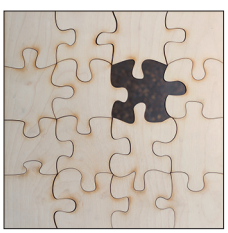
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

COVID-19 and inhaled corticosteroids—another piece in an expanding puzzle



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The role of inhaled corticosteroids in the prevention and treatment of COVID-19 has been widely discussed since the start of the SARS-CoV-2 pandemic, when initial descriptions of patients admitted to hospital with COVID-19 from China showed a lower prevalence of chronic respiratory disease than that in the general population.[1] The rationale for further investigation of any role of inhaled corticosteroids in offering some protection—either against SARS-CoV-2 infection or against the development of severe COVID-19—has been strengthened following the publication of several in-vitro studies[2,3] and the results of the RECOVERY trial, showing that oral or intravenous administration of the corticosteroid dexamethasone significantly reduces 28-day mortality among patients admitted to hospital with COVID-19 receiving invasive mechanical ventilation or oxygen.[4] However, uncertainty still remains about the role of inhaled corticosteroids in SARS-CoV-2 pathogenesis and prognosis.

The findings presented by Chloe Bloom and colleagues[5] in *The Lancet Respiratory Medicine* are therefore a welcome addition to this topic. Using data from the impressive International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) cohort study of patients admitted to hospital with COVID-19 in the UK, they describe outcomes in patients with asthma or chronic pulmonary disease according to whether or not these patients used inhaled corticosteroids in the 2 weeks before their admission to hospital. Compared to patients with no respiratory disease, those with severe asthma or chronic pulmonary disease had increased mortality rates after adjustment for a range of demographic and clinical comorbidities. This finding is in line with various other studies showing that although chronic pulmonary diseases, including chronic obstructive pulmonary disease (COPD), are associated with an increased risk of mortality from COVID-19, the picture seems more complex for asthma, where the increased mortality risk appears to have been confined to people with more severe disease.[6–8] Interestingly, when looking at the risk of death from COVID-19 according to treatment received, Bloom and colleagues found that inhaled corticosteroid use was associated with a reduction in the risk of death from COVID-19 in patients with asthma aged 50 years or older compared to patients with no respiratory disease. However, this finding was not consistently observed in other groups receiving inhaled corticosteroids; no apparent mortality benefit was seen among younger patients with asthma or patients with chronic pulmonary disease. If inhaled corticosteroids do have a protective effect, it would be important to understand why this effect is not observed in all patients receiving inhaled corticosteroids, and we should remain cautious in our interpretation of the encouraging association seen in older patients with asthma.

At first glance, the findings by Bloom and colleagues would appear to contrast with our own research, using the OpenSAFELY platform,[9] on the relationship between inhaled corticosteroid use and COVID-19. We reported an increased risk of death from COVID-19 among people with asthma prescribed high-dose inhaled corticosteroids compared to those prescribed SABAs only, as well as an increased mortality risk among people with COPD prescribed inhaled corticosteroid combination therapy compared to those prescribed a LABA and LAMA. Although various sensitivity analyses indicated that this increased mortality risk could be explained by unmeasured confounding, our data nonetheless provided little support for the hypothesis that people using inhaled corticosteroids regularly have experienced strong protection from the risk of death from COVID-19 during the ongoing pandemic. However, it is important to emphasise that although these two studies might appear to be conflicting, they report different answers to separate—and in our opinion complementary—questions.

It has recently been proposed that observational studies should be designed with reference to the target trial—the ideal randomised controlled trial that would be done in that setting given unlimited resources and time.[10] Specifying such a trial can not only help researchers design better studies, it also has the benefit of clarifying the causal question under investigation. The target trial underlying the study we did in OpenSAFELY would be a trial randomly assigning patients with asthma and COPD to switch from

one type of maintenance therapy to another, in order to quantify the potential benefit (or harm) associated with remaining on inhaled corticosteroid maintenance therapy during the pandemic. By contrast, the study by Bloom and colleagues would correspond to a very different trial in which patients admitted to hospital with COVID-19 are randomly assigned to receive inhaled corticosteroids on admission. These are both questions of clinical importance, but notably with potentially different answers.

Conclusive answers to either study question are likely to come not from observational studies, but from randomised controlled trials, given the number of largely unquantifiable biases that pharmacoepidemiological studies are often subject to. Luckily, several randomised controlled trials are underway to address the role of inhaled steroids in treating COVID-19 once patients have become infected with SARS-CoV-2 (NCT04355637, NCT04331470, NCT04377711, NCT04330586, and NCT04416399); however, we are not aware of any trials assessing the impact of changes to maintenance therapies for patients with asthma or COPD on COVID-19 outcomes. Until evidence from randomised controlled trials addressing both of these questions emerges, the available observational evidence should be interpreted with caution, and with a clear emphasis on the research question in each given study.

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SARS-CoV-2 reinfection in a closed setting: lessons for the community

In a study published in *The Lancet Respiratory Medicine*, Andrew Letizia and colleagues[1] analysed the subsequent infection risk for SARS-CoV-2 in healthy young adults with and without previous antispike IgG antibodies. They followed Marine recruits for 6 weeks after a 2-week supervised quarantine period. Serology and PCR tests for SARS-CoV-2 were performed upon arrival to supervised quarantine, and PCR was repeated on weeks 1 and 2 of quarantine, and then every other week (weeks 2, 4, and 6) thereafter.

A positive PCR test after quarantine in this setting most likely represents a new viral infection. However, a positive PCR test from nasopharyngeal swabs merely reflects the detection of RNA fragments that might be related to a new viral infection, viral persistence with reappearance of virus in mucosae, or non-viable viral debris. Recurrent infections have already been reported for patients with previous infections of a different coronavirus[2] and have been convincingly demonstrated for SARS-CoV-2.[3] In addition, new positive PCR tests might reflect persistence of viral replication from reservoir tissues, as has been described for coronaviruses and other RNA viruses such as Zika or Ebola.[4] Waning immunity can be the reason for reinfection, viral persistence, or reactivation but seems unlikely in the context of young healthy individuals.

In the absence of viral sequencing with phylogenetic analyses, viral cultures, or information regarding

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