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Letter to Editor

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Post-HSCT COVID-19 Vaccination in Resource-Limited Settings: Why Adaptation Should Not Mean Compromise

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Editorial

Recipients of hematopoietic stem cell transplantation (HSCT) remain among the patients at highest risk for severe COVID-19 because vaccine responsiveness is frequently attenuated in the setting of delayed immune reconstitution, ongoing immunosuppression, graft-versus-host disease (GVHD), and prior exposure to B-cell–depleting therapy. For this reason, contemporary guidance from the European Society for Blood and Marrow Transplantation (EBMT)[1], the American Society of Hematology in collaboration with ASTCT(ASH/ASTCT)[2], and the National Comprehensive Cancer Network (NCCN)[3] supports vaccination of HSCT recipients beginning from about 3 months after transplant in clinically stable patients, together with repeated booster strategies in those at continued risk.

In real-life transplant programs, however, the challenge has never been limited to whether post-HSCT vaccination should be given. The harder question has been how to implement an evidence-based strategy when access to mRNA vaccines is inconsistent, cold-chain requirements are difficult, and booster schedules compete with financial and logistical constraints. This is precisely why the Iranian experience deserves broader attention. It offers not only data from a resource-limited environment, but also a coherent clinical framework for adapting international recommendations without abandoning scientific rigor.

One of the most instructive aspects of the Iranian data is the consistency across autologous and allogeneic HSCT settings. In a prospective open-label study in autologous HSCT recipients vaccinated 3 to 9 months after transplant, we showed that two doses of the recombinant receptor-binding domain–tetanus toxoid conjugated vaccine (PastoCovac) were safe and immunogenic. Mean immune status ratio (ISR) rose from 1.39 at baseline to 2.48 after the first dose and 3.73 after the second dose, while seropositivity increased to 81.6% and 93.3%, respectively. Importantly, no grade 3 adverse events were reported, and higher lymphocyte count as well as prior pre-transplant COVID-19 infection predicted stronger post-vaccination response[4]. These findings are clinically relevant because they suggest that even within the first post-transplant year, a protein-conjugated platform can generate a substantial humoral response in autologous recipients when access to more expensive platforms is limited.

We subsequently extended this line of inquiry by evaluating a 3-dose early vaccination strategy after allogeneic HSCT. In that prospective single-arm study, patients vaccinated between 3 and 12 months after transplant experienced a stepwise improvement in serologic response: ISR rose from 1.55 at baseline to 2.32 after the second dose and

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3.87 after the third dose, with seropositivity reaching 91.66% after the third dose and no grade 3–4 vaccine-related toxicity. Particularly notable was the association between female donor sex, higher donor ISR at the time of transplant, and stronger recipient response after vaccination, raising the provocative but biologically plausible concept that donor immunization may help shape recipient immune recovery and post-transplant vaccine responsiveness[5].

These data are reinforced by the randomized trial in autologous HSCT recipients comparing homologous and heterologous booster strategies. We found that after early RBD-TT priming, a heterologous inactivated booster generated a significantly higher humoral response than a homologous booster, with mean ISR increasing to 5.12 versus 3.42 and seropositivity reaching 100% versus 93.0%, respectively. Reactogenicity was somewhat more frequent in the heterologous arm, but no serious vaccine-related adverse events were identified[6]. For transplant physicians working in settings with fluctuating vaccine availability, this is more than an academic observation; it supports a practical immunization strategy that values flexibility without sacrificing efficacy.

The need for repeated dosing is further supported by the recent systematic review and meta-analysis. After a third vaccine dose, seroconversion among prior HSCT non-responders was 46.10%, and overall post-third-dose seropositivity in HSCT recipients reached 87.14%. After a fourth dose, overall seropositivity rose further to 90.04% in the HSCT group. These pooled results provide a strong evidence base for moving beyond a conventional 2-dose mindset in transplant recipients and support the view that additional doses are often rescue doses rather than optional boosters[7].

The broader policy context in Iran also matters. The Iranian consensus guidance developed during the pandemic emphasized that transplant-related COVID-19 recommendations must be adapted to local health-system limitations, donor logistics, and available resources rather than copied mechanically from high-income settings[8]. That principle remains should be actively considered in patients with ongoing immunosuppression, GVHD, recent anti-

highly relevant for vaccination policy. In many low- and middle-income countries, the question is not whether the ideal platform exists in theory, but whether a safe, scalable, non-live platform can be delivered repeatedly and on time. The Iranian studies suggest that the answer can be yes.

Another instructive point emerging from the autologous HSCT vaccine study is that pre-transplant exposure matters. In that trial, pre-HSCT COVID-19 infection and pre-HSCT vaccination were associated with better post-transplant humoral responses, and prior infection remained an independent predictor in multivariable analysis[4]. This observation deserves attention because it supports a more integrated view of transplant immunization: SARS-CoV-2 vaccination should not be seen solely as a post-transplant task, but as a continuum that begins before transplantation whenever feasible. This concept is also aligned with older transplant vaccinology literature showing that pre-transplant immunization of donors and recipients is often an underused opportunity for immunoprotection.

The Iranian experience outside vaccination studies also highlights the value of structured follow-up in vulnerable populations. In a one-year follow-up study of Wharton's jelly–derived mesenchymal stromal cell therapy for severe COVID-19, Saleh et al. documented no serious late safety signals, no tumor formation, and normalization of inflammatory markers after extended surveillance[9]. Although this was not a vaccine trial, it reflects a disciplined clinical approach that is equally important in post-HSCT vaccination programs: one should not assume that interventions used under constrained conditions are inherently inferior or unsafe, but should instead study them carefully and longitudinally.

In our view, several practical conclusions follow. First, vaccination should generally start at 3 months after HSCT in clinically stable recipients rather than being postponed in search of an ideal but often unattainable immune window. Second, in HSCT recipients, a 3-dose primary strategy is more rational than a traditional 2-dose approach, particularly in the first post-transplant year and especially after allogeneic transplantation. Third, a fourth dose

CD20 exposure, delayed lymphocyte recovery, or weak serologic response. Fourth, heterologous

boosting is not merely acceptable in resource-limited settings; based on current evidence, it may be advantageous. Finally, donor and recipient vaccination before transplantation deserves more deliberate consideration in allogeneic HSCT programs.

Table 1 summarizes the principal SARS-CoV-2 vaccine platforms relevant to HSCT practice, while Figure 1 proposes a pragmatic algorithm for post-HSCT COVID-19 vaccination in settings where ideal vaccine access cannot always be guaranteed.

The most important lesson from these studies is not that transplant programs in low-resource settings should accept less. It is the opposite. They should insist on vaccination strategies that are early, repeated, adaptable, and evidence-based. Our data show that meaningful post-HSCT protection can be achieved with accessible platforms, provided that clinicians use them thoughtfully, intensify schedules when needed, and remain attentive to host factors that predict response. That lesson is relevant far beyond Iran.

Table 1: Comparison of SARS-CoV-2 vaccine platforms in HSCT recipients

Vaccine platform	Examples	Immunogenicity in HSCT	Advantages	Limitations
mRNA	BNT162b2, mRNA-1273	Moderate to high, strongly time-dependent	Most robust international evidence base; preferred when available	Cold-chain, cost, and access constraints in many LMICs
Adenoviral vector	ChAdOx1-S, Ad26.COV2.S	Moderate	Simpler logistics than mRNA in some systems	Less extensively studied in HSCT; variable availability
Inactivated	BBIBP-CorV, CoronaVac	Low to moderate as primary platform; useful as booster	Accessible and easier to distribute in many LMICs	Usually requires repeated doses; lower immunogenicity than mRNA in many settings
Protein subunit / RBD-based	PastoCovac (Soberana 2 / RBD-TT conjugate)	Moderate to high with repeated dosing	Affordable, stable, non-live, practical for LMICs	Requires repeated dosing; less global HSCT experience than mRNA
Heterologous boosting	Mixed platform approach	Often superior to homologous boosting	Flexible and potentially more immunogenic when supply is inconsistent	May increase mild reactogenicity; optimal sequence still evolving
Additional doses (3rd/4th and beyond)	Platform-agnostic	Critical for many HSCT recipients	Rescues a substantial proportion of initial non-responders	Requires repeated access and follow-up

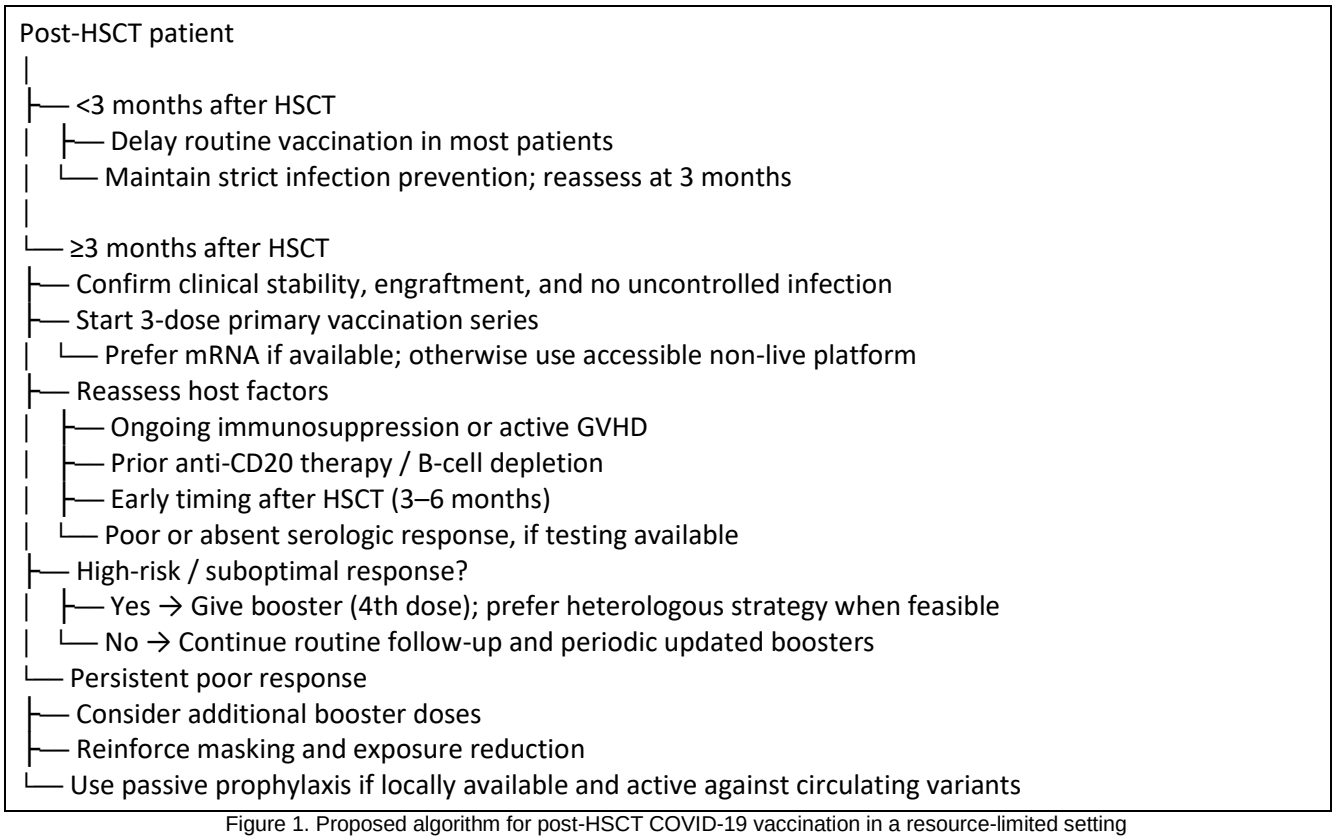

Figure 1. Proposed algorithm for post-HSCT COVID-19 vaccination in a resource-limited setting

CONFLICT OF INTEREST

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Ethics statement

This editorial is based on published studies and guideline documents and did not involve new human participant research.

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