converse. Moreover, the absence of effective treatments for a disease does not preclude its existence; AIDS did not become a disease only after effective treatments were found, and amyotrophic lateral sclerosis remains a disease without effective treatments.

Nevertheless, the question arises as to whether metformin simply would help anybody (whether they have COVID-19 or not) and if the results of the present trial might have simply reflected reductions of symptoms due to undiagnosed metabolic syndromes found among the trial participants. Indeed, the rate of undiagnosed diabetes in the USA appears to be substantial.[7] However, participants received metformin for just 14 days, during the acute phase of their SARS-CoV-2 infection. It is difficult to imagine that such a short course of metformin would modify the symptoms of chronic undiagnosed metabolic syndromes many months later, when most (though not all) of the trial participants received their long COVID diagnoses.

Furthermore, the mechanism of action by which metformin might reduce the incidence of long COVID remains unclear. Although laboratory findings suggest an antiviral mechanism, it could be that metformin modifies autoimmune cascades triggered by host responses to infection. If metformin reduces long-term sequelae of other infections (especially those in which metformin is not shown to have antiviral activity in vitro or in vivo), a modulation of autoimmune processes would become the more likely explanation.

The key message is simple. When a disease is too poorly defined, it follows that it is almost impossible to modify either the incidence of that disease or the distribution of its outcomes—that is, unless the treatment effect is so great, and the true target population so common in the assembled denominator, that any corresponding signal dilutions are offset. The present study suggests that, even with definitions as amorphous and heterogenous as those currently in use for diagnosing long COVID, there was to be found within this study population an ample cohort of individuals with syndromes similar enough that disease incidence could be modified, and metformin appeared to achieve that. Furthermore, the finding that long COVID is modifiable, although here showing prevention, offers hope that future trials might find treatments that are effective in people with established long COVID. Trials studying the prevention and treatment of long COVID should be a priority.

I declare no competing interests.

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Safety of COVID-19 booster dose: is the juice worth the squeeze?

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In this issue of *The Lancet Infectious Diseases*, Dan Yamin and colleagues' Article[1] used a self-controlled case series design to evaluate the safety of COVID-19 vaccine boosters. The authors compared mRNA monovalent and bivalent boosters (ie, third to fifth doses) of the mRNA monovalent and bivalent (mainly used as a fifth dose) boosters by comparing a 28-day post-booster period (and a sensitivity analysis period up to 42 days post booster) with a 28-day baseline period that ended 7 days before vaccination. The analysis was focused primarily on individuals categorised as being at high risk of susceptibility to severe COVID-19, and was limited to analysis of only those patients hospitalised for 29 medical conditions (collectively termed as non-COVID-19 hospitalisations) that are potential adverse events associated with COVID-19 vaccination.


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Overall, the study found no indication that booster doses of mRNA COVID-19 vaccine were associated with an elevated risk of non-COVID-19 hospitalisation. Nevertheless, following the first booster dose, the rate of hospitalisation of vaccinated individuals increased for thrombocytopenia (absolute excess rate per 100 000 vaccinated individuals 2·6), seizures (2·2), myocarditis (0·7), although the population size under surveillance might have been suboptimal to evaluate for difference in risk for rare potential serious adverse events such as Guillain-Barré syndrome and central venous thrombosis.

The use of a self-controlled case series design has advantages over case-control or large cohort study designs, which would require cases to be matched with appropriate controls or the measurement of confounding factors.[2] Additionally, the self-controlled case series design accounts for non-time varying confounders (eg, genetic related conditions, socioeconomic status, or other non-time varying confounders including being an at-risk individual), which are immeasurable or have yet to be considered.

Yamin and colleagues excluded events of interest that culminated in deaths, premised on deceased people who had not been boosted being ineligible for the analysis, and a sensitivity analysis that includes such deaths should be done. The limitations of the study include the assumption that the decision to receive a booster dose was independent of the occurrence of an adverse event. This view might not hold true if previous adverse events related to COVID-19 vaccination deter an individual from receiving subsequent vaccinations; how this factor could affect the findings should be considered. Other essentials of a self-controlled case series design include accurate ascertainment of exposure, ascertainment of case, and date of onset of event. The case ascertainment might vary depending on the clinician and be subject to additional bias if the clinician is aware of a patient's vaccination history. Also, the focus on only reporting on hospitalised cases of the events under consideration, and the issue of the population size under surveillance not being powered to identify risk differences for event rates lower than 1 per 10 000, warrants caution when interpreting the full risk–benefit ratio of booster doses of COVID-19 vaccines. Notably, a second dose of BNT162b2 was reported to have prevented an estimated 89 COVID-19 hospitalisations per 100 000 population in Israel among individuals older than 60 years of age, when the B.1.1.529 (Omicron) variant of concern was dominant.[3]

WHO's Scientific Advisory Group of Experts on Immunization recommended on March 24, 2023, that additional booster doses of COVID-19 vaccine should be given 6–12 months after the most recent dose only to high-priority groups (defined similarly to the Israeli definition used in the study) during 2023.[4] The risk–benefit ratio of booster doses needs to be contextualised against the persistent dominance of the highly transmissible and relatively neutralising antibody-evasive omicron sublineages that have dominated globally since the evolution of the BA.1 variant of concern in November, 2021.[5,6] The global dissemination of omicron has been associated with widespread infection-induced immunity, including serological evidence of infection in 63·9% of individuals infected or reinfected during the initial BA.1-dominant wave in South Africa.[7] A systematic review and meta-analysis done by WHO's Serotracker Team reported that, by April 2022, the proportion of the population who were sero-positive was 89·8% globally, and as of June 2022, seropositivity (inclusive of vaccine-induced immunity) was 96·1% in Europe, 100% in the Americas and 99·0% in the Western Pacific.[8] The combination of infection-induced and vaccine-induced immunity, referred to as hybrid immunity, reportedly provides 97·4% (95% CI 91·4–99·2) protection against COVID-19 hospital admission or severe disease caused by omicron and its sublineages, up to 12 months after the primary series of vaccine alone. This protection is higher than that from previous infection or vaccination alone. Similarly, protection from hybrid immunity against omicron-related COVID-19 hospital admission or severe disease is projected to be 95·3% (95% CI 81·9–98·9) for up to at least 6 months after the first booster vaccine that follows the most recent SARS-CoV-2 infection or preceding vaccine dose.[9] Consequently, the added value of a booster dose warrants interrogation, including in the context of vaccinated high-risk groups who could remain susceptible to severe COVID-19. The risk–benefit ratio was factored into the WHO recommendation not to advocate for further booster doses during 2023 in individuals outside of the high-priority group.[4]

In summary, Yamin and colleagues' study showed no increase in the risk of adverse events after additional

booster doses of COVID-19 vaccine. Nevertheless, the absence of data on non-hospitalised adverse events that could be associated with severe additional morbidity, and the limited power of the study to identify events occurring in fewer than 1 in 10 000 people, warrant consideration when making decisions about recommendations for booster doses of COVID-19 vaccines. Such consideration is especially important in the context of the entrenched dominance of omicron sublineages, which have reduced rates of hospitalisation and infection fatality risk (0·03%),[7] and widespread hybrid immunity with lasting protection against severe disease.

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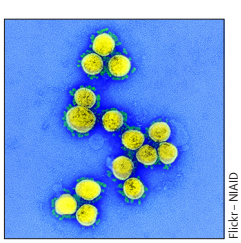
Exploring the potential benefits of mucosal COVID-19 vaccines: opportunities and challenges

Vaccination remains the primary preventative strategy against COVID-19. Currently, all available vaccines are administered through injection, and there is concern regarding diminishing protection.[1,2] Intranasal, oral, or inhaled vaccines present an alternative immunological approach, stimulating a localised mucosal immune response within the respiratory tract. It is postulated that these mucosal COVID-19 vaccines could offer more sustained and potent protection against SARS-CoV-2 infection.[3] Furthermore, the induced mucosal immune response might potentially curtail virus transmission from infected individuals.[3] Administration of mucosal vaccines is uncomplicated, negating the necessity for health-care professionals and needles and streamlining the immunisation process.

In *The Lancet Infectious Diseases*, Li and colleagues[4] reported the results of an open-label trial to assess the safety and immunogenicity of a heterologous booster regimen using aerosolised Ad5-nCoV. A cohort of 10 059 participants who received the aerosolised Ad5-nCoV booster were included in the safety analysis, with 416 participants included in the immunogenicity analysis. Within 28 days after vaccination, 1299 (13%) patients reported adverse reactions, predominantly mild to moderate in nature. Participants who received aerosolised Ad5-nCoV had significantly elevated levels of neutralising antibodies against the omicron BA.4/5 variant on day 28 compared with those receiving an inactivated vaccine (107·7 [95% CI 88·8–130·7] versus 17·2 [16·3–18·2]).

The approved mucosal adenovirus vector vaccines by national agencies in China and India for high-risk groups signifies substantial progress. However, challenges persist, including the necessity to amend these vaccines to counter emerging variants, like omicron.[5,6] Aerosolised Ad5-nCoV had a modest relative protection of 35·1% (95% CI 23·0–45·2) against COVID-19, compared with the inactivated COVID-19 vaccine, roughly 12 months after the booster during the omicron period.[4]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