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SHORT COMMUNICATION

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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.[3] 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 Astra Zeneca 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.[4] 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.[5]

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%.

TABLE 1 Characteristics of included studies

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	Retrospectkive/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

(Continues)

TABLE 1 (Continued)

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
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[b]	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[a]	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 month[b]	NA	Inactivated vaccine/2 (100)	8 months	Inactivated vaccine

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

[a]Patients that received three doses in Phase 1 + Phase 2 studies.

[b]Time to serum collection.

TABLE 2 Efficacy and 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	-	-	-[a]	-	−91.2% and −95% less infection and severe cases	-
Benotmane/2021	No	<50 AU/ml (1 month) IgG II Quanttest (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 (-) 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 (-) IgG II Quanttest (Abbott, USA)	298 AU/ml^ (1 month) IgG II Quanttest (Abbott, USA)	0	6.4	1%	0%
Dekervel/2021		1056 UI/ml and 17.8 U/mL in two cohorts (≥21 days) IgG II Quanttest (Abbott, USA) and Roche Elecsys Assay	6464 UI/ml and 1180 U/ml in two cohorts (≥21 days) IgG II Quanttest (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	-	440 AU/ml (-) IgG II Quanttest (Abbott, USA)	25 468 AU/ml (10–19 days) IgG II Quanttest (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	≤300 AU/ml IgG II Quant test (Abbott, USA)	> 3500 AU/ml in 73% IgG II Quant test (Abbott, USA)	Low titer	88.5	-	-
Hall/2021	No	0.37 U/ml (-) Roche Elecsys Assay	313.8 U/ml (4 months) Roche Elecsys Assay	11.7[b]	55[b]	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)

TABLE 2 (Continued)

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	-	-
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

TABLE 2 (Continued)

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 (-) 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.

[a]After ≥12 days from third dose.

[b]At least 100 UI/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 (two levels) doses of an anti-RBD vaccine: from 95%–97% to 97%–99%. This response was confirmed in two large studies in the general Israeli population, in which the effectiveness of a third dose (given at least 5 months after the second) was higher compared to that of the initial two doses (reductions of 91% and 95% and 88% and 91% for infection 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.[6,7]

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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REFERENCES

1. Bergman P, Blennow O, Hansson L. Safety and efficacy of the mRNA BNT162b2 vaccine against SARS-CoV-2 in five groups of immunocompromised patients and healthy controls in a prospective open-label clinical trial. *EBioMedicine*. 2021;74:103705.
2. Yan Z, Yang M, Lai CL. Covid-19 vaccinations: a comprehensive review of their safety and efficacy in special populations. *Vaccines*. 2021;9:1097. doi:10.3390/vaccines9101097
3. Bar-On YM, Goldberg Y, Mandel M, et al. Protection of BNT162b2 vaccine booster against Covid-19 in Israel. *N Engl J Med*. 2021;385:1393-1400. doi:10.1056/nejmoa2114255
4. Cohn BA, Cirillo PM, Murphy CC, Krigbaum NY, Wallace AW. SARS-CoV-2 vaccine protection and deaths among US veterans during 2021. *Science*. 2021;375(6578):331-336.
5. Cromer D, Steain M, Reynaldi A, et al. Articles neutralising antibody titres as predictors of protection against SARS-CoV-2 variants and the impact of boosting: a meta-analysis. *Lancet Microbe*. 2021;5247(21):e52-e61. doi:10.1016/S2666-5247(21)00267-6
6. Hause AM, Baggs J, Gee J. Safety monitoring of an additional dose of COVID-19 vaccine—United States, August 12th–September 19th, 2021. *MMWR Morb Mortal Wkly Rep*, 70(39):1379-1384. doi:10.15585/mmwr.mm7039e4
7. Shapiro Ben David S, Shamir-Stein N, Baruch Gez S, Lerner U, Rahamim-Cohen D, Ekka Zohar A. Reactogenicity of a third BNT162b2 mRNA COVID-19 vaccine among immunocompromised individuals and seniors—a nationwide survey. *Clin Immunol*. 2021;232:108860. doi:10.1016/j.clim.2021.108860

SUPPORTING INFORMATION

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

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