SHORT COMMUNICATION

Third dose of SARS-CoV-2 vaccine: A systematic review of 30 published studies

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Abstract
We analyzed published studies on the efficacy and safety of the third dose of the COVID-19 vaccine in various general population settings. We conducted systematic searches of PubMed and EMBASE for series published in the English language through November 15, 2021, using the search terms "third" or "booster" or "three" and "dose" and "COVID-19" or "SARS-CoV-2." All articles were selected according to the MOOSE guidelines. The seroconversion risk after third doses was descriptively expressed as a pooled rate ratio ([seroconversion rate after the third dose]/[seroconversion rate after the second dose]). The search returned 30 studies that included a total of 2,734,437 vaccinated subjects. In more than 2,700,000 Israeli patients extracted from the general population, the reduction in the risk of infection ranged from 88% to 92%. Conversion rates for IgG anti-spike ranged from 95% to 100%. In cancer or immunocompromised patients, mean IgG seroconversion was 39.4% before and 66.6% after third doses. A third dose seems necessary to protect against all COVID-19 infection, severe disease, and death risk.

KEYWORDS
booster, COVID-19, third dose, vaccination

1 | INTRODUCTION

The fourth wave of the COVID-19 pandemic is ongoing around the world. Despite new approved antiviral drugs and established supportive therapies, the role of vaccination remains crucial, particularly for at-risk populations. In particular, cancer patients, elderly or frail subjects, and other immunocompromised people (e.g., organ transplant patients on immunosuppressive agents) may still be at risk despite full-dose vaccination.1,2 A study published in the New England Journal of Medicine, based on data from the Israeli Ministry of Health, shows that cases of infection and serious illness dropped "substantially" after a third booster dose of the Pfizer vaccine was administered to more than 3 million subjects in the general population.2 We analyzed published reports about the efficacy and safety of the third dose of the COVID-19 vaccine in various settings in 2021.

2 | MATERIAL AND METHODS

This review was performed following Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.

We conducted a systematic search in PubMed and EMBASE for series published in the English language through November 15, 2021, using the terms ("third" or "booster" or "three") and "dose" and...
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("COVID-19" or "SARS-CoV-2"). Studies were included if they reported the efficacy of the third dose in terms of infection rates and/or mortality. Seroconversion rates before and after booster were also reported. Both observational and retrospective studies and clinical trials were analyzed. References of eligible studies were also screened for any other potential publication suitable for inclusion in this review.

Data were extracted from two reviewers (F. P. and M. C.). Information extracted regarded type of study, year and country of origin, type and number of boosted patients, type of initial two-dose vaccine received, type and timing of third doses, median anti-spike IgG titers before and after the booster, seroconversion rates, effectiveness, and safety. Descriptive statistic was used to explain results. The primary immunogenicity outcome of anti-spike IgG was reported for each study before and after the third dose. In particular, the ratio of seroconversion rates after third and second doses (rate ratios) where this value was not reported directly. Other outcomes were infection rates and mortality due to COVID-19. Informed consent was not necessary in this paper because it provides a review of the literature. The risk of bias was evaluated with Nottingham–Ottawa Scale.

3 | RESULTS

The search process identified 30 studies (Table 1; Supporting Informations S1, S2, and S3), including four population-based observational studies from Israel, one retrospective analysis of the US Phase 1–3 trials in which 23 patients received third doses of the Pfizer-BioNTech vaccine after the recommendation released by health authorities, one Chinese Phase 1–2 study in which patients were randomized to two different vaccine doses (or placebo), an additional cohort of 80 subjects from two previous trials who received third doses of the AstraZeneca vaccine. Two studies that reported safety data alone were excluded. A third study reported relative viral loads of Delta-variant in unvaccinated and boosted subjects was not included. Twenty-one publications were retrospective or prospective case series in different high-risk populations (hemodialyzed, transplant, or cancer patients). Finally, two other series reported effects in health care workers and volunteers. Only seven studies reported the rate of infections as the outcome. The others reported seroconversion rates after the third dose and IgG titers before and after the third dose, as well as safety data (Table 2).

Abbott or Roche assays were used in almost all studies. Samples for all serologic tests were attained within 1 month after the third dose date. Overall, 2 734 437 received three COVID-19 vaccine doses (range: 10–1 137 804).

3.1 | General population (infection rate reduction)

In more than 2 700 000 Israeli patients extracted from the general population, the reduction in the risk of infection ranged from 88% to 92%.

3.2 | General population (seroconversion rate)

Conversion rates for IgG anti-spike ranged from 95% to 100%, including a non-mRNA Chinese vaccine (ZF2001) assessed in a Phase 2 study by Yang et al. These were studies in the uninfected population that received two previous doses of anti-COVID vaccines.

3.3 | Special populations (seroconversion rate)

In cancer patients or the immunocompromised (e.g., transplant recipients), mean IgG seroconversion was 39.4% before and 66.6% after third dose administration (rate ratio IgG titers of pre-and post-third-dose vaccination 1.69).

3.4 | Adverse events

Safety was usually satisfactory with no serious adverse effects and usually mild to moderate local and general side effects (adverse events are reported in Table 2).

3.4.1 | Risk of bias and quality of evidence

The overall risk of bias was moderate-good for all studies except three publications that scored 5 with NOS score (see Table 1 for details).

Quality of evidence was moderate for seroconversion rate with a booster. Data from two observational cohorts and one case-control study showed high evidence of a reduction in the risk of infection with a third versus no third dose vaccination against COVID-19.

4 | DISCUSSION

Despite the vaccines’ decline in effectiveness against infection over time, as shown in the large-scale veteran analysis, vaccination against COVID-19 remains the most effective means of fighting the pandemic. In the paper recently published in Science, Cohn et al. in fact demonstrated that the vaccines’ effectiveness against infection declined from 87% to 48% from February to October 2021, but they remained protective against death. Protection levels against variants and the ancestral virus is expected to decline over time. However, boosting with mRNA vaccines may lead to high titers of neutralizing antibodies, which may protect from symptomatic infection with variants, probably during the first year. Despite a progressive decline over time, neutralization strongly correlated with protection from symptomatic infections with variants.

Overall, the effectiveness of the third dose of the vaccines was about 90% for the infection rate in the general population; for immunocompromised patients, the rate of seroconversion increased from 39% to 66% and effective IgG concentrations increased post booster by about 69%.
| Author/year | Type of study/NOS score | Country/n° pts received three doses | Setting/median follow-up | Immunosoppressive therapies | Previous vaccine type/n° doses (%) | Third dose timing from second dose | Third dose type |
|-------------|-------------------------|------------------------------------|--------------------------|----------------------------|-----------------------------------|----------------------------------|----------------|
| Barda/2021  | Observational (vs. matched-control with two doses) Ministry of Health criteria/9 | Israel/728 321 | General population/13 days | 3.6% | -/2 (100) | ≥5 months | BNT162b2 |
| Bar-on/2021 | Retrospective/9          | Israel (Ministry of Health)/1 137 804 | ≥60 years/7 days | 0% | -/2 (100) | ≥5 months | BNT162b2 |
| Benotmane/2021 | Retrospective/7         | France/159 | Kidney transplant | 100% | mRNA-1273 (Moderna)/2 (100) | ≥1 month and <50 AU/ml | mRNA-1273 |
| Bensouna/2021 | Prospective case series/7 | French/69 | Hemodialysis or peritoneal dialysis/30 days | 13% | BNT162b2/2 (100) | ≥1 month | BNT162b2 |
| Bertrand/2021 | Retrospective/7          | France/80 | Kidney transplant/- | 100% (various) | BNT162b2/2 (100) | ≥1 month | BNT162b2 |
| Chavarot/2021 | Retrospective/7          | France/62 | Kidney transplant/44 days | 100% (betalacept + steroids) | BNT162b2/2 (100) | 69.5 days (median) | BNT162b2 |
| Dekervel/2021 | Two prospective cohorts/6 | France/66 + 34 | Hemodialysis/NR | 11% | BNT162b2/2 (100) | ≥1 month | BNT162b2 |
| Del Bello/2021 | Retrospective/8         | France/396 | Solid organ transplant | 100% | BNT162b2/2 (100) | - | BNT162b2 |
| Eliakim-Raz/2021 | Retrospective (Israel, Rabin Medical Center)/7 | Israel/97 | ≥60 years/NR | 0% | -/2 (100) | - | BNT162b2 |
| Falsey/2021  | Retrospective analysis of a Phase 1-2-3 trial/7 | US/11 + 12 (two cohorts) | ≥18 years/30 days | 0% | BNT162b2/2 (100) | 7.9–8.8 months | BNT162b2 |
| Flaxman/2021 | Retrospective analysis of UK COV001 and COV002/7 | UK/75 | ≥18 years/- | 0% | ChAdOx1 nCoV-19/2 (100) | 20–38 weeks | AZD1222 |
| Gounant/2021 | Retrospective/7          | France/30 | Cancer patients/- | 100% | BNT162b2/2 (100) | 4 weeks | BNT162b2 |
| Hall/2021    | Randomized study (vaccine vs. placebo)/- | Canada/60 | Transplant patients/- | 100% | mRNA-1273/2 (100) | 2 months | mRNA-1273 |
| Karaba/2021  | Retrospective/6          | US/47 | Transplant recipients/- | 77% | 64% BNT162b2 or mRNA-1273/2 (100) | ≥2 months | 70% mRNA, 30% Ad26.COV2.S |
| Keskin/2021  | Retrospective/6          | Turkey/45 | Healthcare workers/- | 0% | CoronaVac/2 (100) | ≥1 month | CoronaVac or BNT162b2 |
| Le Bourgeois/2021 | Retrospective/7       | France/80 | Allogeneic hematopoietic stem cell transplant/119 days | 23.7% | BNT162b2/2 (100) | ≥1 month | BNT162b2 |
| Author/year       | Type of study/NOS score | Country/n° pts received three doses | Setting/median follow-up | Immunosuppressive therapies | Previous vaccine type/n° doses (%) | Third dose timing from second dose | Third dose type                  |
|-------------------|-------------------------|-------------------------------------|--------------------------|------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Marlet/2021       | Retrospective/8         | France/180                          | Kidney transplant (160) and CLL (20)/NR | 100%                         | BNT162b2 and mRNA-1273/2 (100)   | ≥ 1 month                         | BNT162b2 or mRNA-1273           |
| Massa/2021        | Prospective longitudinal study/6 | France/61                            | Kidney transplant/- | 100% (various)               | BNT162b2/2 (100)                  | 1 month                           | BNT162b2                         |
| Masset/2021       | Retrospective/6         | France/71                           | Kidney transplant/-     | 100%                         | BNT162b2/2 (100)                  | -                                | BNT162b2                         |
| Westhoff/2021     | Retrospective/5         | Germany/10                          | Kidney transplant/-     | 100%                         | BNT162b2/2 (100)                  | 4–12 weeks                        | mRNA-1273                       |
| Peled/2021        | Retrospective/7         | Israel/96                           | Heart transplant/18 days | 79%                          | BNT162b2/2 (100)                  | 168 days                          | BNT162b2                         |
| Redjoul/2021      | Retrospective/7         | France/42                           | Allogenic HSCT/53 days  | NR                           | BNT162b2/2 (100)                  | 2 months                          | BNT162b2                         |
| Robert/2021       | Retrospective/6         | France/18                           | Hemodialysis/28 days    | NR                           | BNT162b2/2 (100)                  | -                                | BNT162b2                         |
| Saciuk/2021       | Retrospective cohort study/8 | Israel/865 887                      | General population/70 days | 0%                           | BNT162b2/2 (100)                  | 6 months                          | BNT162b2                         |
| Schmiedeberg/2021 | Retrospective/7         | Switzerland/17                      | Rheumatoid arthritis/2 weeks | Temporarily discontinued mRNA-1273 and BNT162b2/2 (100) | ≥ 4 months                        | mRNA-based from the same manufacturer |                                |
| Shroff/2021       | Retrospective/6         | US/20 (Third dose)                  | Cancer patients/5–11 days | 100%                         | BNT162b2/2 (100)                  | -                                | BNT162b2                         |
| Tillmann/2021     | Prospective cohort/5    | Germany/10                          | Hemodialysis/-          | 29.4%                        | mRNA (94%)/2 (100)                | -                                | mRNA                            |
| Werbel/2021       | Retrospective series/5  | US/30                               | Organ transplant/-      | 100%                         | mRNA (100%)/2 (100)              | 67 days (median)                  | mRNA (50%) and Ad26, COV2.S (50%) |
| Yang/2021         | Phase 1 and randomized Phase 2 studies/- | China/40 + 450 ³                     | 18–59 years/-          | 0%                           | -/2 (100)                        | 1 month                          | ZF2001 Ab targeting receptor binding domain (RBD) of the SARS-CoV-2 S protein |
| Yuer/2021         | Retrospective/7         | China/67                            | Cohort voluntarily/1 montha | NA                           | Inactivated vaccine/2 (100)      | 8 months                          | Inactivated vaccine              |

Abbreviations: NA, not applicable; NOS, Nottingham–Ottawa Scale; -, not reported.

³Patients that received three doses in Phase 1 + Phase 2 studies.

³Time to serum collection.
**TABLE 2** Efficacy of booster dose studies

| Author/year | Previous COVID-19 | Median neutralizing Ab anti-spike concentration pre-third dose (timing) | Median neutralizing Ab anti-spike concentration post-third dose (timing) | Siero-conversion rate after second dose (%) | Siero-conversion rate after third dose (%) | Rate of infection after third dose | Main toxicities |
|-------------|-------------------|-----------------------------------------------------------------------|-----------------------------------------------------------------------|--------------------------------------------|------------------------------------------|-----------------------------------|----------------|
| Barda/2021  | -                 | -                                                                     | -                                                                     | -                                          | -                                        | ~93%, ~91%, ~88%, ~81% ↓ in risk in hospital admission, severe disease, infection, and death | -              |
| Bar-On/2021 | No                | -                                                                     | -                                                                     | ~91.2%                                    | ~95% less infection and severe cases    | -                                 | -              |
| Benotmane/2021 | No               | <50 AU/ml (1 month) IgG II Quant test (Abbott, USA)                    | 586 AU/ml in responders (1 month)                                     | 0                                          | 49                                      | -                                 | 0%             |
| Bensouna/2021 | No                | 284 AU/ml (NR) Roche Elecsys Assay                                     | 7554 AU/ml (≥21 days) Roche Elecsys Assay                             | 78                                         | 91.3 (increase of Ab levels)            | 0%                                 | Pain (27%), systemic (23%) |
| Bertrand/2021 | -                 | 217.1 AU/ml (1) IgG II Quant test (Abbott, USA)                        | 2238.3 AU/ml (1 month) IgG II Quant test (Abbott, USA)                 | 37.5                                       | 61.2                                    | 2.5%                              | 0%             |
| Chavarot/2021 | No                | 0 (1) IgG II Quant test (Abbott, USA)                                | 298 AU/ml (1 month) IgG II Quant test (Abbott, USA)                   | 0                                          | 6.4                                     | 1%                                 | 0%             |
| Dekervel/2021 | 1056 UI/ml and 17.8 U/mL in two cohorts (≥21 days) IgG II Quant test (Abbott, USA) and Roche Elecsys Assay | 664 U/mL and 1180 U/mL in two cohorts (≥21 days) IgG II Quant test (Abbott, USA) and Roche Elecsys Assay | 83.3 and 85.3 (n = 66 and 34) | 92.4 and 97.1 (n = 66 and 34) | 0 | 0% (two deaths for sepsis reported) |
| Del Bello/2021 | No                | -                                                                     | -                                                                     | 41.4                                       | 67.9                                    | -                                 | 0%             |
| Eliakim-Raz/2021 | No             | 440 AU/ml (1) IgG II Quant test (Abbott, USA)                        | 25 468 AU/ml (10–19 days) IgG II Quant test (Abbott, USA)              | 97                                          | 100                                    | -                                 | 0%             |
| Falsey/2021  | No                | 83–41 AU/ml for wt variant in two cohorts (NR) Roche Elecsys Assay    | 2119–2032 for wt variant in two cohorts (1 month) Roche Elecsys Assay   | -                                          | -                                      | Local pain 82 and 67% (fever, fatigue, headache, chills, muscle pain <20% moderate-severe) | -              |
| Flaxman/2021 | No                | 1792 EUs (1 month) IgG ELISA                                         | 3746 EUs (1 month) IgG ELISA                                          | -                                          | -                                      | -                                 | 81% local symptoms |
| Gounant/2021 | No                | ≤3000 AU/mL IgG II Quant test (Abbott, USA)                          | > 3500 AU/mL in 73% IgG II Quant test (Abbott, USA)                    | Low titer                                  | 88.5                                    | -                                 | -              |
| Hal/2021     | No                | 0.37 U/mL (1) Roche Elecsys Assay                                    | 313.8 U/mL (4 months) Roche Elecsys Assay                              | 11.7                                       | 55                                      | 0                                 | No G3-4 AEs |
| Karaba/2021  | No                | NR (EUROIMMUN anti-SARS-CoV-2 IgG ELISA)                             | NR (EUROIMMUN anti-SARS-CoV-2 IgG ELISA)                              | 23                                          | 72                                      | -                                 | -              |

(Continues)
| Author/year          | Previous COVID-19 | Median neutralizing Ab anti-spike concentration pre-third dose (timing) | Median neutralizing Ab anti-spike concentration post-third dose (timing) | Siero-conversion rate after second dose (%) | Siero-conversion rate after third dose (%) | Rate of infection after third dose | Main toxicities |
|----------------------|-------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|---------------------------------------------|-------------------------------------------|-----------------------------------|----------------|
| Keskin/2021          | -                 | Abbott Architect i2000 (Abbott Laboratories)                            | Abbott Architect i2000 (Abbott Laboratories)                            | -                                           | 1.8 and 46.6 higher IgG titers with CoronaVac or BNT162b2 vaccine | 4.4 and 6.6                        | -              |
| Le Bourgeois/2021    | No                | Roche Elecsys (Rotkreuz, Switzerland)                                   | Roche Elecsys (Rotkreuz, Switzerland)                                   | 50                                          | 81                                        | 0                                 | -              |
| Marlet/2021          | Yes               | In kidney transplant recipients 0.19 BAU/ml in CLL 0.63 BAU/ml (median 43 days) SARS-CoV-2 IgG II Quant assay on an Alinity i system (Abbott) | In kidney transplant recipients 5.28 BAU/ml in CLL 10.7 BAU/ml (median 44 days) SARS-CoV-2 IgG II Quant assay on an Alinity i system (Abbott) | 30 and 57                                   | 39 and 50                                  | -                                 | -              |
| Massa/2021           | No                | 1620 AU/ml (1 month after second dose) IgG II Quanttest (Abbott, USA)    | 8772 AU/ml (1 month after third dose) IgG II Quanttest (Abbott, USA)    | 44.3                                        | 62.3                                      | -                                 | No SAE         |
| Masset/2021          | No                | >cutoff (1 month after second dose) Roche Elecsys Assay                 | >cutoff (1 month) Roche Elecsys Assay                                   | 50                                          | 70                                        | -                                 | -              |
| Westhoff/2021        | No                | <0.8 U/ml Roche Elecsys Assay                                          | 76 U/ml (median) 14 days Roche Elecsys Assay                            | 0                                           | 60                                        | -                                 | -              |
| Peled/2021           | No                | -                                                                       | IgG >3-fold of the range achieved after the two primary doses (ELISA Test “in-house”) (17.5 days) | 23                                          | 67                                        | -                                 | 60% local and 20% systemic. No SAEs |
| Redjoul/2021         | -                 | 4.160 AU/ml (28 days after 2nd dose) SARS-CoV-2 IgG Quant II assay (Abbott, Sligo, Ireland) | 11.099 AU/ml (1 month after third dose) SARS-CoV-2 IgG Quant II assay   | 50                                          | 48                                        | 0                                 | No SAEs         |
| Robert/2021          | Yes               | -                                                                       | In partial responder 776.7 138.3 to 3038] BAU/ml at 3 months; (-)       | 55.5                                        | 66.6                                      | -                                 | -              |
| Saciuk/2021          | No                | -                                                                       | -                                                                       | -                                           | -                                         | -92.9% less infection             | -              |
| Schmiedeberg/2021    | -                 | 19.5 U/ml (before 2 weeks) Roche Elecsys Assay                          | 2500 U/ml (after 2 weeks) Roche Elecsys Assay                           | -                                           | -                                         | 35 and 53% of local and systemic effects | -              |
| Author/year | Previous COVID-19 | Median neutralizing Ab anti-spike concentration pre-third dose (timing) | Median neutralizing Ab anti-spike concentration post-third dose (timing) | Siero-conversion rate after second dose (%) | Siero-conversion rate after third dose (%) | Rate of infection after third dose | Main toxicities |
|-------------|------------------|---------------------------------------------------------------|---------------------------------------------------------------|------------------------------------------|------------------------------------------|-------------------------------|---------------|
| Shroff/2021 | -                | 80% of the cancer cohort had detectable neutralizing antibodies, with a median titer of 60 (1 University of Arizona COVID-19 ELISA pan-Ig Antibody Test) | 3-fold increase in median virus-neutralizing antibody titers (1 week after 3rd dose) University of Arizona COVID-19 ELISA pan-Ig Antibody Test | -                                        | -                                        | -                            | No SAEs were noted (fig. 5a), with nine (45%) participants experiencing injection site pain |
| Tillmann/2021 | No              | 4.3 AU/ml median (4–5 weeks after second dose) anti-SARS-CoV-2 S-RBD IgG (Snibe Diagnostics, New Industries Biomedical Engineering Co., Ltd. Snibe) | >100 median (1 month) anti-SARS-CoV-2 S-RBD IgG (Snibe Diagnostics, New Industries Biomedical Engineering Co., Ltd. Snibe) | 0                                        | 70                                       | -                            | -                          |
| Werbel/2021 | No              | (-) EUROIMMUN anti-S1 IgG assay or Roche Elecsys anti-RBD pan-Ig assay | (-) (9 days) EUROIMMUN anti-S1 IgG assay or Roche Elecsys anti-RBD pan-Ig assay | 0                                        | 40                                       | -                            | 50% mild or moderate local symptoms and fatigue |
| Yang/2021   | No              | 1077–825 (Phase 1) and 419–344 (Phase 2) (1 month) ELISA kits (Wantai BioPharm, Beijing, China) | 2719–2776 (Phase 1) and 1782–1140 (Phase 2) (1 month) ELISA kits (Wantai BioPharm, Beijing, China) | 100% (Phase 1) 95%–97% (Phase 2) | 100% (Phase 1) 99%–97% (Phase 2) | -                            | 45% any AEs (3.5% G3–5) |
| Yue/2021    | No              | -                                                              | -                                                              | 86.6                                     | 95.5                                     | -                            | -                          |

Abbreviations: AU, arbitrary units; CLL, chronic lymphocytic leukemia; ELISA, enzyme-linked immunosorbent assay; RBD, receptor-binding domain; SAE: serious adverse events; °, at median follow-up of 30 days post-third dose; ^, only in seroconverted patients; -, not reported.

aAfter ≥12 days from third dose.
bAt least 100 U/I/ml of serum antibodies.
This overview can be summarized in three main messages, given the limitations of limited follow-up, different vaccines administered, and the various cut-off values used to validate serologic response with antibodies. First, there is good evidence from prospective and randomized studies (one with Moderna and one with a Chinese vaccine) that seroconversion increased with a three-dose program compared to the standard two-dose schedule, with only a minor increase in local and systemic adverse events. In the transplant recipient trial conducted by Hall et al, the increase in serologic response was characterized by an anti-receptor-binding domain (RBD) antibody level of at least 100 U/ml 4 months after the third dose (Moderna), a 5-fold increase compared to placebo. In the general Chinese population (median age 43 years), the serologic response was excellent either before and after the third dose. Finally, safety data were available in immunocompromised patients and severe disease, respectively). Second, immunocompromised patients have less robust serologic responses after booster vaccination but still attain a significant benefit from the third dose. Finally, safety data were scarce but with no indication of the new or added burden of toxicity compared to data reported by other authors for two-dose regimens.

The limited observation period represents the main limitation of the published literature in verifying the effectiveness (reduction in the risk of infection compared to those vaccinated with the two-dose regimen) of a third dose against, in particular, the Delta-variant. Other significant limitations include (1) the lack of data on the booster effect magnitude in those who previously received a non mRNA vaccine (e.g., Astra Zeneca) and on the safety and effectiveness in children and adolescents; (2) the retrospective and observational nature of included studies with lack of large, well-conducted, Phase III trials; (3) absence of data about Omicron emergent infection type.

In conclusion, a third-dose booster seems necessary, despite not providing complete protection at all against the risk of COVID-19 infection, severe disease, and death. We confirmed the efficacy of mRNA vaccine boosters for the general population not previously exposed to COVID-19 infection, particularly in those over 40 years of age with few or no comorbidities (from one large observational study conducted in Israel), in those over 60 (from over 1 million vaccinated patients in the real-world Israeli population), in those over 18 (from a retrospective cohort study of >800,000 Israeli subjects), and those at risk for severe COVID-19 because of comorbidities (from several small studies conducted in transplant, hemodialyzed, or oncologic patients). In particular, a weaker immune response may occur in these frail patients compared to the response in healthy subjects (median increase of 70% in seroconversion rates). However, how long the increased antibody response from the third dose will last remains uncertain.

Continuous monitoring of the vaccines' effectiveness is also warranted.

CONFLICT OF INTERESTS
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher's website.

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