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.

of the Immunization Agenda 2030[3] is broader: a world where everyone benefits from vaccines at every age.

Immunisation during pregnancy protects both women and newborn babies against several infectious diseases,[4] including tetanus, pertussis, and influenza.[5] Robust maternal immunisation programmes also serve as key platforms for introducing new and future vaccines (eg, COVID-19, respiratory syncytial virus, and group B *Streptococcus*).[5] Yet differences in access to and inequities in these programmes long predate the COVID-19 pandemic. Formal maternal immunisation policies and guidelines, which "underpin the quality and scope of health services",[4] have been fairly limited among lower income countries for some vaccines (eg, pertussis[5] and influenza[6]), and there are serious data challenges for comprehensively monitoring vaccination across the life course. Aside from maternal tetanus immunisation, multi-country health surveys rarely collect information on the vaccines received beyond childhood, and global syntheses of reported administrative data often do not have detailed coverage estimates for older age groups. As underscored by Saso and colleagues, the absence of timely, granular data poses large obstacles to understanding acute and long-term gaps in immunisation services beyond childhood vaccination.

Improving vaccination across the life course, from infancy to old age, is a strategic priority of the Immunization Agenda 2030.[3] Increasing the reach of maternal immunisation services contributes to these aims, and formally including more vaccines—namely, pertussis, influenza, and now COVID-19, among others—through such programmes will benefit many. However, fully implementing a life course approach will require expanding vaccine policy and administration in most countries. For instance, universal influenza and diptheria, tetanus, and pertussis booster vaccinations could additionally protect individuals not reached through maternal immunisation or routine childhood programmes (eg, men and older adults).[3] In parallel, data systems that effectively track vaccination status and needs over the lifespan are necessary for monitoring progress and promoting equitable access.

The COVID-19 pandemic has substantially affected immunisation services for all populations. The global roll-out of COVID-19 vaccines, which includes age groups often missed by traditional immunisation platforms, offers an opportunity to rethink how, and to whom, vaccines are delivered. Leveraging the lessons learned and successful strategies used during the pandemic could not only augment child and maternal immunisation services but also pave the way for a future in which "everyone, everywhere, at every age fully benefits from vaccines for good health and well-being".[3]

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High-dose budesonide for early COVID-19

The importance of effective community-based treatments for COVID-19 cannot be overstated. We applaud Ly-Mee Yu and colleagues[1] for addressing this issue in the PRINCIPLE trial and would like to share some comments.

The study included participants onset of COVID-19 within 14 days; however, those closer to 14 days since illness onset might be approaching spontaneous resolution, which could confound effectiveness and expose patients to unnecessary inhaled corticosteroids. We are concerned that the subjective self-reporting of obesity might be biased and wonder if any criteria were placed for participants to classify themselves as obese. Likewise, symptom severity was self-reported from no problem to major problem.[1] Was this subjective scale controlled for, particularly in quantifiable variables like fever.

It is important to understand the illness severity of the study population, such as how many participants were symptomatic versus asymptomatic at enrolment, how many were compliant with treatment versus non-adherent, and if there were any outcome differences among them. We are curious if time from enrolment to treatment initiation differed among participants. The Article's Table 1 includes 833 participants from the inhaled budesonide group and 1126 participants from the usual care group, respectively, which does not coincide with the 787 and 1069 included for primary analysis.[1]

Finally, the study faced limitations such as the predominantly white population (92%), which does not represent the high-risk community,

the small number of participants with chronic lung conditions due to exclusion of those taking corticosteroids, and the self-reported nature of symptoms, which could be inaccurately assessed and biased by multiple factors.

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We were encouraged by the results of the PRINCIPLE trial,[1] which in vulnerable individuals showed inhaled budesonide to confer a non-significant –25% (95% CI –45 to 3) relative reduction in the composite coprimary endpoint of hospital admission or death, with the number needed to treat being 50.[1] Notably, the study had 90% power to detect a 50% reduction in the composite endpoint. The investigators appear to have attributed any protective effects of budesonide to its local glucocorticoid activity in the lung.

We were, however, surprised that no mention was made regarding the possibility for appreciable systemic bioavailability of inhaled corticosteroid from the lungs, especially given the high 1600 µg dose of budesonide. For example, in one study of mild asthma patients with a mean forced expiratory volume in 1 s of 86% predicted, treatment for 1 week with 1600 µg budesonide via the same dry powder inhaler device produced –44% (95% CI –47·5 to –40·0) suppression of 24 h serum cortisol relative to placebo.[2] As such, we would welcome comment with regards to the other coprimary endpoint of time to first reported recovery, in particular whether the observed median difference of –2·94 days might be explained by patients feeling better due to a systemic glucocorticoid effect per se rather than a local effect.

Observational health informatics data found that previous use of conventional doses of intranasal corticosteroid were associated with a 22% (95% CI 15–28) reduced risk of hospital admission, a 23% (8–35) reduced need for intensive care, and a 24% (6–39) lower risk of death in hospital for patients with COVID-19.[3] Moreover, these protective effects were replicated when excluding patients with allergic rhinitis and the use of inhaled corticosteroid.

In the meantime, we believe further randomised controlled trials are warranted to investigate whether the use of lower doses of either inhaled budesonide (400 µg) or intranasal budesonide (200 µg), which are devoid of meaningful systemic effects,[2,4] might ameliorate recovery and attenuate disease progression in ambulatory patients with early COVID-19.

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Authors' reply


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We thank Ivan Berezowski and colleagues for highlighting the importance of the PRINCIPLE trial finding a safe, effective, and inexpensive community repurposed medication that shortens COVID-19 illness and reduces the need for hospitalisation and use of oxygen.[1] Most participants (85%) had up to 10 days' illness duration (63% fewer than 7 days in the concurrent population). Inclusion of those almost recovered would reduce rather than increase the chance of showing an effect. In addition, if people without obesity incorrectly reported as people with obesity (32% self-reported a body-mass index >35, but only 27·4% of those were eligible on this criterion alone), this would also probably bias the results towards the null because obesity can be associated with worse outcomes. For patient-reported recovery, asking participants how they feel is appropriate.[2] Indeed, we have reported three treatments not benefiting patient recovery,[3–5] with one tending to worsen[3] patient recovery. Furthermore, several well validated patient-reported outcomes were also used, including the WHO-5 Wellbeing Scale, with differences favouring inhaled budesonide statistically significant at days 7, 14, and 28. Other measures of recovery were modifications of scales used in several large-scale clinical trials shown to be highly responsive to change. All measures showed benefit—while people were recovering, they felt less ill; once recovered they stayed well more often (10% absolute difference, nearly 50% relative difference in sustained recovery over 28 days); and they used fewer health-care resources.