VACCINEINSIGHTS

COVID-19: HOW IS THE PANDEMIC CHANGING THE VACCINES SPACE?

SPOTLIGHT

COMMENTARY

Should we vaccinate against long-COVID?

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The primary goal of current COVID-19 vaccination programs is preventing hospitalizations and deaths from acute disease. However, an important additional role for vaccination could be in preventing or treating post-acute COVID-19 syndrome, known as long-COVID. Here, we outline the burden of long-COVID, discuss the limited evidence currently available on the impact of vaccination on the syndrome, and propose next steps to further our understanding of this important issue.

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According to the European Centre for Disease Control and Prevention, the most cited goal of COVID-19 vaccinations has been the prevention of hospitalizations and deaths due to COVID-19, but depending on the levels and type of protective immunity achieved, vaccination could also potentially prevent SARS-2 coronavirus (SARS-CoV-2) infection and interrupt disease transmission [1]. In addition, a more nuanced, yet vital role for vaccination could be in the prevention of the post-acute COVID-19 syndrome, often referred to as 'long-COVID'.

The case definition of long-COVID is undergoing refinement as we learn more about the natural history of COVID-19 caused by

a series of variants of concern, but it generally refers to the persistence of symptoms beyond the 3–4 week period when it is no longer routine to isolate intact, replication-competent SARS-CoV-2 [2].The World Health Organization (WHO) describes long-COVID in terms of a "post COVID-19 condition" that "occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19 with symptoms that last two months and cannot be explained by an alternative diagnosis" [3]. Some investigators further differentiate persistent symptoms as subacute COVID-19, occurring 4–12 weeks after the acute infection, and those ascribed to a lingering and chronic post-COVID-19 syndrome that extends more than 12 weeks beyond the acute period (and which cannot be linked to an alternative diagnosis). The US Centers for Disease Control and Prevention (CDC) define a post-COVID condition as an "umbrella term" for a range of health conditions that are present four or more weeks post-infection with SARS-CoV-2. Shown in Box 1 is a list of long-COVID-defining conditions from the US CDC. Some investigators prefer to categorize these conditions by systems, including cardiopulmonary sequelae with tachycardia, dyspnea, persistent cough, and an ongoing oxygen requirement; hematological with thrombotic events; renal insufficiency; arthralgias, myalgias and other rheumatologic symptoms; and neuropsychiatric disturbances associated with 'brain fog', fatigue, mood disturbances, and anosmia or dysgeusia [2,4,5], among others. Furthermore, there is the potential role of persistence of virus and/or viral antigens in many of these organs.

BOX 1

Long-COVID-defining conditions from the US CDC.

- Dyspnea or increased respiratory effort
- Fatigue
- Post-exertional malaise and/or poor endurance
- 'Brain fog' or cognitive impairment
- Cough
- Chest pain
- Headache
- Palpitations and/or tachycardia
- Arthralgia
- Myalgia
- Paresthesia
- Abdominal pain
- Diarrhea
- Insomnia and other sleep difficulties
- Fever
- Lightheadedness
- Impaired daily function and mobility
- Generalized pain
- Rash (e.g., urticaria)
- Mood changes
- Anosmia or dysgeusia
- Menstrual cycle irregularities
- Depression

Adapted from [6].

BRAIN FOG

The neurologic complications linked to long-COVID may rank among the most concerning. A UK biobank of more than 40,000 brain scan images collected prior to COVID-19 pandemic made it possible to study almost 400 of those individuals who subsequently tested positive for SARS-CoV-2, together with an almost equal number of matched controls. The findings were striking and included significant gray matter degeneration and a neuroimaging pattern resembling that linked to cognitive declines seen in extreme aging or even Alzheimer's disease [7]. The underlying mechanisms are under investigation, but so far have been attributed to viral neuroinvasion, hypoxia and oxidative stress, or neuroimmunologic phenomena including microglial cell activation, neuronophagia, microglial nodules, and autoantibodies [8,9].

Such dire findings could emphasize the importance of vaccinating individuals to prevent long-COVID, especially to prevent chronic

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neurological complications and deterioration. A comprehensive analysis of data from electronic health records of almost 300,000 COVID-19 patients (mostly in the US), found that a third exhibit at least one feature of long-COVID in a 3–6 month window post-infection (including cognitive declines and anxiety or depression), with the highest risk in those with severe illness [10]. Younger long-COVID patients suffer predominantly from anxiety, depression, and headaches, as well as abdominal symptoms, compared to cognitive symptoms, fatigue, pain, and difficulties in breathing in older patients [10]. Data are mostly lacking for children less than 12 years of age, and there are widely divergent estimates on the health impact of long-COVID in these groups [11].

THERAPEUTIC VS PREVENTATIVE VACCINE

Given the important health and socioeconomic consequences of long-COVID, especially those related to neurologic complications and cognitive declines, there is an urgent need to study the potential benefits of COVID-19 vaccines for long-COVID. Current COVID-19 vaccines have two potential uses in this context.

The first use is as a therapeutic vaccine. This concept is based on anecdotal evidence and a few reported non-peer-reviewed studies from the UK-based longcovidSOS [12], together with hypotheses that long-COVID may in some cases be linked to the persistence of the virus or potentially delayed clearance of virus fragments [13]. In such cases, boosting antivirus immunity through immunization could accelerate patient recovery. Immunizing long-COVID patients with either mRNA or adenovirus-vectored COVID-19 vaccines was shown to be safe, offering slight improvements in terms of symptom resolution [14]. A large French study of a national cohort of patients with long COVID (known as ComPaRe) found that patients vaccinated with one of the available vaccines, including ChAdOx1 nCoV-19 (Astra Zeneca), BNT162b2 mRNA (Pfizer-BioNTech), Ad26.COV2. S (Johnson & Johnson), or mRNA-1273 (Moderna) vaccines, showed improvements relative to those unvaccinated in terms of symptoms and remission rate [13]. However a US-based study reported aberrant T cell memory responses following vaccination in long-COVID patients, suggesting that protection against re-infection in the long term may be impaired [15].

The other use for a vaccine is to prevent infection and, if infected, to prevent progression to long-COVID. In the UK, those fully vaccinated (two doses) with ChAdOx1, BNT162b2, or mRNA-1273 were found to exhibit a 50% reduction in the risk of developing long-COVID [16]. But, there is urgency to conduct additional studies.

NEXT STEPS

The prospect of establishing a therapeutic versus preventive vaccination indication and strategy against long-COVID is potentially attractive, but success on this front will require further clinical studies and information. Strict case-definitions of long-COVID are still lacking, as is epidemiologic information on the groups at highest risk or the extent to which younger groups, including children and adolescents, suffer from this condition. Furthermore, the healthcare community does not have consensus guidelines that can be used to treat long-COVID patients. Clinical guidelines must also be developed as the number of long-COVID patients continues to rise. Also complicating the disease burden assessments of long-COVID is the unknown frequency of this condition following mild versus severe illness. The absence of long-COVID biomarkers is yet another issue and a barrier to sorting out whether long-COVID is the consequence of host inflammatory processes – such as microglial activation in the brain – or whether it reflects active viral persistence.

Without the information outlined above, it is difficult to design the optimal studies

needed to pin down or confirm an impact of vaccination on long-COVID. This is also a barrier to assessing the cost-effectiveness of long-COVID vaccinations. However, consideration of long-COVID may prove to be essential for approving future COVID-19 vaccines, including additional primary series or booster doses [17]. Ultimately, preventing COVID-19 hospitalizations and deaths may not be sufficient if the disease impact of long-COVID turns out to be substantial or results in life-long impairments and disabilities. Assembling a consensus panel or charging immunization technical advisory groups such as the CDC's Advisory Committee on Immunization Practices (ACIP) to make recommendations on this issue may represent a logical first step.

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