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.

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Commentary

Questioning the justification for a fourth SARS-CoV-2 vaccine

Ronit Calderon-Margalit [1], Jacob Strahilevitz [2, 3, *], Ora Paltiel [1, 4]

[1] Braun School of Public Health, Hadassah Medical Center, Faculty of Medicine, Hebrew University, Jerusalem, Israel
[2] Department of Clinical Microbiology and Infectious Diseases, Hadassah Hebrew University Medical Center, Jerusalem, Israel
[3] Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel
[4] Department of Hematology, Hadassah Medical Center, Jerusalem, Israel

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Considerable uncertainty exists worldwide as to the appropriate vaccination strategy in the face of repeated waves of SARS-CoV-2 caused by new variants. As of December 31, 2021, 65% of Israel's population aged ≥5 years had been fully vaccinated against SARS-CoV-2 (defined as <6 months since second dose or recovery from COVID-19, or having received a third dose). Of the 1.5 million Israelis aged ≥60 years, 1.3 million (86.8%) were fully vaccinated, 94 008 (6.2%) were partially vaccinated, and 104 712 (7.0%) were unvaccinated.

Israel was the first country to authorize a third, booster, dose of the BNT162b2 vaccine in July 2021, when faced with a resurgence of COVID-19 caused mainly by the Delta variant. This campaign was successful, resulting in estimated decreases of 91.1% and 94.8% for confirmed and severe cases, respectively [1]. Since the booster campaign, daily rates of severe COVID-19 have remained highest among the unvaccinated and lowest among the fully vaccinated who received the booster dose, with ratios of over 10:1 in the group ≥60 years of age.

Starting in early December 2021, there was a gradual increase in confirmed COVID-19 cases in Israel, with an unprecedented steep rise in January 2022, associated with social disruptions, hospital admissions, and a shortage of healthcare personnel, similar to that observed in other countries afflicted by the SARS-CoV-2 Omicron variant of concern.

In anticipation of the Omicron surge, on December 21, 2021, Israel's Outbreak Control Team recommended a fourth dose for all healthcare workers, individuals with immunodeficiencies, and all adults aged ≥60 years. The major argument for this decision was that the expected benefit of reduced transmission and disease from a booster dose would outweigh potential risks. This recommendation was adopted by the director-general of the Ministry of Health in a rapid, stepwise fashion first for immunosuppressed individuals (on December 31, 2021) and then for all healthcare workers and individuals ≥60 years of age (January 2, 2022). On January 26, the Ministry of Health expanded the indications for a fourth dose to include individuals at high risk and their immediate family or caretakers.

There is a debate regarding whether this fourth dose is justified in the general population and whether it would mitigate the effects of the Omicron surge. In view of the reduced effectiveness of the BNT162b2 vaccines in preventing transmission of the Omicron variant [2,3], the only realistic aim of the current campaign would appear to be prevention of severe COVID-19–related disease, hospitalizations, and deaths. Attendant costs and potential harms of re-boosting have not been addressed.

Given the uncertainty regarding both protection and harms associated with a fourth dose, we conducted a simple assessment of the number needed to treat (NNT) to prevent one severe case of COVID-19 among those aged ≥60 years of age (Table 1). We tested varying scenarios, assuming a high cumulative infection rate of 15% and changing assumptions regarding vaccine efficacy (including preserved and reduced effectiveness, lower even than that described in the United Kingdom [3]) and risk of severe infection [4]. The NNT, computed as 1 divided by the absolute risk reduction, was calculated for (a) fully vaccinating the unvaccinated population and (b) administering a fourth vaccine for those who had already received a third

* Corresponding author: Jacob Strahilevitz, Department of Clinical Microbiology and Infectious Diseases, Hadassah-Hebrew University Medical Center, Ein Kerem, Jerusalem 91120, Israel.
E-mail address: jstrahilevitz@hadassah.org.il (J. Strahilevitz).

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Table 1
Estimated NNT to prevent one severe case of SARS-CoV-2 infection among individuals aged ≥60 years and corresponding estimates of associated adverse events under various assumptions

Scenario	Vaccinating the unvaccinated				Adding a fourth dose to those who have received a third dose		
	Assumptions regarding incidence of severe disease in people aged ≥60 y	Assumptions regarding vaccine efficacy	NNT	Estimated systemic adverse events[a] per one case averted	Assumed effectiveness of fourth dose in preventing severe disease	NNT	Estimated systemic adverse events[b] per one case averted
High incidence, high virulence, maximum effectiveness	Cumulative incidence: 10% Risk of severe cases: 6.4%	94.8%	109	**Total nonlocal: 0.09** Systemic: 0.07 Neurological: 0.005 Allergic: 0.003 Other significant: 0.007 Serious adverse events: 0.002	Further 5% reduction in risk of severe disease beyond that achieved by a third dose	40 828	**Total nonlocal: 14.2** Systemic: 11.9 Neurological: 0.53 Allergic: 0.20 Other significant: 0.78 Serious adverse events: 0.78
High incidence, high virulence, high effectiveness (similar to the UK estimates [3])	Cumulative incidence: 10% Risk of severe cases: 6.4%	89%	196	**Total nonlocal: 0.16** Systemic: 0.13 Neurological: 0.007 Allergic: 0.005 Other significant: 0.01 Serious adverse events: 0.004	94.5%	2937	**Total nonlocal: 1.02** Systemic: 0.86 Neurological: 0.04 Allergic: 0.01 Other significant: 0.06 Serious adverse events: 0.0**6**
High incidence, reduced virulence, high effectiveness [3]	Cumulative incidence: 10% Risk of severe cases: 3.84%	89%	118	**Total nonlocal: 0.09** Systemic: 0.08 Neurological: 0.007 Allergic: 0.003 Other significant: 0.0 Serious adverse events: 0.002	94.5%	1783	**Total nonlocal: 0.62** Systemic: 0.52 Neurological: 0.02 Allergic: 0.009 Other significant: 0.03 Serious adverse events: 0.03
High incidence, reduced virulence, reduced effectiveness	Cumulative incidence:10% Risk of severe cases: 3.84%	80%	218	**Total nonlocal: 0.17** Systemic: 0.14 Neurological: 0.007 Allergic: 0.006 Other significant: 0.01 Serious adverse events: 0.004	94.5%	1163	**Total nonlocal: 0.40** Systemic: 0.34 Neurological: 0.02 Allergic: 0.006 Other significant: 0.02 Serious adverse events: 0.02

[a] Based on rates reported in the population age ≥60 years for the second dose [7].
[b] Based on rates reported in the population age ≥60 years for the third dose in vaccinated and unvaccinated people between December 21, 2021 and January 15, 2022 [7].

dose (assuming reaching maximal 94.5% effectiveness). For each averted severe COVID-19 case, we estimated the numbers of people expected to develop nonlocal adverse reactions, based on passively reported rates published by the Israeli Ministry of Health [5].

In all scenarios, at least 1000 recipients of a third dose aged ≥60 years would need to receive a fourth dose to prevent one severe case of COVID-19. In all scenarios, vaccinating the unvaccinated is 5 to 370 times more effective in preventing a severe case compared with adding a fourth dose. Even for the lowest NNT estimation, 1163 people would need to receive a fourth dose to prevent one severe case. This means that in a population with 1.3 million people aged ≥60 years, 1118 severe cases would be averted if all were vaccinated. Although the reported rates of adverse events are low, these 1118 averted cases would be associated with 30 serious adverse events. In fact, in all scenarios tested, rates of expected adverse events associated with averting a single severe case in the unvaccinated are a fraction of those foreseen in third-dose recipients. It should be noted that our last assumption of a change in vaccine effectiveness from 80% for third-dose recipients to 94.5% among fourth dose recipients is in accordance with the findings of a very recent analysis from Israel showing a relative risk of 0.25 for a fourth versus third dose in preventing severe disease [6]. Notably, since the option of receiving the fourth dose became available, over 700 000 Israelis have received this dose; however, only 132 000 new individuals have received a first and second dose, most of them children [7].

Although the BNT162b2 vaccine is generally safe, in a scenario of limited added benefit of vaccinating the already vaccinated, additional considerations of both harms and cost are essential. These include the costs of the vaccines themselves, the cost of mounting the vaccination campaign, and the opportunity costs of not focusing efforts on increasing vaccination rates, even marginally, among the unvaccinated, challenging as these efforts would be. Prioritizing mass vaccination with a fourth dose would limit efforts and resources for other accepted measures to avert transmission, such as a campaign to boost the use of masks and investing in ventilation in schools.

Many questions remain regarding frequency of boosting, dosing schedules, and the need for variant-specific boosters [8]. Although a third dose, administered several months following the initial vaccination, has proven its worth in “real world” settings [1] (similar to other well-established vaccination schedules), the assumption that a fourth dose would have similar efficacy has yet to be supported. Theoretical arguments have been made for and against a continuous booster strategy—none, so far, supported by published data [9]. There is some evidence that three vaccine doses are adequate for T-cell responses and adaptation of memory B cells to the Omicron variant [2,10]. However, many professional societies (e.g. ASH (American Society of Hematology), ASTCT (American Society for Transplantation and Cellular Therapy), and the CDC) in the United States have recommended a fourth dose for moderate to highly immunocompromised individuals. Denmark has approved this approach for the ‘highly vulnerable’, although other European countries have not followed suit.

Given the current level of knowledge, we question whether more is necessarily better and whether other countries should follow Israel's lead. Other remedies quickly taken up under the cloud of COVID-19 uncertainty were eventually abandoned due to

lack of efficacy and evidence of harm [10]. Given the impressive protection of the third dose against severe disease and the lower reported risk of adverse COVID-19 outcomes with the Omicron variant [3,11], it behooves the scientific community to initiate proper research, including active surveillance of adverse reactions, before making mass recommendations for a fourth dose, which may yet prove beneficial. We must direct public health efforts toward the groups at highest risk for severe disease, namely the unvaccinated, to preserve both public trust and public resources.

Transparency declaration

Nothing to disclose.

Author contributions

All authors contributed to the conceptualization, writing, and revision of this paper.

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