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.

Stewardship of COVID-19 volunteers by nested trial design


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A credit to clinical research volunteers, the global community is blessed with a panoply of pharmaceutical agents to mitigate COVID-19 in this third year of the SARS-CoV-2 pandemic. Multiple vaccines and therapeutic interventions with small molecule antivirals (ritonavir-boosted nirmatrelvir[1] and remdesivir[2]) and macromolecular anti-spike neutralising monoclonal antibodies[3-5] have reached the front lines of the war against COVID-19. The deluge of cutting-edge basic, translational, and clinical knowledge accrued in this unprecedented timespan underpin dynamically updated evidence-based guidelines. Yet, a knowledge paradox emerges from our success: further incremental advances are necessarily slowed and more challenging as event rates have, thankfully, fallen.

The assessment of previous exposure or recovery from SARS-CoV-2, or related members of the *Betacoronavirus* genus (eg, SARS-CoV-1 or Middle East respiratory syndrome coronavirus), was straightforward during the early period of the pandemic, when the population was mostly seronegative. Subsequently, as natural infections surged and vaccination rates increased among our population, community seroprevalence and individual serostatus assessment lost their binary yes versus no simplicity, as both wild-type virus exposure and vaccination result in anti-spike seroconversion, and even anti-nucleocapsid responses can wane after a year, rendering serology imperfect for assessment of lifetime viral exposure. Seroconversion to previous vaccination or virus variant no longer imply the same humoral protection, even as cellular responses to conserved epitopes provide adjunctive benefit. Regulatory agencies and ethics boards are facing the dilemma of whether to allow head-to-head non-inferiority trials using evidence-based comparators when event rates are reduced. Passive immunotherapies are dynamically changing, as the virus has escaped the previous bulwarks of anti-spike neutralising monoclonal antibodies initially authorised for use from late 2020 to early 2022, with the only currently remaining agent in the USA emerging from a pragmatic, partly immune-bootstrapped phase 2 study.[6]

In this context, we are duty-bound to learn as much as possible from clinical trials done in the pivotal early period of the pandemic. Findings from well conducted, completed trials merit publication even if the circulating variants of SARS-CoV-2 are no longer susceptible to the therapy studied. Such is the value of the report in *The Lancet Infectious Diseases* by Gary Herman and colleagues detailing the efficacy of subcutaneous casirivimab and imdevimab (CAS+IMD) for prevention of COVID-19 in patients who had previously been exposed to a SARS-CoV-2-infected household contact.[7] This study was a randomised, double-blind, placebo-controlled trial done in the USA, Romania, and Moldova. 2317 uninfected and unvaccinated household contacts of infected individuals were randomly assigned (1:1) to receive 1200 mg CAS+IMD (600 mg of each) or placebo and were assessed monthly during 8 months of follow-up. 1683 participants (841 assigned to CAS+IMD and 842 assigned to placebo) were seronegative at baseline and were included in the full analysis set. Although the participants were enrolled initially at a time before the emergence of delta (B.1.617.2) and subsequent variants of concern, they were at risk of delta variant exposure during the follow-up period from July to October, 2021.

This randomised trial elegantly addressed a nested set of separate questions in different trial arms based on serostatus, the results of which did not guide initial randomisation and dosing. Utility was maximised with complementary questions posed within the primary efficacy versus follow-up surveillance periods. The original month 1 efficacy data has been published,[8,9] and Herman and colleagues' study expands the work by describing the extended benefit of subcutaneous casirivimab and imdevimab over the course of months 2–8, including the era when the delta variant emerged. The authors found that CAS+IMD reduced the risk of COVID-19 by 81·2% (nominal p<0·0001) versus placebo during the full 8 months, with protection being greatest during months 2–5, with an observed 100% relative risk reduction in COVID-19 and an 89.5% relative risk reduction in any SARS-CoV-2 infection detected by RT-PCR regardless of symptoms (nominal p<0·0001 for both; post-hoc analysis), and efficacy waning during months 6–8 (also in a post-hoc analysis). Seroconversion of anti-nucleocapsid IgG, a proxy for any productive SARS-CoV-2 infection, occurred in 38 (4·5%) of 841 participants in the CAS+IMD group and in 181 (21·5%) of 842 in the placebo group during the 8-month study (79·0% relative risk reduction *vs* placebo; nominal p<0·0001).

This poly-purposed design effectively constructed pre-exposure prophylaxis cohorts nested within the original post-exposure prophylaxis trial. As household infections harbour the greatest risk of transmission in the first month, acquisition of SARS-CoV-2 thereafter is likely related to community spread or new exposures in the household, independent of the original qualifying exposure. This neo-pre-exposure prophylaxis cohort was naive to previous wild-type SARS-CoV-2 (baseline seronegative for anti-SARS-CoV-2 spike S1 IgA and IgG and anti-nucleocapsid IgG, and SARS-CoV-2 RT-PCR-negative).

To steward volunteer's health and welfare and to respect autonomy, vaccination was permitted during the follow-up period, upon availability. To manage the confounding effect of vaccination on biomarker surrogates, Herman and colleagues tracked immunisation status and distinguished seroconversion from natural infection by the presence of anti-nucleocapsid IgG, because anti-spike IgG was acutely rendered uninformative upon spike-sequence-based SARS-CoV-2 vaccination.

The report is a refreshingly clear, detailed yet concise, summary of the efficacy and safety of what is ultimately a mooted therapy at the current juncture of the pandemic. Casirivimab and imdevimab are no longer authorised for use during the omicron (B1.1.529 and BA subvariants) era, yet the findings in Herman and colleagues' study inform expectations of passive humoral therapy safety and efficacy, as a field, and complement the pre-exposure[10] and post-exposure[11] prophylaxis data derived from other neutralising monoclonal agents or combinations. Collectively, these seminal prevention trials serve as proof that passive immunoprophylaxis is highly effective. In our view, they might be particularly useful among immunocompromised populations unable to generate endogenous humoral immunity from vaccination or natural infection.

Most importantly, this study illustrates the ability to maximise the scientific and medical contributions from each participant without increasing risk and is an example of excellent stewardship of human participants' welfare and autonomy.

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Redressing the gender imbalance across the publishing system

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In *The Lancet Infectious Diseases*, Katharina Last and colleagues[1] show that a higher proportion of women editors is associated with a higher proportion of women first and last authors in a sample of 11 027 articles from infectious diseases journals published in 2018 and 2019. The finding that women comprise about 49·3% of first