INPLASY

Long COVID: A Systematic Review of Preventive Strategies

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 1 March 2025 and was last updated on 1 March 2025.

INTRODUCTION

R**eview question / Objective** We aim to systematically review vaccines, antivirals, or other treatments against Long COVID, using the definition of Long COVID as symptoms persisting for 3 months or longer after SARS-CoV-2 infection.
P: adults aged 18 years or older
I: vaccines, antivirals, COVID-19 convalescent plasma (CCP), or other drugs.
C: vaccinated vs. unvaccinated; antivirals vs. no antivirals; CCP vs. no CCP; drugs (e.g. metformin, corticosteroids) vs. no drugs
O: Prevalence or incidence of Long COVID.

Rationale Long COVID (LC) negatively impacts quality of life, leading to significant health and economic strain on individuals and health care system. Prevention of LC is essential to reduce this toll on individuals and the society. Studies demonstrating the impact of vaccines or antivirals on LC are accumulating, however, systematic reviews synthesizing these outcomes are lacking.

We aim to shed light on interventions for prevention of LC.

Condition being studied A proportion of individuals infected with SARS-CoV-2 may experience persistent somatic symptoms, a condition known as long COVID (LC), also referred to as Post-Acute Sequelae of COVID-19 (PASC), Post-Acute COVID Syndrome (PACS), or Post-COVID Conditions (PCC). The most recognized definition of LC is provided by the World Health Organization (WHO), which describes it as the continuation or development of new symptoms — over 200 different symptoms that can impact everyday functioning — occurring 3 months after the initial SARS-CoV-2 infection, lasting for at least 2 months with no other explanation.

METHODS

Search strategy We searched the PubMed/ MEDLINE database for articles published between December 2019 and September 2024 using the following MeSH terms: "Post-Acute COVID-19

Syndrome (PACS)" AND "prevention and control", "PACS" AND "Vaccines", "PACS" AND "remdesivir", "PACS" AND "nirmatrelvir", and "PACS" AND "molnupiravir".

Participant or population The patients are adults aged 18 years or older between December 2019 and September 2024, meeting the eligibility criteria set by each study's researchers.

Intervention Vaccines, antivirals, or other drugs/treatments before developing Long COVID.

Comparator The comparator for the vaccinated group is unvaccinated group; Comparator for group who received the antivirals is group who did not receive antivirals; the comparator for the group who received other drugs/treatments is group who did not receive other drugs/treatments.

Study designs to be included Randomized trial, prospective cohort, retrospective cohort, and cross-sectional studies.

Eligibility criteria (1) Adults aged 18 years or older, (2) studies that defined as Long COVID (LC) as symptoms lasting 3 months or longer, (3) individuals who were categorized as vaccinated or treated should have received vaccines or treatment before the onset of Long COVID.

Information sources We used the PubMed/MEDLINE database as our main information sources. We contacted authors to clarify information and referred to the references of the relevant articles.

Main outcome(s)
1. Of the fifteen articles, ten studies demonstrated a protective effect of vaccines against development of Long COVID (LC). Among five studies that did not demonstrate a statistically significant protective effect on the development of LC, one study showed a trend toward protection and two reported a reduction in a few LC symptoms due to vaccination.
2. We found equivocal protective effect of antivirals against LC
3. We found no protective effect of COVID-19 convalescent plasma, in contrast, we found protective effect of metformin in outpatients and protective effect of corticosteroids in hospitalized patients against LC.

Additional outcome(s) We also investigated effect of vaccines or antivirals when Long COVID is defined as symptoms lasting 28 days or longer. We found a more robust effect of vaccines or antivirals

against LC, indicating their effect on acute COVID-19 illness as acute symptoms of COVID-19 can last more than 28 days.

Data management Identified articles were exported from PubMed into End note, where duplicate records were removed. Titles and abstracts were independently reviewed by the authors, with conflicts resolved through discussion. Eligible full-text articles were assessed by the authors for eligibility. Data including study design, period, countries, participants, demographics, age, interventions, were extracted and recorded in excel.

Quality assessment / Risk of bias analysis JBI's critical appraisal tools were reviewed. Two reviewers independently assessed quality and risk of bias of the studies.

Strategy of data synthesis We prioritized randomized trials, prospective studies, and studies with a large patient population. We assessed the effect size of each study and determined the number of studies demonstrating a protective effect compared to the ones demonstrating no effect against Long COVID.

Subgroup analysis We investigated/analyzed the study outcomes in outpatient settings vs. hospitalized settings.

Sensitivity analysis We compared our major findings on vaccines or antivirals when Long COVID (LC) was defined as symptoms lasting 3 months or longer to those when LC was defined as symptoms lasting 28 days or longer.

Language restriction We limited our search to articles written in English only.

Country(ies) involved We/authors carried out the study in the USA/University of Southern California.

Other relevant information Our review included studies from 16 diverse countries. While further studies are needed due to insufficient number of studies and conflicting outcomes to draw definitive conclusions, it is possible that the effect size of booster vaccination, when compared to full vaccination, may not be large enough to reach statistical significance in certain patient population.

Keywords Long COVID; Post-Acute Sequelae of COVID-19 (PASC); Post-Acute COVID Syn-drome (PACS); Post-COVID Conditions (PCC); COVID-19; prevention.

Dissemination plans We plan to publish our manuscript in a peer-reviewed journal and share our findings in social media once published.

Contributions of each author
Author 1 - Sun O. Park - S.P. conceptualized & designed the study, performed analyses, and wrote the manuscript.
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