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.

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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different SARS-CoV-2 variants, a positive PCR test cannot be assumed to represent new viral infections in all settings. Strict scientific criteria for the definition of reinfection might have contributed to an underestimation of the real rate of reinfection. A pragmatic approach for a clinical classification of subsequent PCR-positive cases as reinfection, relapse, or PCR re-positivity has been proposed.[5]

This study[1] was conducted in a closed setting but provides some interesting insights regarding the risk of subsequent SARS-CoV-2 infection in the general population or other settings. First, the rate of new SARS-CoV-2 PCR positive results is about 80% lower among seropositive individuals (incidence rate ratio 0·18 [95% CI 0·11–0·28]; p<0·001). These data confirm that seropositive individuals have an important, albeit limited, protection for new infections. The degree of protection is somewhat lower than that described for health-care workers (adjusted incidence rate ratio [RR] 0·11 [0·03–0·44])[6] but similar to that of the general population (adjusted RR 0·195 [0·155–0·246]).[7] The degree of protection reduces with advancing age.[7] The high risk of recurrence among recruits might be related to close contact in platoons or rooms, or to the programmed screening in asymptomatic individuals.[8] Second, the rate of new SARS-CoV-2 PCR detection among seropositive Marines cases is not negligible (1·1 cases per person-year), even in this young and healthy population. Overall, these results indicate that COVID-19 does not provide an almost universal and long-lasting protective immunity, unlike that seen in measles, for example.

Letizia and colleagues[1] show that recurrent SARS-CoV-2 infection is inversely related to the titre of antispike IgG antibodies. In addition, neutralising antibodies were lower among subsequently PCR-positive participants than in negative participants. It has been shown that the severity of the clinical presentation is associated with a higher titre of neutralising antibodies. As the authors acknowledge, they do not provide information regarding SARS-CoV-2 infection before the supervised quarantine.[1] Given the heterogeneity of the immunological response after SARS-CoV-2 infection, seropositivity cannot guarantee effective SARS-CoV-2 neutralisation activity or protection against subsequent infection. The level of antibody titre needed to confer protection is at present unknown. Moreover, immunity induced against previous SARS-CoV-2 infection might confer a limited protection against new variants of concern.

Of note, most cases with a new or subsequent SARS-CoV-2 positive test were asymptomatic or oligosymptomatic and thus were detected by repeated PCR tests rather than because of new symptoms.[1] Since there is a high percentage of asymptomatic infection among young adults, they might be an important source of transmission in the community. Reports suggest that vaccine-induced immune response might be higher than that elicited by SARS-CoV-2 infection,[9,10] suggesting that vaccination might be more effective in preventing new infections.

Efforts must be made to reduce the risk of SARS-CoV-2 transmission from young oligosymptomatic individuals. Results from Letizia and colleagues[1] suggest that even young individuals with a previous SARS-CoV-2 infection should be vaccinated to target a recognised source of transmission. However, the most adequate vaccination schedule following SARS-CoV-2 infection remains unknown. Reports have described robust responses to a single dose of an mRNA vaccine among patients with previous SARS-CoV-2 infection that exceeds that of the full 2-dose vaccination among SARS-CoV-2-naive individuals.[9,10] In times of worldwide vaccine shortage, a single-dose vaccination among SARS-CoV-2 seropositive individuals is worth considering.

In summary, well conducted studies from closed settings, such as the study from Letizia and colleagues, offer useful information for the general population. Despite a wealth of information regarding SARS-CoV-2 infection, important questions remain unanswered: the frequency and clinical relevance of reinfection and its associated risk of transmission, the impact of reinfection on the immune response, and the most adequate vaccination options that might help to control the COVID-19 pandemic.

We declare no competing interests.

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Combination CFTR modulator therapy in children and adults with cystic fibrosis

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For most of the 83 years since its pathological description, treatment of cystic fibrosis has focused on ameliorating its associated signs and symptoms. Following approval of the first cystic fibrosis transmembrane conductance regulator (CFTR) modulator in 2012,[1] treatment could target the basic defect in people with cystic fibrosis in whom CFTR protein dysfunction is amenable to such therapy. As the availability of therapies in this drug class has expanded to more and younger people with cystic fibrosis over the past decade,[2] some questions remain. As these drugs might be needed throughout the lifespan of patients, do new safety issues arise with long-term use? Do these drugs show efficacy beyond the phase 3 trials? Can initiation early in life prevent or mitigate complications of cystic fibrosis? In patients with established complications, can we modify the course of the disease? To begin to answer these questions, studies published in *The Lancet Respiratory Medicine* by Jordana E Hoppe and colleagues,[3] Mark A Chilvers and colleagues,[4] and Patrick A Flume and colleagues[5] evaluated the safety and efficacy of combination CFTR modulator therapy (either lumacaftor–ivacaftor or tezacaftor–ivacaftor) administered for up to 120 weeks in children aged 2–5 years and 6–11 years, and in older children (aged ≥12 years) and adults.

The primary endpoint of all three studies was safety, and no new safety signals were identified in any study. However, it is important to consider the incidence of aminotransferase abnormalities that led to treatment discontinuations in two (4%) of 57 children aged 2–5 years in the study by Hoppe and colleagues,[3] four (2%) of 239 children aged 6–11 years in the study by Chilvers and colleagues,[4] and four (<1%) of 1052 older children and adults in the study by Flume and colleagues.[5] Although only approximately 3% of people with cystic fibrosis develop advanced liver disease with biliary fibrosis and cirrhosis, mild-to-moderate liver disease is common in cystic fibrosis.[6] Indeed, Woodruff and colleagues[7] reported that, in children (n=298) followed longitudinally after diagnosis of cystic fibrosis by neonatal screening, at least one abnormal aminotransferase result was observed by the age of 21 years in up to 93% of individuals with cystic fibrosis. Furthermore, a retrospective review of participants' aminotransferase concentrations in three separate randomised trials of non-CFTR modulators found that 93 (25%) of 376 patients had at least one occurrence of aminotransferase elevation.[8] In the open-label studies[3–5] reported in *The Lancet Respiratory Medicine*, the cases of elevated aminotransferases were identified due to increased screening beyond the annual evaluation typically recommended for people with cystic fibrosis. Therefore, changes in aminotransferases cannot be definitively attributed to treatment with the study drug without further investigation. Clearly, aminotransferase concentrations should be monitored over time, particularly in children taking CFTR modulator therapies for decades, as the search for a cure continues.

In contrast to the infrequent occurrence of severe liver disease, pancreatic insufficiency with a requisite need for enzyme replacement therapy occurs in more than 80% of people with cystic fibrosis.[6] Importantly,