Interim recommendations for an extended primary series with an additional vaccine dose for COVID-19 vaccination in immunocompromised persons

Interim guidance 26 October 2021



Background

This interim guidance has been developed on the basis of the advice issued by the Strategic Advisory Group of Experts (SAGE) on Immunization at its meeting on 5 October 2021 (1).

Declarations of interests were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the <u>SAGE meeting website</u> and <u>SAGE Working Group website</u>.

The guidance is based on the evidence outlined in this document, which was presented to SAGE on 5 October 2021.

All referenced documents are available on the SAGE COVID-19 webpage: <u>https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials</u>.

Methods

The details of the literature reviews and the summary of the available evidence serving as basis for this guidance are outlined below. As limited direct evidence on the benefits of the intervention (i.e. the level of protection conferred by an additional dose in an extended primary series against severe COVID-19) in the pre-defined population could be retrieved and due to lack of an established immune-correlate of protection against COVID-19, the available heterogenous body of evidence was deemed not to lend itself to formal GRADEing of evidence. Nevertheless, SAGE considered these indirect data from multiple sources in support of the additional dose as sufficient to proceed with issuing this good practice statement.¹

Context

With the support of SAGE and its COVID-19 Vaccines Working Group, WHO is reviewing emerging evidence on the need for and effects of an extended primary series of COVID-19 vaccine, with an additional vaccine dose, for individuals with immunocompromising conditions and those receiving immunosuppressive therapy, hereafter referred to as immunocompromised persons (ICPs). Such individuals are less likely to mount an adequate immune response following a primary vaccination series, leaving them more susceptible to COVID-19 than non-ICPs. If infected, ICPs are more likely to become severely ill from COVID-19 than non-ICPs. SAGE reviewed the evidence to determine whether extending the primary vaccination series for ICPs, through timely administration of an additional dose, would mitigate this risk. These interim recommendations apply to all COVID-19 vaccines that have received a WHO Emergency Use Listing (EUL) as of 5 October 2021 (Ad26.COV2.S, BNT162b2, ChAdOx1-S [recombinant], mRNA-1273, Sinopharm-BIBP, and Sinovac-CoronaVac).²

In this document, a primary vaccination series is as defined in the product-specific EUL, regardless of whether this is a two-dose schedule (for most WHO EUL vaccines) or a one-dose schedule (for Ad26.COV2.S). This document addresses the potential indications for extending the primary series by including an additional dose to improve the immune response rate and clinical protection against COVID-19 in ICPs. It does not address the administration of booster doses that may be given once an initially

¹ Good practice statements represent recommendations that guideline panels feel are important but that are not appropriate for formal ratings of quality of evidence. Good practice statements characteristically represent situations in which a large and compelling body of indirect evidence, made up of linked evidence including several indirect comparisons, strongly supports the net benefit of the recommended action (2).

² For certain products, an additional dose may constitute off-label use in some countries.

sufficient immune response rate in a vaccinated population has waned over time to an insufficient level of protection (as outlined in the WHO interim statement on COVID-19 vaccine booster doses (3)).

Definition of immunocompromised persons for the purpose of these recommendations

Persons with immunocompromising conditions and those receiving immunosuppressive treatment are considered immunocompromised persons. For the purposes of these interim recommendations, only moderately to severely immunocompromised persons will be addressed, as defined in Table 1 (see Annex 1 for literature review methods). This definition applies to all vaccine-eligible age groups.

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Group	Details									
Active cancer	• Active immunosuppressive treatment for solid tumour or haematological malignancy (including									
	leukaemia. lymphoma, and myeloma), or within 12 months of ending such treatment									
Tuenanland needintenda	cukacina, tympionia, and mycionia), or within 12 months of children such treatment									
I ransplant recipients	Receipt of solid organ transplant and taking immunosuppressive therapy									
	• Receipt of stem cell transplant (within 2 years of transplantation, or taking immunosuppressive									
	therapy)									
	incrapy)									
Immunodeficiency	Severe primary immunodeficiency									
	Chronic dialysis									

HIV	• HIV with a current CD4 cell count of <200 cells/µl, evidence of an opportunistic infection, not on									
	HIV treatment, and/or with a detectable viral load (i.e. advanced HIV disease)									
Immunosuppressives	• Active treatment causing significant immunosuppression including high-dose corticosteroids									
	alludeting exacts antimatchelitan transfort related immunosuppression, dates contestants,									
	aikylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer									
	chemotherapeutic agents, tumour-necrosis factor (TNF) blockers, or other highly									
	immunosuppressive drugs									
	• Immunosuppressive chemotherapy or radiotherapy within the past 6 months									

Table 1. Definition of immunocompromised persons, as included in these recommendations

Evidence of reduced vaccine response in immunocompromised persons

Multiple clinical trials and post-introduction observational studies have shown that ICPs often fail to mount an adequate response to a primary series of COVID-19 vaccine, as reflected by lower protective immune response rates and vaccine effectiveness (VE) compared with non-ICPs. While the number of studies available varies for different vaccines, this finding appears to be consistent across vaccine platforms and products. WHO continuously reviews the literature on this topic, as well as guidance issued by regional and national technical advisory groups on immunization.

Immune response rates in ICPs given the mRNA vaccines BNT162b2 and mRNA-1273 have been extensively studied in highincome countries. Following a primary series comprised of two mRNA vaccine doses, low antibody response rates relative to non-ICPs have been demonstrated for cancer, haemodialysis, organ transplant, and immunosuppressed patients (4). ICPs are also less protected against symptomatic and severe disease than non-ICPs (Annex 2), and may make up over 40% of hospitalised breakthrough cases despite comprising a substantially smaller fraction of the total population (5).

Although fewer studies have been reported for other COVID-19 vaccines, a reduced response to the primary vaccination series in ICPs compared with non-ICPs has been demonstrated, based on immunogenicity and VE data, for the ChAdOx-1 S [recombinant] vaccine and Ad26.COV2.S vaccine, and based on immunogenicity data for the Sinovac-CoronaVac and Sinopharm-BIBP vaccines (Annexes 2 and 3). Although data are not available across all subgroups of ICPs for all vaccine products, on the basis of the available evidence and extrapolating from knowledge of vaccine immunology, it is expected that all current WHO EUL COVID-19 vaccine products will induce a lower immune response rate in ICPs than in non-ICPs.

Evidence on the potential benefit of an extended primary series including an additional dose in immunocompromised persons

Several observational studies and clinical trials have reported on the immunogenicity of additional COVID-19 vaccine doses among ICPs (summarised in Annex 4). These have predominantly involved the administration of a third dose of mRNA vaccine (BNT162b2 or mRNA-1273) at an interval of 1–3 months after a homologous primary vaccination series, although findings for the Ad26.COV2.S and ChAdOx-1 S [recombinant] vaccines have been reported in several recent studies using a heterologous additional dose following a primary series with an mRNA vaccine.

Overall, the current evidence suggests that an additional dose increases the immune response rate of the primary vaccination series in ICPs. This includes induction of an antibody response in a portion (typically 25–50%) of individuals with a low or undetectable

antibody response after the standard primary vaccination series. The implications of these findings for disease protection remain uncertain given the lack of an established correlate of protection and the absence of data on VE for additional doses in ICPs.

Additional doses of inactivated WHO EUL COVID-19 vaccines have not been studied directly in the context of ICPs, and WHO encourages further research to address this evidence gap. WHO also acknowledges the trade-offs between resources allocated to ensure additional doses for ICPs versus ensuring high vaccine coverage rates of first and second dose in other priority groups.

Given that the protective immune response rate may remain insufficient in ICPs even after the administration of an additional dose, WHO further recommends that the close contacts (especially caregivers and family members in multigenerational households) of such individuals should be vaccinated with the standard primary vaccine series if eligible (according to the product-specific EUL), subject to country-specific vaccine prioritization considerations. WHO emphasises that achieving high vaccination coverage in priority-use groups, as defined in the WHO Prioritization Roadmap (6), should continue to be the focus while vaccine supply remains constrained. Additional public health and social measures (7) are also warranted, depending on the local epidemic circumstances, including measures within households or care facilities to mitigate the risk of transmission to ICPs.

Safety data on an additional dose in ICPs, where reported, have generally been consistent with those observed for the standard primary series of the vaccine being administered. Given the significant risk of disease for ICPs if infected, on the basis of available data WHO considers that the benefits of an extended primary series including an additional dose outweigh the risks, though additional safety monitoring should be conducted.

Homologous versus heterologous additional doses in an extended primary series

The benefit of an additional dose in an extended primary series administered to ICPs has largely been assessed using the same vaccine product for the initial dose(s) and the additional dose (Annex 4). Accordingly, a homologous additional dose as part of an extended primary series should currently be considered standard practice.

Evolving evidence in non-ICPs suggests that a heterologous series (using a WHO EUL vaccine product from a different platform for the additional dose) may be more immunogenic than a homologous series, depending on the specific platforms and order of the products used. However, data on safety, immunogenicity, and VE of heterologous versus homologous additional doses are currently limited.

Recommendations (good practice statement)

WHO recommends that the primary vaccine series in moderately to severely immunocompromised persons should be extended to include an additional dose for all COVID-19 vaccines that have received WHO EUL.

On the basis of available evidence, the additional dose in an extended primary series should be given at least 1 month and within 3 months after the primary series in order to increase protection for ICPs. If more than 3 months have elapsed since the last dose in the standard primary series, the additional dose in an extended primary series should be given at the earliest opportunity. For individuals receiving or scheduled to receive immunosuppressive therapy, the most appropriate timing for the additional dose may vary depending on the epidemiological setting and the timing and extent of the immunosuppressive therapy, and should be discussed with the treating physician. WHO encourages further research into the optimal timing of an additional dose in an extended primary series administered to ICPs.

A homologous additional dose in an extended primary series should currently be considered standard practice, but alternative heterologous platforms for the additional dose may also be considered, taking into account current vaccine supply, vaccine supply projections, and other access considerations. Recommendations as to whether the additional dose should be a homologous or heterologous vaccine will be reviewed once more data are available.

WHO emphasises the need for key gaps in the evidence to be addressed, including:

- immunogenicity and effectiveness of COVID-19 vaccines in ICPs, especially for vectored and inactivated vaccines;
- immunogenicity and effectiveness of COVID-19 vaccines in subpopulations with different immunocompromising conditions;
- immunogenicity and effectiveness of COVID-19 vaccines in people living with HIV with a current CD4 cell count of <200 cells/µl, evidence of an opportunistic infection, not on HIV treatment, and/or with a detectable viral load (i.e. advanced HIV disease);
- safety, effectiveness, and duration of protection provided by additional doses in an extended primary series in ICPs;
- optimal timing of additional doses in an extended primary series in ICPs;
- relative benefits of heterologous versus homologous additional doses in ICPs; and
- programme considerations on how best to integrate COVID-19 vaccination within broader health care delivery to ICPs.

Annex 1. Search strategy for review of evidence on COVID-19 vaccine response in immunocompromised persons

1. Search strategy for defining immunocompromised persons at risk of a reduced response to COVID-19 vaccination (as presented in Table 1)

A search in PubMed was performed to identify English-language articles published from inception of the database to 10 September 2021, using the following search terms:

(("Coronavirus"[Mesh] OR "Coronavirus Infections"[Mesh] OR "coronavirus"[tiab] OR "coronaviruses"[tiab] OR "nCoV"[tiab] OR "COVID"[tiab] AND ("Vaccines"[Mesh] OR "vaccine"[tiab] OR "vaccines"[tiab] OR "vaccination"[tiab] OR "vaccinations"[tiab] OR "immunization"[tiab] OR "immunizations"[tiab] OR "immunisation"[tiab] OR "immunisations"[tiab]) AND (("Immunocompromise"[Mesh] OR "Immunocompromise"[tiab] OR "Immunocompromised"[tiab] OR "Immunosuppress"[tiab] OR "Immunosuppressed"[tiab] OR "Immunodeficient"[tiab]) NOT (Comment[ptyp] OR Editorial[ptyp] OR Letter[ptyp] OR News[ptyp] OR Newspaper Article[ptyp]) NOT ("animals"[Mesh] NOT "humans"[Mesh]) AND English[lang])

Duplicates were removed, and publications were screened for those reporting on COVID-19 infection outcome or COVID-19 vaccine response in ICPs. The immunocompromising conditions, where available, were then extracted.

The search was extended by scanning the reference lists of the included articles. A grey literature search was performed in Google, Google Scholar, and national regulatory and national vaccine advisory committee websites, using combinations of the targeted search terms listed below:

(Immunocompromise OR Immunosuppress OR Immunodeficient) AND (COVID-19 OR Coronavirus) AND (vaccine OR vaccination OR immunization OR immunisation) AND (booster OR third dose OR 3rd dose OR additional dose OR primary series)

The conditions resulting in moderate or severe immunosuppression, either generally or specifically with respect to COVID-19 vaccine response, from both searches were combined and summarised in clear language (as agreed by the WHO SAGE Working Group on COVID-19 Vaccines).

2. Search strategy for rapid review of COVID-19 vaccine response in immunocompromised persons (as presented in Annexes 2–4)

A search in MEDLINE was performed to identify English-language 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 "SARS-coronavirus- 2*" or "SARS-coronavirus 2*" or "SARS coronavirus- 2*" or "SARS-coronavirus 2*" or "SARS coronavirus- 2*" or "SARS-coronavirus 2*" or "SARS coronavirus- 2*" or "SARS-coronavirus-2*" or "SARS coronavirus-2*" or (coronavirus* or coronavirus* or coronaviruae* or CoV) or ((corona* or coronav) adj1 (virus* or viral* or virinae*))).mp.	Free text terms for COVID-19 (adapted from (8))
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

Duplicates were removed, and titles and abstracts were screened to identify articles reporting on safety, immunogenicity, and/or VE in ICPs, including response to additional doses.

The search was extended by scanning the reference lists of included articles and guidance issued by national vaccine advisory committees. We also included one relevant article that was published after the search was performed. Furthermore, *medRxiv* preprints were identified using the search strategy given below, implemented on 29 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)

Articles identified via this rapid review were used to populate the tables in Annexes 2–4. Specifically, the following articles were included:

- all articles reporting on VE in ICPs;
- all articles reporting on immunogenicity of inactivated WHO EUL COVID-19 vaccines in ICPs;
- selected articles reporting on immunogenicity of vectored WHO EUL COVID-19 vaccines in ICPs (an illustrative subset spanning vaccine products and ICP groups);
- all articles reporting on the safety, immunogenicity, or VE of additional doses in ICPs.

A summary of immunogenicity studies for mRNA WHO EUL COVID-19 vaccines in ICPs has recently been published (4). This topic was beyond the scope of the present review. One article reporting on response to a fourth COVID-19 vaccine dose in ICPs was not included.

Annex 2. Evidence of reduced COVID-19 vaccine effectiveness in immunocompromised persons

The table below includes studies reporting estimates of VE following a complete primary vaccine series, as defined in the product-specific EUL (i.e. one dose for Ad26.COV2.S and two doses for all other vaccines). Specific definitions for IC/IS varied by study. Where reported, this typically included some combination of the following: solid organ/haematological cancer, HIV/AIDS, congenital immunodeficiency syndrome, solid organ transplant, receipt of immunosuppressive therapy, advanced kidney disease, and inflammatory bowel disease.

Study	Group	Country	Design	Vaccine(s)	Start date	End date	Outcome	VE in ICPs (95% CI)	VE in non- ICPs (95% CI),	VE overall (95% CI),
Tenforde et al. $(5)^a$	IC/IS	USA	Case-control	BNT162b2/ mRNA-1273	11 Mar 2021	5 May 2021	Hospitalisation	63 (21–83)	91 (86–95)	87 (81–91)
Tenforde et al. (9) ^b	IC/IS	USA	Case-control	BNT162b2/ mRNA-1273	11 Mar 2021	14 Jul 2021	Hospitalisation	63 (44–76)	90 (87–92)	86 (82–88)
Young-Xu et al.	IC/IS	USA	Test-negative	BNT162b2/	14 Dec 2020	14 Mar	Infection	88 (82–92)	n.r.	94 (92–95)
(10)°			case-control	mRNA-12/3		2021	Symptomatic disease	83 (72–89)	n.r.	91 (87–93)
Chodick et al. (11) ^d	IC/IS	C/IS Israel	Cohort	BNT162b2	19 Dec 2020	20 Feb 2021	Infection	71 (37–87)	n.r.	90 (75–95)
							Symptomatic disease	75 (44–88)	n.r.	94 (87–97)
Khan et al. $(12)^{e}$	IC/IS	C/IS USA	Cohort	BNT162b2/ mRNA-1273	18 Dec 2020	20 Apr 2021	Infection	80 (n.r.)	n.r.	n.r.
							Severe disease	70 (n.r.)	n.r.	n.r.
Chemaitelly et al.	SOT	SOT Qatar	Cohort	BNT162b2/ mRNA-1273	1 Feb 2021	21 Jul 2021	Infection	47 (0–74)	n.r.	n.r.
$(13)^{1}$							Severe/fatal disease	72 (0–91)	n.r.	n.r.
Whitaker et al. (14) ^g	IC/IS	IC/IS United Kingdom	Cohort	BNT162b2	7 Dec 2020	13 Jun 2021	Symptomatic disease	73 (34–89)	n.r.	93 (86–97)
				ChAdOx-1 S				75 (19–92)	n.r.	78 (70–84)
Polinski et al. (15) ^h	IC/IS	USA	Cohort	Ad26.COV2.S	1 Mar 2021	31 Jul 2021	Symptomatic disease	64 (57–70)	79 (78–81)	79 (77–80)
							Hospitalisation	68 (54–77)	83 (80-85)	81 (79–84)

CI, confidence interval; IC/IS, immunocompromised/immunosuppressed; ICP, immunocompromised person; n.r., not reported; SOT, solid organ transplant; VE, vaccine effectiveness.

^a Test-negative and syndrome-negative controls were combined for primary VE calculations. Median interval between last vaccine dose and onset of illness was 44 days (interquartile range (IQR) 25–54 days) for cases and 42 days (IQR 27–60 days) for test-negative controls.

^b Extension of earlier study (5) with longer follow-up. Test-negative and syndrome-negative controls were combined for primary VE calculations. Median interval between last vaccine dose and onset of illness was 65 days (range 14–166 days).

^c Study performed in Veterans Health Administration patients. VE estimates were adjusted for age, body mass index, race, sex, and other factors.

^d Follow-up period of 7–27 days after the second dose.

^e Study performed among Veterans Health Administration patients with inflammatory bowel disease. Most patients were receiving immunosuppressive therapy. Median follow-up period of 123 days (IQR 70–123 days) in unvaccinated individuals versus 38 days (IQR 20–55 days) in fully vaccinated individuals.

^f Cohort of immunosuppressed kidney transplant recipients. Follow-up period of 14–120 days after the second dose.

^g Subset of individuals aged 16–64 years used as reference. Follow-up period of \geq 14 days after the second dose. VE estimates were adjusted for sex, ethnicity, shielding status, and other factors.

^h Follow-up period of 14–152 days after the second dose. VE estimates were adjusted for under-recording of vaccinations.

Annex 3. Evidence of reduced immunogenicity of vectored and inactivated WHO EUL COVID-19 vaccines in immunocompromised persons

The table below includes studies reporting on SARS-CoV-2-specific binding antibody responses following a complete primary vaccine series, as defined in the product-specific EUL (i.e. one dose for Ad26.COV2.S and two doses for all other vaccines). All eligible studies are presented for inactivated vaccines. For vectored vaccines, an illustrative subset is included, spanning different vaccine products and ICP groups. Other immunogenicity endpoints, including neutralising antibody and T-cell responses, were also reported in several studies. IC/IS definitions included, among others, autoimmune rheumatic disease, psoriasis, inflammatory bowel disease, multiple sclerosis and conditions requiring immunosuppressive therapy. Although we did not identify any studies reporting vaccine-specific antibody responses in cancer patients following two doses of ChAdOx-1 S, reduced responses relative to healthy controls have been reported following a single dose (*16, 17*). An additional study reporting on Sinopharm-BIBP found no significant differences in post-vaccination RBD-Ig levels between people living with controlled HIV (n = 42) and healthy controls (n = 28), but did not report RBD-Ig response rates or geometric mean concentrations (GMCs) (*18*).

Study	Group	Country	Design	Vaccine	Time of sampling	Definition of response	Assay	Response rat	e after primary	GMC (95% CI concentration) [<i>N</i>] or median (IQR) (marked
					after	•		series, % (N)		as *) [<i>N</i>] after	primary series
					primary series (weeks) ^a			ICPs	Non-ICPs	ICPs	Non-ICPs
Thuluvath et al. (19) ^b	SOT + IC/IS	USA	OBS	Ad26.COV2.S	6	S-Ig >0.4 U/ml	Roche	89% (19)	n.r.	n.r.	n.r.
Boyarsky et al. (20) ^c	SOT	USA	OBS	Ad26.COV2.S	5	RBD-Ig ≥0.8 U/ml	Roche	17% (12)	n.r.	n.r.	n.r.
Garcia et al. (21) ^d	DIAL	USA	OBS	Ad26.COV2.S	4-9	RBD-Ig negative to positive	Siemans	67% (173)	n.r.	n.r.	n.r.
Hsu et al. (20) (22) ^e	DIAL	USA	OBS	Ad26.COV2.S	2–10	RBD-IgG ≥1 U/ml	ADVIA Centaur	37% (325)	n.r.	n.r.	n.r.
Ollila et al. (23) ^f	CAN	USA	OBS	Ad26.COV2.S	8	Detectable RBD-Ig	Wondfo	9% (11)	n.r.	n.r.	n.r.
Thakkar et al. (24) ^g	CAN	USA	OBS	Ad26.COV2.S	>1	RBD-IgG ≥50 AU/ml	Abbott	85% (19)	n.r.	1121* (n.r.) [19]	n.r.
Chiang et al. (25) ^h	IC/IS	USA	OBS	Ad26.COV2.S	4	RBD-Ig ≥0.8 U/ml	Roche	80% (45)	n.r.	n.r.	n.r.
Prendecki et al. (26) ⁱ	SOT	United Kingdom	OBS	ChAdOx-1 S	4	S-IgG ≥7.1 BAU/ml	Abbott	44% (358)	100% (8)	7.1* (7.1–39) [358]	88* (47–395) [8]
Clarke et al. (27) ^j	DIAL	United Kingdom	OBS	ChAdOx-1 S	6	S-IgG ≥7.1 BAU/ml	Abbott	83% (272)	100% (8)	79* (20–213) [272]	88* (47–395) [8]
Shenoy et al. (28) ^k	IC/IS	India	OBS	ChAdOx-1 S	4	Detectable S1-IgG	Roche	95% (120)	100% (30)	238* (70.5–825.5) [93]	278* (205–603.1) [30]
Whitaker et al. (14) ¹	IC/IS	United Kingdom	OBS	ChAdOx-1 S	>1	Detectable S- Ig	Roche	97% (39)	99% (493)	832* (85.6–>2,500) [39]	1778* (552–3,189) [493]

Madhi et al. (29) ^m	HIV	South Africa	RT	ChAdOx-1 S	2	S-IgG ≥32 BAU/ml	Luminex	94% (32)	96% (23)	453.1 (267.4–767.7) [32]	504.9 (337.1–756.2) [23]
Bruminhent et al. (30)	SOT	Thailand	OBS	Sinovac- CoronaVac	2	n.r.	Abbott (RBD- IgG)	n.r.	n.r.	7.8 (0.2–15.5) [35]	2691 (1581–3802) [38]
Karacin et al. (31)	CAN	Turkey	OBS	Sinovac- CoronaVac	n.r.	Ig ≥1 IU/ml	Atellica IM	64% (47)	n.r.	n.r.	n.r.
Medeiros-Ribeiro et al. (32)	IC/IS	Brazil	OBS	Sinovac- CoronaVac	6	S1/S2-IgG ≥15 AU/ml	Liaison	70% (859)	96% (179)	27.0 (24.7–29.5) [859]	67.0 (59.8–74.9) [179]
Seyahi et al. (33) ⁿ	IC/IS	Turkey	OBS	Sinovac- CoronaVac	4	S1-IgG ≥0.8 U/ml	Roche	77% (22)	98% (47)	n.r.	n.r.
Holt et al. <i>(34)</i> °	DIAL	United Arab Emirates	OBS	Sinopharm-BIBP	2–3	S1/S2-IgG ≥15 AU/ml	Liaison	50% (270)	n.r.	12.2 (11.1–16.9) [270]	n.r.
Ariamanesh et al. (35)	CAN	Islamic Republic of Iran	OBS	Sinopharm-BIBP	4	S-IgG ≥8 µg/ml	Pishtazteb Diagnostics	77% (unclear)	n.r.	n.r.	n.r.

AU, arbitrary units; BAU, binding antibody units; CAN, cancer; CI, confidence interval; DIAL, dialysis; IC/IS, immunocompromised/immunosuppressed; ICP, immunocompromised person; IQR, interquartile range; n.r., not reported; OBS, observational study; RBD, receptor binding domain; RT, randomised trial; S, spike; SOT, solid organ transplant.

^a Average interval rounded to nearest week.

^b Cohort of liver transplant recipients and patients with chronic liver disease with or without cirrhosis. S-Ig antibodies were detected in 94% of patients who received BNT162b2 (n = 104) and 91% of patients who received mRNA-1273 (n = 110). At a higher threshold of ≥ 250 U/ml, response rates were 2%, 44%, and 55% in Ad26.COV2.S, BNT162b2, and mRNA-1273 recipients, respectively. ^c RBD-Ig antibodies were detected in 59% of patients who received mRNA vaccines (n = 725).

ely, assuming exclusion of individuals who were RBD-Ig

received mRNA-1273 (n = 766) and 87% of patients who

who received BNT162b2 (n = 96).

A cohort of health care workers was used for the non-ICP ombining across vaccines, median antibody concentrations ith autoimmune rheumatic disease (n = 93). The median

al therapy for at least 3 months and had a plasma HIV viral ected in 93% of ICPs (n = 82) and 100% of non-ICPs (n =

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