal surveillance for Long COVID planned at the outset of the COVID-19 pandemic, highlighted the need for future 'hibernating' pandemic studies for post-infectious sequelae. Hibernating studies require funding, a team of experts to design a research study with a peer-reviewed study protocol, and full ethical approval to enable rapid activation when necessary. In addition, these studies require study sites ready to implement, including contracting, ahead of any future pandemic.

- There needs to be pre-existing broad plans for how to deal with the consequences of infectious pathogen-related pandemics with established research plans including how to embed research into clinical care. Earlier development of clinical services with a clear ambition to embed research into the clinical care might have led to earlier recognition of Long COVID. The reality was clinical care followed the research. Similar to the 'hibernating pandemic studies' there should be a 'hibernating clinical plan' around follow-up care to include agreed lead sites with hub and spoke models across regions. How to embed the research studies into these clinical care models needs to be pre-established.

- Pandemic preparedness and the proposed hibernating studies and clinical care plans need to occur across the four nations of the UK.

- There remain many important research questions for Long COVID which require further clarity including prevalence, ongoing severity and duration over many years to decades including children and young adults, further understanding the mechanisms behind the risk factors for Long COVID, and the need for further research in high-risk groups such as key workers. There is a clear need to further investigate the potential effects of ethnicity and other protected characteristics or vulnerable groups on Long COVID including the effect of culture and language in describing ongoing symptoms underpinned with biological mechanisms. Maximising understanding from Long COVID is a priority to inform future pandemic preparedness. If this is not being done to the full potential then policy makers, research, and clinical communities will be minimally further forward than for the COVID-19 pandemic.

- There are good examples of co-development of research programmes with people with lived experience and continued public involvement in future research and clinical

service is important. It is essential that post-infectious sequelae research and access to clinical care is inclusive and accessible to diverse groups of people.

- For future pandemics, policy makers need to consider and prioritise mitigation of morbidity from post-infectious sequelae in addition to mortality.

- Pandemic planning for research needs to include but not be limited to: surveying the population at scale, how to recruit patients as early as possible into more detailed research studies to understand the specific pathogen sequelae (and we suggest embedding research into clinical care), pre-planned use of control groups specific to the research question, promote efficiencies using existing controls where possible and avoiding duplication, embed collection and storage of biological samples in observational studies and clinical trials, improve data linkage with routine health records and between studies, and improve the ability to nest intervention studies within the observational study framework.

- Whilst the next pandemic pathogen is unknown there are broad principles and learning from the COVID pandemic and previous infectious disease pandemics that should be in place to reduce the long-term effects to individuals, the healthcare system and the economy.

Relevant Qualifications and Experience

Professor Christopher E Brightling GMC reference number: 4021092

Professor Chris Brightling is a Fellow of the Academy of Medical Sciences (AMS), National Institute for Health and Care Research (NIHR) Senior Investigator (Emeritus), Director for the Leicester Institute for Precision Health, Director Institute for Lung Health, Respiratory and Infection Theme Lead for Leicester NIHR Biomedical Research Centre and Honorary Consultant Respiratory Physician, Leicester, UK. He has been a consultant since 2004, and a professor since 2007. He is the former Science Council Chair of the European Respiratory Society (ERS) (2019-2022).

Beyond COVID-19, his main research focus is on improving the clinical management and understanding the immunopathogenesis of asthma, chronic cough and chronic obstructive pulmonary disease (COPD). He is Coordinator the MRC Molecular Pathology Node EMBER and Respiratory lead for the EU-IMI 3TR. He is a member of the Global INitiative for Asthma - GINA scientific committee. He has published over 635 peer-reviewed articles including more than 70 in either the New England Journal of Medicine or Lancet family of journals.

Of relevance to this report, Professor Brightling led the acute COVID-19 research for Leicester, with Leicester recruiting the largest number of patients for the national acute study platforms such as the RECOVERY study. Professor Brightling is the chief investigator for the UK Research and Innovation (UKRI) Post-Hospital COVID-19 study (PHOSP-COVID), and a co-investigator/collaborator for the UKRI funded studies OpenSAFELY, PHOSP-COVID, ISARIC collaboration and UK-ILD. He has co-authored 99 peer-reviewed scientific publications on COVID-19, of which 53 are focussed on Long COVID. During his tenure as ERS science council chair Professor Brightling led the ERS Long COVID scientific response and established the Long COVID clinical research collaboration END-COVID and co-authored the ERS COVID-19 guidelines.

Professor Brightling participated in the Secretary of State Roundtable Research into the long-term impacts of COVID-19 meeting 31st July chaired by the Department of Health and Social Care (DHSC) Secretary of State ahead of the formation of the SoS/ministerial-led (Lord Bethell or Matthew Hancock MP) Long Covid Roundtable meetings which were held between 13 Oct 2020 to 21 July 2021. He co-authored the AMS report published in July 2020 and gave evidence to the House of Lords Science and technology committee on the Science of COVID-19 in September 2020. He co-authored a report to SAGE, attended and presented on 22nd July 2021. He is a member of the National Long Covid Research Group chaired by Professor Kamlesh Khunti, University of Leicester.

Professor Rachael Andrea Evans GMC reference number 4418441

Professor Rachael Evans is a Professor of Respiratory Medicine at University of Leicester and an Honorary Respiratory Consultant Physician at Glenfield Hospital, University Hospitals of Leicester NHS Trust. She has been a Consultant Respiratory Physician since 2013, an Associate Professor since 2016, and promoted to full Professor 2024.

As part of her clinical care, Professor RA Evans initiated, implemented and led the Leicester, Leicestershire, Rutland Long Covid service from June 2020 to present. The service has seen more than 8000 patients to date and over 1200 patients have been recruited to national in-person research studies. Her clinical work outside of Long COVID includes delivering healthcare for people with advanced chronic obstructive pulmonary disease (COPD), and people living with breathlessness. Professor RA Evans' clinical work also includes being part of her local respiratory consultant team working on the acute medical admissions unit outside of usual working hours on the 'on call' rota.

Professor RA Evans is the lead clinical co-investigator for the UKRI Post-Hospital COVID-19 study (PHOSP-COVID), and chief investigator for a UK multicentre randomised controlled trial of Tocilizumab compared to placebo in Long COVID (PHOSP-I). She is also a principal investigator/co-investigator for a number of nationally funded UK Long Covid studies: NIHR Long Covid Multidisciplinary consortium: Optimising Treatments and services across the NHS (LOCOMOTION) study, the NIHR Symptoms, Trajectory, Inequalities and Management: Understanding Long Covid to Address and Transform Existing Integrated Care Pathways (STIMULATE-ICP) study, UKRI HEAL-COVID study, NIHR Policy Research Programme PHOSP Health Services Research (PHOSP-HSR) and the Wolfson Foundation C-Fog study. She was part of the NIHR Therapies for Long Covid (TLC) study steering committee.

Professor RA Evans was a member of the NHS England Long Covid Taskforce since inception until it ceased in 2024 and participated in the Lord Bethell Long Covid Roundtable meetings 13 Oct 2020 to 21 July 2021. She is a member of the National Long Covid Research Group chaired by Professor Kamlesh Khunti and she co-authored a report to SAGE from the group which was presented 22nd July 2021. She was part of the development of the Your COVID Recovery website and provided initial content.

Beyond Covid-19, her research work focuses on symptom-based models of healthcare, using breathlessness as an exemplar symptom, from diagnosis through to interventions including exercise rehabilitation. On this topic, she held an NIHR clinician scientist fellowship from 01 March 2017 to 30 Aug 2022. She is the American Thoracic Society Pulmonary Rehabilitation Assembly Chair and the European Respiratory Society Pulmonary Rehabilitation and Chronic Care Chair.

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