

Intended for healthcare professionals



## Opinion

# Long covid: where are we, what does it say about our pandemic response, and where next?

BMJ 2023; 383 doi: <https://doi.org/10.1136/bmj.p2972> (Published 19 December 2023) Cite this as: BMJ 2023;383:p2972**Daniel M Altmann, professor of immunology<sup>1</sup>, Christina Pagel, professor of operational research and co-director CHIMERA hub for mathematics in healthcare<sup>2</sup>**<sup>1</sup>Imperial College London, UK<sup>2</sup>Clinical Operational Research Unit, University College London

The UK Office for National Statistics (ONS) Infection Survey was the best estimate that we had on the number of people experiencing long covid. When it ended in March 2023, there were an estimated 1.7 million people living with symptoms of long covid lasting at least 12 weeks.<sup>1</sup> Almost a third of these are people who first caught covid in 2020, and 40% first caught covid over two years ago. Almost 400 000 people are estimated to have had their daily activities impacted a lot by long covid.<sup>1</sup> A recent paper by Atchison et al.<sup>2</sup> using data from the Imperial REACT study, reported that only 31% of people who had symptoms after 12 weeks recovered within a year of their infection. After one year, rates of recovery slow even further. The chance of developing long covid was highest for those infected in 2020 (approximately 23%<sup>2</sup>), before vaccination, and likely on their first infection. Long covid symptoms also tended to last longer for those infected during 2020.

As 2023 draws to a close, we have tens of thousands of people who have had persistent symptoms for over three years. But people are still developing long covid following (re)infection now. While the probability of developing long covid is now low for an individual (likely a few percent), continuing waves of covid ensure that that small percentage translates into thousands affected. While many with long covid experience mild ongoing symptoms, a significant proportion report substantial impact on their daily lives,<sup>1</sup> and long covid is associated with significant increases in health service use.<sup>3</sup> The number of people out of work due to chronic sickness is growing, and that growth is faster than it was pre-pandemic.<sup>4</sup> At least some of this will be due to long covid, with research estimating that 80 000 had left the workforce due to long covid as of summer 2022.<sup>5</sup> A German study estimated the production loss in Germany due to long covid to be in the order of three to six billion Euros.<sup>6</sup>

Long covid is a result of physiological mechanisms. A substantial and growing body of evidence has shown distinct serum biomarkers associated with long covid, with different biomarkers associated with different clusters of symptoms. Long covid researchers increasingly now regard the term as an umbrella for divergent symptomologies, potentially arising through distinct molecular pathways, for example, the consequences of either hypercoagulation or immune stimulation by a persistent virus reservoir in the gut.<sup>7</sup> Findings are rapidly moving to a point where it will be possible to reach an objective, laboratory-defined diagnosis, both for referral into care pathways and into clinical trials. For example, Liew and colleagues<sup>8</sup> recently looked at different clusters of persistent symptoms and associated serum biomarkers in the UK PHOSP COVID cohort. They described the complement component, C1QA as a serum biomarker of neurocognitive long covid, while raised interleukin-1R expression was a biomarker of cardiorespiratory symptoms.

Our increasing understanding of the underlying physiology should be good news: it allows us to design potential treatments for long covid. It seems highly likely now that different treatments will be needed for different clusters of symptoms and/or different physiological markers. There will be no "one-size-fits-all" long covid cure which means that well designed trials—and many of them—will be needed, each targeting plausible patient subgroups. Such treatments are desperately needed for those with debilitating symptoms or symptoms lasting longer than a year. However, there are far too few trials evaluating potential treatments for long covid, with seeming continual falls in interest and research funding. The perception is still that it is "too early" for randomised controlled trials and that rigorous evaluations are impossible in the absence of agreed biomarkers or outcomes. This perception is false. We know enough right now to design, run, and report on treatment trials if the will and funding existed. A recent workshop of the European Medicines Agency<sup>9</sup> considered the routes to circumventing these apparent regulatory roadblocks to progress and made considerable progress towards the terms of engagement for large scale trials.

The current inertia is in marked contrast to the incredible efforts during the first few years of the pandemic to accelerate finding new treatments for acute covid through the Recovery Trial<sup>10</sup> encompassing nearly 50 000 participants. Therapeutic insights from the simple act of putting momentum (and funding) behind speedy and properly powered RCTs—something the UK was arguably uniquely placed to do—saved many tens of thousands of lives.

Long covid first started being reported (by patient support groups) from the summer of 2020 and was quickly recognised as a serious problem for a significant minority of infected patients.<sup>11</sup><sup>12</sup><sup>13</sup> However, it never made it into UK science advice modelling as an adverse outcome of infection. Instead, the main adverse outcomes modelled to inform government covid policy remained deaths and hospital admissions from acute infection.<sup>14</sup><sup>15</sup> When SAGE did discuss long covid, it was acknowledged as an adverse outcome, but the emphasis was on the uncertainty in the evidence on its prevalence, causes, and impact, even by the summer of 2021.<sup>16</sup> We would argue that, given the prevalence of infection, especially with the arrival of the Delta variant in April/May 2021, even the most conservative estimates on long covid's prevalence and impact were high enough to explicitly warrant inclusion of long covid within the mathematical models and as an important consideration for policy makers. The past few weeks of evidence at the UK covid-19 Inquiry seem to emphasise that, while issues around acute infection prevalence, spread, and case fatality rate were a matter of urgent scrutiny, albeit sometimes poorly grasped, the more long term, chronic, healthcare impacts of long covid fell largely outside the remit. That is, while deaths from acute infection and the risk of the NHS becoming overwhelmed have been an indisputable political focus, the slow, rumbling ruin of lives, healthcare planning, and economies by years or decades of chronic disease is perhaps harder to grapple with and easier to kick down the road for some other, future administration.

Post-viral syndromes are nothing new.<sup>7</sup>, <sup>17</sup> We already knew of the significant ongoing burden of disease in many infected with SARS-CoV-1 almost 20 years<sup>18</sup> and MERS over 10 years ago.<sup>19</sup> The chances that another new coronavirus like SARS-CoV-2 which causes significant long term morbidity should have been a consideration from the very beginning of the pandemic. It should have been explicitly factored into the debates on policies which suggested allowing millions to be infected in the first two waves as long as they didn't die or need hospital admission. With 23% of those infected in 2020 developing long covid,<sup>2</sup> such policies would have caused devastation within the UK population. As it happened only about 13% of people had

been infected by the end of 2020.<sup>2021</sup> As the covid-19 inquiry Module 2 on government decision making during 2020 has drawn to a close, we hope that it reflects not just on the deaths and hospital admissions, but also on the impact of long covid and how much worse it could have been under a “let it rip” policy. We also hope that consideration of post-viral syndromes in a significant proportion of patients is factored into responses to the *next* pandemic. After all, the next one may well be a related, bat-derived, coronavirus.<sup>22</sup>

## Footnotes

- Competing interests: Christina Pagel is a member of Independent SAGE; Daniel Altmann is a member of Independent SAGE and has received honoraria for consultancies with AstraZeneca, Pfizer and Novavax.
- Provenance and peer review: not commissioned, not peer reviewed.

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Should we introduce trainees and medical students to the idea of uncertainty earlier in their careers?

Yes

No

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