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Supplementary appendix

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Supplement to: Parker EPK, Desai S, Marti M, et al. Response to additional COVID-19 vaccine doses in people who are immunocompromised: a rapid review. *Lancet Glob Health* 2022; **10:** e326–28.

Appendix

The material below is adapted from the WHO's *Interim recommendations for an extended primary series with an additional vaccine dose for COVID-19 vaccination in immunocompromised persons*[1] (published under a CC BY-NC-SA 3.0 IGO license).

Rapid review methods

Search terms

A search in MEDLINE was performed to identify articles published between 1 July 2020 and 27 September 2021 using the search terms listed below.

Row	Term	Purpose
1	Coronavirus/ or Coronaviridae/ or SARS-CoV-2/ or coronaviridae infections/ or coronavirus infections/ or covid-19/	Controlled MEDLINE vocabulary terms for COVID-19
2	("covid*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or (coronavirus* or coronovirus* or coronavirinae* or CoV) or ((corona* or corono*) adj1 (virus* or viral* or virinae*))).mp.	Free text terms for COVID-19 (adapted from [2])
3	1 or 2	Combine articles identified by rows 1 or 2
4	Vaccines/ or COVID-19 Vaccines/ or immunization/ or immunization schedule/ or vaccination/	Controlled vocabulary terms for vaccine
5	(vaccin* or immunis* or immuniz*).mp.	Free text terms for vaccine
6	4 or 5	Combine articles identified by rows 4 or 5
7	(immunosuppress* or immunocomp* or immunodeficien* or deficien* or autoimmun* or HIV or transplant* or cancer* or malignan* or tumo?r* or leuk?emia or oncol* or dialysis or h?em* or rheumat* or malnutrition).mp.	Free text terms for immunodeficiency
8	3 and 6 and 7	Select articles identified by rows 3, 6, and 7
9	limit 8 to dt="20200701-20210927"	Limit to studies uploaded from 1 July 2020

medRxiv preprints were identified using the search strategy below, implemented on 29th September 2021 with the package *medrxivr* using the programming language R.

Row	Term	Purpose
1	("coronavirus" or "COVID-19" or "SARS-CoV-2")	Free text terms for COVID-19
2	("vaccine" or "vaccines")	Free text terms for vaccine
3	("immunosuppressed" or "immunosuppressive" or "immunocompromised" or "immunocompromising" or "immunodeficient" or "immunodeficiency" or "autoimmune" or "autoimmunity" or "HIV" or "transplant" or "cancer" or "malignancy" OR "tumor" or "tumour" or "leukemia" or "leukaemia" or "dialysis" or "hemodialysis" or "haemodialyis" or "rheumatic" or "rheumatoid" or "malnutrition")	Free text terms for immunodeficiency
4	("additional" or "extra" or "third" or "three" or "boost" or "booster" or "boosters" or "boosting")	Free text terms for additional doses

5	("dose" or "doses")	
6	**Search #1:** 1 and 2 and 3	Final search for vaccine response in ICPs (articles identified by rows 1, 2, and 3)
7	**Search #2:** 1 and 2 and 4 and 5	Final search for studies of additional doses (articles identified by rows 1, 2, 4, and 5)

Additional articles were identified by scanning the reference lists of included articles.

Scope and eligibility criteria

Following removal of duplicates, titles and abstracts were screened to identify articles reporting on safety, immunogenicity, and/or vaccine effectiveness (VE) of an additional COVID-19 vaccine dose in immunocompromised persons (ICPs). The population of interest included ICPs with active cancer, solid organ or stem cell transplants, immunodeficiency (including severe primary immunodeficiency or chronic dialysis), HIV, or active treatment causing significant immunosuppression. We also included studies reporting on a broader category of immunosuppressed individuals overlapping with the conditions listed above. Articles reporting outcomes for fewer than 10 ICPs were excluded. The intervention of interest included a single additional dose of a COVID-19 vaccine with a WHO Emergency Use Listing (EUL). At the time of the search, this included Ad26.COV2.S (Janssen), BIBP (Sinopharm), BNT162b2 (Pfizer/BioNTech), ChAdOx1-S (AstraZeneca), CoronaVac (Sinovac), and mRNA-1273 (Moderna), wherein a standard primary series comprised a one-dose schedule (for Ad26.COV2.S) or two-dose schedule (for all other vaccines) as per the product-specific EULs.

Our primary outcome of interest was the proportion of individuals with detectable spike-specific binding antibodies before versus after the additional dose. Secondary outcomes of interest included: (i) antibody response rates among individuals with low or undetectable antibodies prior to the additional dose; and (ii) product-specific VE of an extended primary series including an additional dose in ICPs. For the purposes of this rapid review, we allowed the antibody response criteria (e.g. assay and thresholds) to be defined on a case-by-case basis for each study. We included clinical trials (including randomised and non-randomised trials) and observational studies (including case series, case–control studies, and cohort studies).

Data extraction

We extracted data on study location, ICP group (solid organ transplant, dialysis, cancer, or other), design, age, sex, sample size (N receiving additional dose), vaccine(s) used for primary series, vaccine(s) used for additional dose, dosing interval prior to additional dose, timing of sample collection after the additional dose, antibody response criteria (assay and threshold), and antibody response rate before and after the additional dose. Where the study cohort received a mixture of vaccine products for both the primary series and additional dose, we combined across vaccine groups during data extraction. Formal extraction and analysis of reactogenicity and cellular immune response data were beyond the scope of this rapid review, as was a formal assessment of the quality of evidence. However, we comment on key trends in adverse events across from the included studies in the main text.

Using the programming language R, we visualised data on: (i) cumulative antibody response rates before and after the additional dose, stratified by ICP group; and (ii) antibody response rates among with low or undetectable antibodies prior to the additional dose. Code can be made available by the corresponding author on request.

Evidence on the immunogenicity of an additional COVID-19 vaccine dose in immunocompromised persons.

Study	Group	Country	Design	Vaccine(s)		Interval, primary series to additional dose (months)[a]	Time of sampling after additional dose (weeks)[b]	Definition of response	Assay	*N* receiving additional dose	Male, %	Age (years), mean (sd) or median (IQR) (marked as *)	Overall response rate after primary series, % (*N*)	Response rate after additional dose, % (*N*)	
				Primary series	Additional dose									Overall	Subset with low/ absent response after primary series
Del Bello et al.[3]	SOT	France	R-COH	BNT162b2	BNT162b2	2	4	Detectable S-Ig (multiple assays)	Multiple	396	65%	59 (15)	41% (396)	68% (396)	45% (232)
Masset et al.[4c]	SOT	France	R-COH	BNT162b2	BNT162b2	2	4	Detectable S-IgG (multiple assays)	Multiple	136	60%	61 (12)	50% (456)	69% (136)	n.r.
Kamar et al.[5]	SOT	France	R-COH	BNT162b2	BNT162b2	2	4	S-Ig S/Co >1.1	Wantai	99	69%	58 (2)	40% (99)	68% (99)	44% (59)
Chavarot et al.[6d]	SOT	France	R-COH	BNT162b2	BNT162b2	2	4	S-IgG >50 AU/ml	Abbott	62	58%	64.5 (51–72)*	0% (62)	6% (62)	6% (62)
Stumpf et al.[7e]	SOT	Germany	P-COH	BNT162b2	BNT162b2	2	4	S1-IgA S/Co ≥1.1 or S1-IgG ≥35.2 BAU/ml	Euro-immun	48	63%	57 (14)	32% (71)	55% (71)†	n.r.
Massa et al.[8]	SOT	France	P-COH	BNT162b2	BNT162b2	1	4	RBD-IgG >50 AU/ml	Abbott	61	72%	58 (47–66)*	44% (61)	62% (61)	32% (34)
Charmetant et al.[9f]	SOT	France	P-COH	BNT162b2	BNT162b2	n.r.	2	RBD-IgG ≥142 BAU/ml	Maglumi	66	56%	56 (12)	n.r.	n.r.	42% (66)
Peled et al.[10g]	SOT	Israel	P-COH	BNT162b2	BNT162b2	6	3	Detectable RBD-IgG	In-house	96	71%	61 (50–68)*	23% (96)	67% (96)	n.r.
Westhoff et al.[11]	SOT	Germany	P-COH	BNT162b2	mRNA-1273	2	2	S-IgG ≥0.8 U/ml	Roche	10	80%	60 (12)	n.r.	n.r.	60% (10)
Frantzen et al.[12h]	DIAL	France	P-COH	BNT162b2	BNT162b2	2–3	4	S-Ig >15 U/ml	Roche	88	73%	76 (65–83)*	n.r.	n.r.	88% (17)
Espi et al.[13i]	DIAL	France	P-COH	BNT162b2	BNT162b2	≤3	1–2	RBD-IgG ≥977 BAU/ml	Maglumi	75	64%	66 (14)	38% (106)	n.r.	54% (56)
Ducloux et al.[14]	DIAL	France	P-COH	BNT162b2	BNT162b2	n.r.	4	RBD-IgG >50 AU/ml	Abbott	45	n.r.	n.r.	89% (45)	93% (45)	40% (5)
Longlune et al.[15j]	DIAL	France	R-COH	BNT162b2	BNT162b2	1	4	S-Ig S/Co >1.1	Wantai	12	69%	64 (14)	84% (82)	90% (82)†	42% (12)

Bensouna et al.[16k]	DIAL	France	R-COH	BNT162b2	BNT162b2	1	4	S1-Ig ≥0.8 AU/ml	Roche	69	65%	68 (53–76)*	96% (69)	97% (69)	33% (3)
Re et al.[17]	CAN	France	P-COH	BNT162b2	BNT162b2	3	4	S-IgG ≥0.8 U/ml	Roche	43	63%	77 (n.r.)*	58% (43)	58% (43)	0% (18)
Gounant et al.[18l]	CAN	France	P-COH	BNT162b2	BNT162b2	≥1	4	S-IgG ≥300 AU/ml	Abbott	26	59%	67 (27–92)	87% (269)	n.r.	88% (26)
Benotmane et al.[19m]	SOT	France	P-COH	mRNA-1273	mRNA-1273	2	4	RBD-IgG ≥50 AU/ml	Abbott	159	62%	58 (50–66)*	n.r.	n.r.	49% (159)
Hall et al.[20n]	SOT	Canada	RT	mRNA-1273	mRNA-1273	2	4	RBD-Ig ≥100 U/ml	Roche	60	62%	67 (64–72)*	12% (60)	55% (60)	n.r.
Greenberger et al.[21o]	CAN	USA	P-REG	BNT162b2/ mRNA-1273/ Ad26.COV2.S	BNT162b2/ mRNA-1273/ Ad26.COV2.S	3	4	RBD-IgG ≥0.8 U/ml	Roche	49	57%	66 (n.r.)	n.r.	n.r.	55% (38)
Connolly et al.[22p]	IC/IS	USA	P-COH	BNT162b2/ mRNA-1273/ Ad26.COV2.S	BNT162b2/ mRNA-1273/ Ad26.COV2.S	3	4	RBD-Ig ≥0.8 U/ml	Roche	18	28%	55 (44–63)*	n.r.	n.r.	80% (10)
Werbel et al.[23q]	SOT	USA	CS	BNT162b2/ mRNA-1273	BNT162b2/ mRNA-1273/ Ad26.COV2.S	2	2	Detectable S1- or RBD-Ig (multiple assays)	Multiple	30	43%	57 (44–62)*	20% (30)	47% (30)	33% (24)
Schrezenmeier et al.[24]	SOT	Germany	P-COH	BNT162b2	BNT162b2	4	3	S1-IgG S/Co ≥1.1	Euro-immun	14	66%	60 (14)	n.r.	n.r.	28% (14)
					ChAdOx-1 S	3				11			n.r.	n.r.	45% (11)
Bonelli et al.[25r]	IC/IS	Austria	RT	BNT162b2/ mRNA-1273	BNT162b2/ mRNA-1273	≥1	4	RBD-IgG ≥0.8 BAU/ml	Roche	28	18%	59 (18)	n.r.	n.r.	32% (28)
					ChAdOx-1 S					27	33%	61 (15)	n.r.	n.r.	22% (27)

The table includes studies reporting on SARS-CoV-2-specific binding antibody responses following an additional vaccine dose in ICPs. Other immunogenicity endpoints, including neutralising antibody and T-cell responses, were also reported in several studies.

AU, arbitrary units; BAU, binding antibody units; CAN, cancer; CS, case series; DIAL, dialysis; IC/IS, immunocompromised/immunosuppressed; n.r., not reported; OBS, observational study; P-COH, prospective cohort; P-REG, prospective registry; RBD, receptor binding domain; R-COH, retrospective cohort; RT, randomised trial; S, spike; S/Co, signal-to-cut-off ratio; sd, standard deviation; SOT, solid organ transplant; † denominator includes subjects who did not receive an additional dose but responded after the primary vaccine series.

[a] Average interval rounded to nearest month.
[b] Average interval rounded to nearest week.
[c] Age and sex reported for parent cohort of 456 individuals.
[d] Restricted to subset of patients without prior COVID-19. All patients were being treated with belatacept.
[e] An additional dose was given to 48 patients with an insufficient response after two doses (specific criteria not defined). Age and sex reported for parent cohort of 71 individuals.

[f] Age reported for parent cohort of 93 individuals. Response rates were 78% in individuals with low but detectable antibodies after dose 2 versus 18% in individuals with no detectable antibodies after dose 2.
[g] Response to primary series was measured immediately before the third dose (i.e. 6 months after dose 2); the low seropositivity rates may partly reflect waning of antibody responses.
[h] Patients with no detectable antibodies (<0.8 U/ml) received a third dose 2 months after their primary series (n = 6), while patients with low but detectable antibodies (0.8–250 U/ml) received a third dose 3 months after their primary series (n = 82). Included here is the response rate for the 17 patients with antibody levels <15 U/ml prior to their third dose. A significant increase in median antibody concentration after dose 3 was observed in the 71 individuals with low but detectable antibodies after dose 2.
[i] All patients received a third dose within 3 months of dose 2. The average interval between dose 2 and dose 3 was not reported. An antibody threshold of ≥977 AU/ml was the lowest concentration observed in a cohort of 30 healthy volunteers and was therefore used as a threshold for an "optimal" response. Response rates were 66% in individuals with low antibodies after dose 2 (n = 44) versus 8% in individuals with no detectable antibodies after dose 2 (n = 12). An additional 19 individuals who received a third dose had an optimal response after dose 2 and were excluded here.
[j] Age and sex reported for parent cohort of 112 individuals. An additional dose was offered to 12 patients with no detectable antibodies after dose 2.
[k] An additional 12 patients had a weak S1-Ig response after dose 2 (<50 AU/ml). S1-Ig levels rose to ≥50 AU/ml in 11/12 (92%) of these patients after dose 3.
[l] Age and sex reported for parent cohort of 306 individuals. Patients with S-IgG concentrations of <300 AU/ml were offered a third dose from 1 month after dose 2. The average interval between dose 2 and dose 3 was not reported.
[m] Response rates were 81% in individuals with low antibodies after dose 2 (n = 64) versus 27% in individuals with no detectable antibodies after dose 2 (n = 95).
[n] Patients were enrolled without knowledge of their antibody response after dose 2. Response rate was 18% in placebo recipient (n = 57).
[o] Results for the 38 patients who had RBD-IgG concentrations <0.8 AU/ml prior to the additional dose. These patients received a primary series of BNT162b2 (n = 27), mRNA-1273 (n = 10), or Ad26.COV2.S (n = 1), followed by an additional dose of Ad26.COV2.S (n = 17), BNT162b2 (n = 11), or mRNA-1273 (n = 10). Results are combined across vaccine groups given the small numbers involved. A further 11 individuals were seropositive following the primary series; all exhibited higher antibody concentrations after the additional dose.
[p] Cohort of patients with autoimmune disease. Results are for the 10 patients who were seronegative prior to the additional dose. These patients received a primary series of BNT162b2 (n = 5), Ad26.COV2.S (n = 3), or mRNA-1273 (n = 2), followed by an additional dose of Ad26.COV2.S (n = 4), mRNA-1273 (n = 4), or BNT162b2 (n = 2). Results are combined across vaccine groups given the small numbers involved. A further 8 individuals were seropositive following the primary series; all exhibited higher antibody concentrations after the additional dose.
[q] Patients received a primary series of BNT162b2 (n = 17) or mRNA-1273 (n = 13), followed by an additional dose of Ad26.COV2.S (n = 15), mRNA-1273 (n = 10), or BNT162b2 (n = 5). Results are combined across vaccine groups given the small numbers involved. A follow-up study reporting additional third-dose immunogenicity data on the same cohort has also been published[26].
[r] All patients were being treated with rituximab. Patients received a third dose at least 4 weeks after the primary series.

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