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PERSONAL VIEWPOINT

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Ethical review of COVID-19 vaccination requirements for transplant center staff and patients

Olivia S. Kates¹ | Peter G. Stock² | Michael G. Ison³ | Richard D. M. Allen⁴ | Patrizia Burra⁵ | Jong Cheol Jeong⁶ | Vivek Kute⁷ | Elmi Muller⁸ | Alejandro Nino-Murcia⁹ | Haibo Wang¹⁰ | Anji Wall¹¹

¹Division of Infectious Diseases, Department of Medicine, Johns Hopkins University, Baltimore, Maryland

²Department of Surgery, University of California, San Francisco, San Francisco, California

³Division of Infectious Diseases, Feinberg School of Medicine, Northwestern University, Chicago, Illinois

⁴Bosch Institute, University of Sydney, Sydney, New South Wales, Australia

⁵Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Padua, Italy

⁶Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea

⁷Department of Nephrology and Transplantation Science, Institute of Kidney Diseases and Research Center, Dr HL Trivedi Institute of Transplantation Sciences (IKDRC-ITS), Ahmedabad, India

⁸Transplant Unit, Department of Surgery, Groote Schuur Hospital, Cape Town, South Africa

⁹Surgery Department, Colombiana de Transplantes, Bogotá, Colombia

¹⁰Clinical Trial Unit, First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

¹¹Baylor University Medical Center, Annette C. and Harold C. Simmons Transplant Institute, Dallas, Texas

Correspondence

Peter G. Stock, Department of Surgery, University of California, San Francisco, San Francisco, CA. Email: peter.stock@ucsf.edu Transplant centers seeking to increase coronavirus disease 2019 (COVID-19) vaccine coverage may consider requiring vaccination for healthcare workers or for candidates. The authors summarize current data to inform an ethical analysis of the harms, benefits, and individual and societal impact of mandatory vaccination, concluding that vaccine requirements for healthcare workers and transplant candidates are ethically justified by beneficence, net utility, and fiduciary duty to patients and public health. Implementation strategies should mitigate concerns about respect for autonomy and transparency for both groups. We clarify how the same arguments might be applied to related questions of caregiver vaccination, allocation of other healthcare resources, and mandates for non-COVID-19 vaccines. Finally, we call for effort to achieve global equity in vaccination as soon as possible.

KEYWORDS

editorial/personal viewpoint, ethics, ethics and public policy, infection and infectious agents—viral, infectious disease, law/legislation, organ transplantation in general, recipient selection, vaccine, waitlist management

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) vaccine mandates have been proposed in a wide range of contexts. COVID-19 vaccines decrease the risk of acquiring COVID-19, experiencing severe disease or death, and passing COVID-19 to others, whereas reports of serious harm from vaccines are extremely rare. Transplant centers responsible for the care of vulnerable patients and for stewardship of donor organs are among the institutions contemplating vaccine mandates. For transplant center staff, as for all healthcare workers, there is a familiar precedent in mandatory influenza vaccination. Many healthcare organizations have already imposed COVID-19 vaccine mandates, and countries like Italy and France have imposed healthcare worker vaccine mandates at the national level. Other countries including South Africa do not constitutionally allow for vaccine mandates.

Mandatory vaccination for transplant candidates may also be ethically justifiable. A recent manuscript summarized ethical arguments in favor of and against requiring routine vaccines prior to solid organ transplant listing citing net utility, stewardship, and beneficence in the justification of mandates versus justice and respect for persons in arguments against mandates. At least one transplant center in the United States has been named in the media as denying liver transplantation to a candidate who refused pretransplant COVID-19 vaccination.

We believe that it is essential to specify the ethical analysis of vaccine mandates for staff and candidates to the novel context of COVID-19 vaccination. Such policies have individual and public health implications, so we present an analysis incorporating individual- and public health-oriented bioethics principles, including non-maleficence, beneficence, and respect for autonomy; net utility, transparency, and justice. 11,12 We first address COVID-19 vaccine mandates for transplant center staff, drawing on previous literature for influenza vaccines. Indeed, many of the ethical arguments supporting COVID-19 vaccine mandates for transplant center staff apply equally to all healthcare workers. We then address requirements for transplant candidates. We conclude by acknowledging the broader context surrounding proposed COVID-19 vaccine mandates, including vaccination of caregivers, use of vaccination status in allocation of other healthcare resources, mandates for other vaccines, and stark inequities in vaccine availability around the world.

2 | REQUIRING COVID-19 VACCINES FOR TRANSPLANT STAFF

Regarding the relationship between an individual healthcare worker and patient, it is a familiar tenet of all codes of medical ethics that the healthcare worker has a fiduciary duty to promote the wellbeing of the patient, and to not harm the patient. ¹³ Previous authors have argued that these duties establish an obligation for healthcare workers to be vaccinated and justify influenza vaccine mandates, whereas objections point out that there are few data demonstrating

hypothesized benefits and harms.¹⁴⁻¹⁶ For COVID-19, there have been confirmed nosocomial outbreaks beginning with asymptomatic healthcare workers or amplified by transmission chains involving healthcare workers resulting in patient illness and death.^{17,18} Transplant patients are particularly vulnerable, even if they are themselves vaccinated.¹⁹⁻²³ Infections among transplant candidates may lead to waitlist inactivation, missed transplant opportunities, or death; infections among transplant recipients may lead to death or graft loss.^{24,25} Additionally, transplant centers and other healthcare institutions have fiduciary obligations to protect their patients by overseeing vaccination among their staff.

The proposed duty of healthcare workers and institutions to protect patients through vaccination is in tension with healthcare workers' autonomy, although autonomy is not an absolute overriding ethical primary.²⁶ Mandates may also conflict with other expectations in the employer-employee relationship. Mandates applied with short notice may appear to abruptly change terms of employment for existing employees and conflict with an expectation for transparency, and mandates that are applied differently for different types of employees may conflict with an expectation for just treatment. Even if all employees are treated the same, some will be affected differently by vaccine mandates because of differences in knowledge, for example, between clinical and nonclinical staff, differences in vaccination preferences, or differences in the probability of certain harms, such as thrombocytopenic thrombosis syndrome affecting mostly young women after vaccination with Ad26.COV2.S or ChAdOx1.^{27,28} Moreover, disparities in vaccination may overlap with other disadvantages in the healthcare workplace from racism, sexism, or power differentials between professional roles.²⁹

These concerns could be mitigated through thoughtful implementation strategies: providing sufficient time for employees to contemplate a vaccination decision, creating accessible educational materials for all members of the healthcare workforce, and allowing for reasonable medical objections to prevent serious harms. Religious and philosophical objections, an exercise of autonomy, would not be supported on the basis of avoidance of harms, but may be legally protected in some settings. Importantly, vaccination would be expected to benefit, not harm healthcare workers; thus, mandatory vaccination is not in conflict with employers' duty to not harm their employees. Vaccination also promotes a safe working environment for all staff—most healthcare workplace-related severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposures come from contact with other healthcare workers, whereas a minority come from contact with patients. 30,31

Healthcare workers and institutions are also public health agents and should seek to promote the public health and not to detract from it.¹² Vaccinated healthcare workers can accomplish this directly through their participation in community immunity—in one US study, state laws promoting influenza vaccination for hospital workers were associated with a statistically significant decrease in population-level mortality from pneumonia and influenza.³² In addition, reducing COVID-19 illnesses among healthcare workers ensures that more workers will be available to participate in patient

care amidst ongoing surges. Vaccine mandates for healthcare workers can also have an indirect impact on public health by setting a positive example, broadcasting vaccine confidence, and building trust between public health agents and the population.¹⁴

Bioethical obligations of beneficence, nonmaleficence and fidelity to patients and to the population favor and indeed necessitate healthcare worker vaccination, justifying some intrusion on healthcare worker autonomy. Experience with influenza vaccine requirements suggests that a COVID-19 vaccine requirement, rather than increasing convenience, education, or incentives, will be the most effective strategy for promoting vaccine uptake in settings where vaccines are already widely available.2 Where COVID-19 vaccines remain scarce, most healthcare workers and institutions are frustrated in their desire to protect themselves and their patients. Increasing vaccine availability would dramatically increase healthcare worker vaccination in such settings and could be followed later by vaccine mandates, where constitutionally permitted, if not all healthcare workers are vaccinated voluntarily.

REQUIRING COVID-19 VACCINES FOR TRANSPLANT CANDIDATES

COVID-19 vaccine mandates raise unique considerations for transplant candidates. As has been shown for influenza vaccines and theorized for COVID-19 vaccines, pre-transplant vaccination can be expected to benefit candidates by conferring better protection than vaccination delayed until after transplant or no vaccination at all.³³ Transplant candidates can be expected to have high rates of seroconversion after COVID-19 vaccination (73%-88%). 34,35 whereas transplant recipients have a reduced humoral response. 36,37 Theoretical risks such as alloimmunization also have not been borne out with other vaccines, although vaccines do transiently impact assays of donor sensitization.³⁸ Overall, COVID-19 vaccines are safe for individuals with end-stage organ dysfunction, and strongly recommended to protect these patients from serious illness and death.³⁹ As for healthcare workers, exceptions should be made for serious medical contraindications to vaccination, where vaccination would be harmful to the candidate.

Although transplant recipients who have not been vaccinated may be at higher risk for COVID-19 complications than those who have been vaccinated, the overall balance of individual benefits and harms will still favor transplantation for candidates with reduced life expectancy or quality of life due to end-stage organ disease, regardless of vaccination status. Mandating vaccination for transplant candidates constrains autonomy by imposing a grave consequence for refusal, although, as for healthcare workers, vaccines would not be forcibly administered. To decrease infringement on autonomy, informed consent requires that transplant professionals recognize and address candidates' informational needs. Candidates frequently come to COVID-19 vaccine decisions with less specific knowledge about the mechanisms, safety, efficacy, and nuances of COVID-19 vaccines than the organizations that would impose requirements on

them. Policies that allow candidates sufficient time to process new information before consequences are enforced also better support autonomy and informed consent. So, while vaccinating candidates are aligned with the principle of beneficence, denying transplantation is clearly in conflict with the principle of non-maleficence toward the individual candidate, and may be at least somewhat in conflict with respect for the candidate's autonomy.

Listing and allocation decisions affecting individual candidates also have public health implications. As public health agents, transplant centers are ethically required to act as transparent, just, and judicious stewards of the scarce resource of donor organs. Ethical considerations in organ transplant listing include the likelihood and magnitude of benefit, such as increased life expectancy or increased quality of life, as well as the likelihood of harms such as graft loss or infectious complications after transplant. To achieve higher net utility across all candidates, it is ethically permissible for transplant centers to deny listing to a candidate expected to have a poor outcome, even if that outcome would be preferred for the individual candidate. In addition to risks related to COVID-19 infection, an additional hypothesized risk is that transplant candidates who refuse recommended vaccination will also be non-adherent to post-transplant instructions, although very limited data exist to evaluate this hypothesis. 40 One study found that families who refused childhood vaccination were also less likely to present for routine pediatric care, but whether this would be true for transplant-specific care or for individuals who refuse COVID-19 vaccines has never been tested. 41

Transplant centers should balance criteria to maximize net utility with attention to justice and equity, and listing criteria should not systematically exclude vulnerable or disadvantaged groups for arbitrary or non-modifiable reasons. For voluntarily and easily modifiable factors that are expected to improve a candidate's probability of lasting benefit from transplantation, like COVID-19 vaccination, transplant centers may be justified in applying stricter criteria including vaccine mandates as long as vaccines are readily available to candidates. How net utility and justice might be balanced when considering COVID-19 vaccine mandates will vary by context. In settings where donor organs or transplant capacity are extremely limited, more strict listing criteria may be appropriate to ensure that the greatest possible benefits of transplantation can be realized. Transplant centers everywhere are obligated to resist inequities affecting their patients, and where systemic injustices are more pronounced or entrenched, that obligation is also magnified. The strongest justification for strict vaccine mandates in transplant listing would be in societies where organs for transplant are very scarce and vaccine refusal affects all groups equally or is not more prevalent among candidates who are otherwise disadvantaged in transplantation. In any case, transplant centers should ensure that their listing policies are clear and transparent to candidates, and that new policies are introduced to candidates proactively.

In addition to their relationship with candidates, transplant centers also have relationships with donors, donor families, and the population of potential future donors. Transplant centers should strive to be good stewards of deceased donor organs-pursuing the greatest net utility, avoiding arbitrary injustices, and operating transparently—to fulfill obligations to these groups and preserve their trust.

Outside of their role in listing and allocation, transplant centers can also enhance the health of candidates, recipients, and the public by promoting vaccination prior to transplantation. Limiting access to transplant facilities for non-vaccinated individuals may reduce the risk of SARS-CoV-2 transmission to vulnerable patients in the clinical setting. Emphasizing pretransplant vaccination as opposed to post-transplant vaccination or transplantation without vaccination would decrease the number of individuals who receive induction immunosuppression without prior protection against COVID-19. Viral evolution observed in such profoundly immunosuppressed patients with prolonged shedding has been proposed as a possible pathway for the emergence of SARS-CoV-2 variants of concern, with potentially enormous, global implications. ⁴²

Although COVID-19 vaccine mandates for transplant candidates might result in some candidates who consistently refuse vaccination being excluded from transplantation, mandates could enhance the net utility from transplantation across all candidates, protect vulnerable candidates and recipients, and benefit overall public health. For these reasons, requiring COVID-19 vaccination for transplant listing is ethically justifiable, as long as implementation sufficiently addresses ethical concerns. These would include empowering candidates to make informed, autonomous choices about vaccination by providing them with understandable and culturally appropriate information about vaccines and allowing them sufficient time to consider that information. For this reason, mandates should not be immediately imposed upon already listed candidates. Instead, transplant centers should establish a timeline to reach out to nonvaccinated listed candidates, inform them of the policy change, and allow them time to consider vaccination based on that new information. Only after a reasonable interval for consideration should candidates who have not been vaccinated and not already been transplanted face removal from the waiting list. Transplant centers must also anticipate and seek to mitigate any possible impact of vaccine mandates on transplant equity, by familiarizing themselves with patterns of vaccine acceptance in their population and preparing to address vaccination concerns that may be specific to disadvantaged groups. Centers should plan prior to implementation to monitor the impact of vaccine mandates and should be prepared to pause mandates if there is an unacceptable impact on transplant equity. Finally, COVID-19 vaccine mandates should be implemented in a way that is transparent to candidates and the public. Ideally, mandates should be consistent across similar populations, that is, at the national level for all candidates.

4 | PEDIATRIC TRANSPLANTATION

Currently, COVID-19 vaccines are not available to most children around the world both because additional data are anticipated to support their use in some age groups and because children have not

been prioritized for vaccination since they tend to have less severe COVID-19 illness when compared with adults. This holds true for pediatric transplant recipients who have less severe COVID-19 illness as compared with adult transplant recipients.⁴³ Sadly, parental refusal of vaccination affects children around the world, and pediatric transplant centers frequently care for children who are denied vaccination by their guardians.⁴⁰ Given limitations of the available data, ethical arguments for vaccine mandates on the basis of maximizing net utility from transplantation are less robust in the pediatric context. At the same time, concerns about doing harm to pediatric transplant candidates are magnified, as these candidates lack agency and could be subjected to grave consequences based on their guardians' choices. Identifying an ethical and legal approach to pretransplant COVID-19 vaccination for children of vaccine-refusing guardians will be complex and affected by rapidly evolving data, state and national laws regarding child well-being and parental authority, and cultural norms, and is beyond the scope of this manuscript.

5 | OTHER ROLES, OTHER PATIENTS, OTHER VACCINES

The ethical arguments for COVID-19 vaccine mandates for either healthcare workers or transplant candidates might be extended in many directions. Transplant caregivers should seek to protect transplant recipients, and cocooning strategy of vaccinating close contacts is recommended for many vaccines. 44 However, transplant centers are not empowered to require caregivers to be vaccinated without imposing consequences harmful to candidates. Because caregiver vaccination status is not readily modifiable by the candidate, it is a less appropriate listing criterion than the candidate's own vaccination status, although both could be expected to improve candidate health, public health, and net utility from transplantation. With enormous strain on healthcare systems around the world from COVID-19, transplantation is not the only scarce healthcare resource. Whether a patient's vaccination status should figure in allocation of scarce hospital beds, ventilators, or COVID-19 therapies, and how, is quite complex. Vaccinated individuals have a more favorable prognosis at every phase of COVID-19 exposure and illness. This could be framed as a higher probability of survival justifying prioritization, or as a lower marginal benefit justifying de-prioritization. Unlike requiring vaccines for transplant candidates during pretransplant evaluation and listing, restricting access to other types of medical care based on vaccination status happens at the point of immediate need and offers the patient no opportunity to reconsider. Potential conflicts with autonomy, justice, and transparency are much greater in these scenarios, such that they must be considered separately from mandates for transplant candidacy. Finally, many of the same arguments presented for COVID-19 vaccine mandates for transplant candidates could be extended to all recommended vaccines. The magnitude of individual harms and harms to public health from the COVID-19 pandemic sets this virus apart, but all other vaccines recommended to transplant candidates are also safe and beneficial for

TABLE 1 Country-specific considerations for COVID-19 vaccine mandates from a limited selection of countries

Country	Transplant activity ⁴⁶ (transplants per 1 million population) ^a	Populations targeted for vaccination	Vaccine coverage ⁴⁵ (September 30, 2021) (doses per 100 people) ^b	Available vaccines	Current vaccine mandates	Comments
Australia	2019: 69	All adults ≥16 years	108	Oxford-AstraZeneca Pfizer-BioNTech Moderna	Healthcare worker vaccine mandates issued through state- level public health directives	Vaccine availability was initially a barrier to achieving desired vaccination rates, even among groups targeted for early distribution More recently, vaccination has been expanded to all adults and healthcare worker and other industry mandates have been issued Australia must consider whether to defer additional or booster doses until other parts of the Asia Pacific region and the world have access to initial vaccination
China	2019: 14 2020: 12.4	All adults and children \$12 years, with priority for healthcare workers; vaccination is encouraged for transplant candidates and recipients	158	Sinopharm-Beijing Sinovac CanSino Sinopharm-Wuhan Anhui Zhifei Longcom ZF2001 Minhai Biotechnology Co SARS-CoV-2 Vaccine Institute of Medical Biology of the Chinese Academy of Medical Sciences (Kunming)	No current mandates	Vaccine availability is not a barrier to achieving high vaccination rates for transplant groups Very low local COVID-19 incidence since March 2020 created low risk environment, decreased motivation for the population to be vaccinated, although current national strategy is driving a high rate of vaccinations in excess of 20 million doses per day Given low COVID-19 burden and high manufacturing capacity, China has been able to share more than 265 million doses of vaccines globally
Colombia	2019: 27	Healthcare workers, essential workers including teachers and institutional caregivers, adults with comorbidities	79	Oxford-AstraZeneca Pfizer-BioNTech Moderna Johnson & Johnson Sinovac	No current mandates	Vaccine availability has been a barrier to achieving desired vaccination rates, even among groups targeted for early distribution Vaccine is available for foreign citizens residing in Colombia or visiting the country who also meet eligibility criteria

(Continues)

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	Comments	A wave of COVID-19 infections from March to June, 2021 posed a barrier to upscaling vaccination efforts because of strain on healthcare infrastructure and efforts by the population to stay distanced. More recently, increased intervals between doses of two-dose vaccine series to achieve better lasting immunity have also slowed progress of "complete" vaccination Healthcare workers have experienced a high burden of COVID-19 infections, morbidity, and mortality during periods of high transmission. Healthcare worker vaccinations have been prioritized but not mandated Transplant centers follow NOTTO guidelines for vaccination, which encourage but do not mandate COVID-19 vaccines	Vaccination is mandatory for healthcare workers in Italy. Although legal challenges to the requirement may arise, the decree is thought to be consistent with Italy's constitution. The Italian strategy for non-healthcare personnel has focused on reducing severe COVID-19 illness and death to protect individuals and ease the burdens on a previously overwhelmed healthcare system. A position paper from the Italian Association for the Study of the Liver (AISF) supported priority vaccination for transplant recipients, ultimately placed in Category 1 on the basis of increased risk for severe illness with COVID-19. In some cases, caregivers were also able to be vaccinated ⁴⁷
	Current vaccine mandates	No current mandates for healthcare workers or transplant candidates; vaccination or negative testing is mandated for air travel	As of April 1, 2021, a national government emergency decree made COVID-19 vaccination mandatory for healthcare workers in Italy Those who refuse may either be re-assigned to duties with lower risk of transmission or suspended without pay for up to 1 year ⁶
	Available vaccines	Oxford-AstraZeneca Moderna Johnson & Johnson Gamaleya (Sputnik V) Bharat Biotech (Covaxin) Cadila Healthcare ZyCoV-D	Oxford-AstraZeneca Pfizer-BioNTech Johnson & Johnson
	Vaccine coverage ⁴⁵ (September 30, 2021) (doses per 100 people) ^b	49	140
	Populations targeted for vaccination	All adults ≥18 years, with priority for healthcare workers, older adults, and adults with medical comorbidities	Healthcare workers, older adults, and vulnerable people including transplant recipients ≥16 years in all regions, the regions of Italy are progressing through additional vaccine priority phases at different rates
	Transplant activity ⁴⁶ (transplants per 1 million population) ^a	2019: 9.3	2020; 57° 2020; 57°
	Country	India	Italy

(Continues)

Comments	South Korea has had a low rate of COVID-19 transmission and COVID-19 mortality, lessening the magnitude of harms/ benefits considerations related to vaccination. After emergence of the delta variant, transmission is increasing Vaccine availability is increasing following authorization of additional vaccine products and shipments of vaccine products from countries like the United States Government is planning to introduce a 'vaccine passport' strategy allowing vaccinated people to attend events without other restrictions, with the aim of increasing vaccination uptake	Vaccine availability had been a barrier to completing vaccination for groups targeted in early phases, including healthcare workers and adults ≥60, in part because of regulatory challenges. This has improved by the Sisonke Programme, a collaboration between the National Department of Health, South African Medical Research Council, Desmond Tutu Health Foundation, CAPRISA,
Current vaccine mandates	No current mandates	No current mandates, nor are mandates permitted by the South African Constitution
Available vaccines	Oxford-AstraZeneca Pfizer-BioNTech Moderna Johnson & Johnson	Pfizer-BioNTech Johnson & Johnson
Vaccine coverage ⁴⁵ (September 30, 2021) (doses per 100 people) ^b	121	29
Populations targeted for vaccination	All adults ≥18 years, with priority for healthcare workers and older adults	All adults ≥18 years
Transplant activity ⁴⁶ (transplants per 1 million population) ^a	2019: 84	2016: 6.6
Country	Republic of Korea	South Africa

(Continues)

to receive a vaccine must always be voluntary and made without any undue influence. The South African Constitution undoubtedly respects and protects such a decision

Based on our constitutional ethos, a person's decision workers initially vaccinated with Ad-CoV2

The government is considering a petition to give additional doses to transplant recipients, as well as to healthcare

Janssen, and Johnson & Johnson

(Continued)

TABLE 1

prominent anti-vaccination movement has limited vaccine vaccines, but has also begun to offer booster doses to its Countries with vaccine availability exceeding demand are in a position to share vaccine supply with other countries of ChAdOx1 vaccine, as well as doses of mRNA-based globally. The U.S. has moved to donate unused doses vaccination rates for transplant groups. Instead, a uptake, particularly in some parts of the country Vaccine availability is not a barrier to achieving high own vaccinated population Comments Multiple businesses, Mandates imposed and healthcare organizations organizations by individual Current vaccine expected to universities, defensible be legally mandates mandates Johnson & Johnson Available vaccines Pfizer-BioNTech Moderna /accine coverage⁴⁵ 2021) (doses per September 30, 100 people)^b 111 All adults and children Populations targeted ≥12 years, initially adults, and adults workers, older for healthcare comorbidities with priority with medical for vaccination 1 million population)^a Fransplant activity46 transplants per 2019: 123 2020: 121 States Country United

Data listed are for the most recent year that data are publicly available. For countries with data available for 2020, 2019 transplant rates are also listed to reflect pre-COVID-19 transplant activity. Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

^cUnpublished data from the Italian Health Ministry and update from National Transplant Center (CNT), Rome, Italy.

^bThe majority of available vaccines require a two-dose series for recipients to be considered fully vaccinated.

the candidate and the public health. After urgently needed policies around COVID-19 vaccination are addressed, mandates for routine vaccines should be considered using a similar ethical analysis.

6 | GLOBAL VACCINE EQUITY

Vaccine coverage and availability are vastly unequal between countries⁴⁵ (Table 1). Vaccine availability significantly modifies this ethical analysis, and mandatory vaccination for individuals who do not have access to vaccines is nonsensical. Which vaccines are available may subtly modify the analysis for some individuals based on safety and efficacy considerations, for example, for young women healthcare workers or transplant candidates offered adenovirus-vectored vaccines but preferring to wait for messenger ribonucleic acidbased vaccines to reduce the risk for thrombosis with thrombocytopenia syndrome. Beyond this analysis, there is an ethical imperative to immediately address global vaccine inequities. These inequities affect transplant professionals, candidates, and recipients, leaving many vulnerable to infection, restricted in their social and economic activity, or suffering because of exhausted healthcare resources. Lack of access to COVID-19 vaccines is also a barrier to building transplant capacity in low-income or middle-income countries, stalling advances toward global transplant equity. When vaccineadvantaged countries propose additional doses of COVID-19 vaccines for their less vulnerable citizens, or open vaccines to off-label and less regulated use, global vaccine disparities can be expected to widen. As transplant organizations consider vaccine mandates in countries where vaccine supply exceeds demand, these same organizations are obligated to advocate for global vaccine sharing to support counterparts in countries where demand for vaccines still far outpaces supply.

7 | CONCLUSION

Exploring individual- and public health-oriented ethical principles within the interconnected networks around healthcare workers and transplant candidates, we conclude that COVID-19 vaccine mandates for both groups are ethically justified. There is a strong justification for mandating COVID-19 vaccination for transplant professionals and all healthcare workers in any context where such mandates would be legal and would not be expected to drastically affect workplace equity. Similarly, there is a justification for mandating COVID-19 vaccination prior to transplant listing, as long as steps are taken to integrate justice, transparency, and patient autonomy in any policy. Although many healthcare workers may feel understandably angry and exasperated toward individuals who continue to refuse vaccination, vaccine mandates should not be imposed in anger, but in honor of the ethical imperatives to beneficence, non-maleficence, and stewardship that we have cited here. Finally, vaccine-advantaged countries must prioritize cooperation to rectify grave and unethical global vaccination disparities.

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No data were used in the production of this manuscript.

ORCID

Olivia S. Kates https://orcid.org/0000-0003-4381-0049

Peter G. Stock https://orcid.org/0000-0002-5806-0167

Michael G. Ison https://orcid.org/0000-0003-3347-9671

Patrizia Burra https://orcid.org/0000-0002-8791-191X

Jong Cheol Jeong https://orcid.org/0000-0003-0301-7644

Vivek Kute https://orcid.org/0000-0002-2854

Anji Wall https://orcid.org/0000-0002-7359-1337

REFERENCES

- World Health Organization. Landscape of observational study designs on the effectiveness of COVID-19 vaccination. who.int/ publications/m/item/draft-landscape-of-observational-studydesigns-on-the-effectiveness-of-covid-19-vaccination. Published May 18, 2021. Accessed May 23, 2021.
- Lytras T, Kopsachilis F, Mouratidou E, Papamichail D, Bonovas S. Interventions to increase seasonal influenza vaccine coverage in healthcare workers: a systematic review and meta-regression analysis. Hum Vaccin Immunother. 2016;12(3):671-681.
- Rucinski T. Delta will require COVID-19 vaccine for new employees. Reuters. May 14, 2021. https://www.reuters.com/world/us/delta
 -will-require-covid-19-vaccine-new-employees. Accessed June 1,
 2021
- Dickler J. Hundreds of colleges say COVID vaccines will be mandatory for fall 2021. CNBC. May 11, 2021. https://www.cnbc. com/2021/05/11/hundreds-of-colleges-to-require-covid-vaccines-for-fall-2021.html. Accessed June 1, 2021.
- Penn medicine to require all health system employees to receive COVID-19 Vaccine [press release]. Penn Medicine News, Penn Medicine. May 20, 2021.
- 6. Amante A. Italy makes COVID-19 vaccine mandatory for all health workers. March 31, 2021. Healthcare & Pharmaceuticals.
- Press TA. France passes law that makes a coronavirus health pass required for dining and travel. NPR. July 26, 2021. The Coronavirus Cricie
- 8. Calitz T. Constitutional rights in south africa protect against mandatory COVID-19 vaccination. *Health Hum Rights J.* hhrjournal. org/2021/04/constitutional-rights-in-south-africa-protect-again

- st-mandatory-covid-19-vaccination/. Published 2021. Accessed June 5, 2021.
- Kates OS, Stohs EJ, Pergam SA, et al. The limits of refusal: an ethical review of solid organ transplantation and vaccine hesitancy. Am J Transplant. 2021;21(8):2637-2645.
- Creitz C. Washington state man claims hospital refusing transplants to the unvaccinated. Fox News. https://www.foxnews.com/media/ washington-man-hospital-refusing-transplants-unvaccinated. Published August 19, 2021. Accessed August 30, 2021.
- 11. Gillon R. Defending the four principles approach as a good basis for good medical practice and therefore for good medical ethics. *J Med Ethics*. 2015;41(1):111-116.
- Association APH. Public Health Code of Ethics 2019. Association APH: 2019.
- 13. Vaughn L. *Bioethics: Principles, Issues, and Cases.* New York:Oxford University Press; 2020.
- Van Hooste WLC, Bekaert M. To be or not to be vaccinated? The ethical aspects of influenza vaccination among healthcare workers. Int J Environ Res Public Health. 2019;16(20):3981.
- Lee LM. Adding justice to the clinical and public health ethics arguments for mandatory seasonal influenza immunisation for health-care workers. J Med Ethics. 2015;41(8):682-686.
- Caplan A. Time to mandate influenza vaccination in health-care workers. Lancet. 2011;378(9788):310-311.
- Borges V, Isidro J, Macedo F, et al. Nosocomial outbreak of SARS-CoV-2 in a "Non-COVID-19" hospital ward: virus genome sequencing as a key tool to understand cryptic transmission. Viruses. 2021;13(4):604.
- Cheng VC, Fung KS, Siu GK, et al. Nosocomial outbreak of COVID-19 by possible airborne transmission leading to a superspreading event. Clin Infect Dis. 2021;73(6):e1356-e1364.
- 19. Craig-Schapiro R, Salinas T, Lubetzky M, et al. COVID-19 outcomes in patients waitlisted for kidney transplantation and kidney transplant recipients. *Am J Transplant*. 2021;21(4):1576-1585.
- Ravanan R, Callaghan CJ, Mumford L, et al. SARS-CoV-2 infection and early mortality of wait-listed and solid organ transplant recipients in England: a national cohort study. Am J Transplant. 2020;20(11):3008-3018.
- Kates OS, Haydel BM, Florman SS, et al. COVID-19 in solid organ transplant: a multi-center cohort study [published online ahead of print August 7, 2020]. Clin Infect Dis. doi: 10.1093/cid/ciaa1097
- 22. Mossad S. Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus: no cause for alarm. *Am J Transplant*. 2021;21(8):2908.
- 23. Boyarsky BJ, Chiang T-Y, Ou MT, et al. Antibody response to the Janssen COVID-19 vaccine in solid organ transplant recipients. *Transplantation*. 2021;105(8):e82-e83.
- Angelico R, Trapani S, Manzia TM, Lombardini L, Tisone G, Cardillo M. The COVID-19 outbreak in Italy: initial implications for organ transplantation programs. Am J Transplant. 2020;20(7):1780-1784.
- 25. Domínguez-Gil B, Coll E, Fernández-Ruiz M, et al. COVID-19 in Spain: transplantation in the midst of the pandemic. *Am J Transplant*. 2020;20(9):2593-2598.
- Shickle D. The ethics of public health practice: balancing private and public interest within tobacco policy. Br Med Bull. 2009:91:7-22.
- Centers for Disease Control and Prevention. Interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html. Published May 14, 2021. Accessed May 23, 2021.
- European Medicines Agency. Vaxzevria (previously COVID-19 Vaccine AstraZeneca).ema.europa.eu/en/medicines/human/ EPAR/vaxzevria-previously-covid-19-vaccine-astrazeneca. Published May 21, 2021. Accessed May 22, 2021.

- -AJT-
- Moniz MH, Townsel C, Wagner AL, et al. COVID-19 vaccine acceptance among healthcare workers in a United States medical center. medRxiv. 2021. doi:10.1101/2021.04.29.2029.21256186
- Chan ER, Jones LD, Redmond SN, et al. Use of whole-genome sequencing to investigate a cluster of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in emergency department personnel. Infect Control Hosp Epidemiol. 2021:1–3.
- Bestilleiro RS, Señaris DM, Rodríguez MJP, et al. Nosocomial infection outbreak due to SARS-COV-2 in a hospital unit of particularly vulnerable patients. *Int J Med Sci.* 2021;18(10):2146-2154.
- Carrera M, Lawler EC, White C. Population mortality and laws encouraging influenza vaccination for hospital workers. Ann Intern Med. 2021;174(4):444-452.
- Danziger-Isakov L, Kumar D. Vaccination of solid organ transplant candidates and recipients: guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant. 2019;33(9):e13563.
- Simon B, Rubey H, Treipl A, et al. Haemodialysis patients show a highly diminished antibody response after COVID-19 mRNA vaccination compared to healthy controls [published online ahead of print May 18, 2021]. Nephrol Dial Transplant. doi: 10.1093/ndt/ gfab179
- Lacson E, Argyropoulos CP, Manley HJ, et al. Immunogenicity of SARS-CoV-2 vaccine in dialysis [published online ahead of print April 22, 2021]. medRxiv. doi: 10.1101/2021.04.08.21254779
- 36. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. *JAMA*. 2021;325(21):2204.
- Cucchiari D, Egri N, Bodro M, et al. Cellular and humoral response after mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients. Am J Transplant. 2021;21(8):2727-2739.
- Mulley WR, Dendle C, Ling JEH, Knight SR. Does vaccination in solid-organ transplant recipients result in adverse immunologic sequelae? A systematic review and meta-analysis. J Heart Lung Transplant. 2018;37(7):844-852.

- Ou MT, Boyarsky BJ, Motter JD, et al. Safety and reactogenicity of 2 doses of SARS-CoV-2 vaccination in solid organ transplant recipients. *Transplantation*. 2021;105(10):2170-2174.
- Ladd JM, Karkazis K, Magnus D. Parental refusal of vaccination and transplantation listing decisions: a nationwide survey. *Pediatr Transplant*. 2013;17(3):244-250.
- 41. Jones MU, Carter CG, Cameron KL, Smith TK. The impact of vaccine refusal on physician office visits during the subsequent 12 months. *Mil Med*. 2017;182(9):e1810-e1815.
- Corey L, Beyrer C, Cohen MS, Michael NL, Bedford T, Rolland M. SARS-CoV-2 variants in patients with immunosuppression. N Engl J Med. 2021;385(6):562-566.
- 43. Goss MB, Galván NTN, Ruan W, et al. The pediatric solid organ transplant experience with COVID-19: an initial multi-center, multi-organ case series. *Pediatr Transplant*. 2021;25(3):e13868.
- Bitsori M, Galanakis E. Vaccine-preventable infection morbidity of patients with chronic kidney disease and cocoon vaccination strategies. Expert Rev Vaccines. 2015;14(10):1385-1395.
- Holder J. Tracking coronavirus vaccinations around the world. The New York Times. August 30, 2021.
- International Figures on Donation and Transplantation. Global Observatory on donation and transplantation. http://www.transplant-observatory.org. Published 2020. Accessed May 24, 2021.
- Russo FP, Piano S, Bruno R, et al. Italian association for the study of the liver position statement on SARS-CoV2 vaccination. *Dig Liver Dis.* 2021;53(6):677-681.

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