Case Report

Brief Report: Declining Rates of SARS-CoV-2 Vaccine Uptake Among Patients With Thoracic Malignancies

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Clinical Practice Points

- Patients with primary thoracic malignancies are at increased risk of complications and death from COVID-19. Multiple studies have demonstrated humoral immune responses to SARS-CoV-2 vaccinations in patients with cancer, though the degree of immunogenicity varies. Over the last year the United States CDC has issued recommendations for multiple additional 'booster' vaccine doses for patients with cancer for protection against severe disease.
- In this study, we found that among 242 patients with primary thoracic malignancies who underwent initial vaccination against SARS-CoV-2, there was a marked decline in uptake of each subsequent additional vaccine dose. Specifically, among patients who received an initial mRNA-based vaccination series (mRNA-1273 or BNT162b2), 75% of eligible patients received the recommended third dose, 39% received the recommended fourth dose, and 5% received the recommended fifth dose at the time of data cutoff. Of note, we assessed serologic responses in a subset of patients receiving booster vaccinations and found that additional vaccinations increased humoral immunity, as expected.
- With the recent CDC recommendation of novel bivalent mRNA-based vaccine booster doses for all individuals over the age of 12, our findings highlight the need for further understanding of the reasons behind decreased vaccine uptake and emphasize the importance of counseling by providers regarding public health recommendations for patients with lung cancer.

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Introduction

Patients with thoracic malignancies are at increased risk of complications and death from SARS-CoV-2 infection.[1-3] While fatality rates among patients with lung cancer were initially reported between 22% and 41%,[4-7] outcomes have improved since the authorization of SARS-CoV-2 vaccines.[8] The efficacy of available vaccines is further supported by multiple studies documenting humoral immune responses to vaccination among patients with cancer.[1,9,10] Factors shown to potentially affect serologic response include age, smoking status, vaccine type, chemotherapy administration, and long-term corticosteroid use, but data remain mixed.[1,2,9,10]

Because of risk factors inherent to immunocompromised patients and demonstration of waning serologic response in the months following initial vaccination,[11] the Centers for Disease Control (CDC) has recommended additional vaccine doses to confer optimal protection for this patient population, according to authorizations made by the FDA on August 12, 2021, September 22, 2021, and March 29, 2022. Of note, the FDA authorization on August 12, 2021 was in reference to moderately or severely immunocompromised individuals, and there was a variable interpretation of what constituted sufficiently immunosuppressed to qualify. Here, we sought to investigate the humoral immune response to SARS-CoV-2 vaccination and rates of administration of recommended additional doses over the last year in our cohort of 242 patients with thoracic malignancies.

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Materials and Methods

Study Population and Data Abstraction

These data represent a subset analysis of the published CANVAX prospective cohort at Massachusetts General Hospital[10] approved by the Mass General Brigham Institutional Review Board Clinical (2021P000746). All participants received at least 1 SARS-CoV-2 vaccine. Eligibility for the current analysis required a diagnosis of a thoracic malignancy at study entry. After informed consent, participants completed a standardized questionnaire querying demographics, medical history, SARS-CoV-2 exposures and infection, and vaccination information. Additional clinical and epidemiologic information was abstracted from the electronic medical record. The data cutoff was July 1, 2022.

Determination of Eligibility for Additional Vaccine Dose(s)

Eligibility for additional vaccine dose(s) following the initial series was defined by whether patients met the following criteria during the time window from FDA Emergency Use Authorization to data cutoff: Alive, not on hospice, and eligible for subsequent vaccine dose based on timing from last dose received or last infection with SARS-CoV-2. Specific recommendations from public health officials regarding eligibility for each additional vaccine dose are summarized in Supplemental Table 1. These guidelines reflect real-time CDC advisory based upon FDA Emergency Use Authorization.

Antibody Assays

Serum antibody assays were performed with the Roche Elecsys Anti–SARS-CoV-2 S assay (Roche Diagnostics, Indianapolis, IN), at the CLIA-certified Massachusetts General Hospital core clinical laboratory, as previously described.[10]

Statistical Analysis

Relationships between clinical and epidemiological factors and the level of antispike antibodies (Figure 1A-C, Supplemental Figure 1A-C) were compared using one-way ANOVA tests.

Results

Patient Characteristics

Between April 29 and July 20, 2021, 1001 patients with solid-organ or hematologic cancers were enrolled in the CANVAX cohort study, as previously published.[10] To examine a more homogeneous patient population, we focused on the subset of patients with thoracic malignancies (n = 242) enrolled in the CANVAX study. Table 1 summarizes clinical and pathologic characteristics. Among this cohort, 53% (n = 128) received BNT162b2 (Pfizer), 35% (n = 86) received mRNA-1273 (Moderna), and 12% (n = 28) received Ad26.COV2.S (J&J/Janssen) for the initial vaccination series, defined as 2 doses of BNT162b2/mRNA-1273 or one dose of Ad26.COV2.S. Within the initial vaccination window (defined as 90 days before or after the first vaccine dose), 72% (n = 173) received systemic cancer-directed therapy. The 2 most common types of systemic therapy during the initial vaccination window were tyrosine kinase inhibitors in 31% of patients (TKI; n = 76) and chemotherapy in 27% (n = 66). Fifteen percent of patients (n = 36) received immune checkpoint inhibitor (IO) monotherapy and 13% of patients (n = 31) received a combination of chemotherapy and IO.

Antispike Antibody Titers Following SARS-CoV-2 Vaccine(s)

We first examined the relationships between SARS-CoV-2 antibody concentration and multiple clinical and epidemiological factors of relevance specifically to patients with thoracic malignancies. The median time from initial vaccination to first antispike antibody testing was 78 days (range 3-251). Twenty-eight percent of patients (n = 68) had antispike antibody testing performed on at least 2 time points. Consistent with previously published data,[12] we found numerically higher antispike antibody titers following mRNA-1273 initial vaccine series compared to other vaccine types, with the median titer of 1157 U/mL (range 3.27-45,500; Figure 1A, $P = .59$). No significant difference was seen in antispike antibody titer among patients by concurrent administration of systemic therapy (Figure 1B, $P = .36$), tumor stage (Figure 1C, $P = .69$), genotype (Supplemental Figure 1A, $P = .99$), or histology (Supplemental Figure 1B, $P = .74$). However, patients with at least 4 prior lines of therapy had statistically significant slightly lower mean antispike antibody levels compared to patients with 0 to 3 prior lines of therapy (Supplemental Figure 1C, $P = .01$).

Rate of Administration of Additional Recommended SARS-CoV-2 Vaccine Doses

Given public health recommendations for additional vaccine doses (Supplemental Table 1), we analyzed the rate of uptake for additional vaccine doses in our cohort. Of note, FDA authorization of the first additional vaccine dose on August 12, 2021 was restricted to immunocompromised individuals, and there has been a variable interpretation of whether patients with thoracic malignancies met these criteria. We, therefore analyzed our data using 2 approaches. First, we analyzed vaccination rates using a more inclusive approach, defining vaccine eligibility according to FDA authorizations on August 8, 2021, September 22, 2021, and March 29, 2022. Thus, individuals would have been potentially eligible for a maximum of 5 total vaccine doses depending on the timing of their vaccinations. Of 214 patients who received a full initial vaccine series of either mRNA-1273 or BNT162b2, 95% (n = 204) were eligible for the third dose (Figure 2A). Among eligible patients, 75% (n = 154) received a third dose, 39% (n = 59) received a fourth dose, and 5% (n = 1) received a fifth dose prior to data cutoff. We observed a similar dropoff in subsequent vaccination rates among the 28 patients who received an initial vaccine dose of Ad26.COV2.S (Supplemental Figure 2). Of note, 46% (n = 71) of patients who received a third vaccine dose following the initial mRNA vaccine series received their third dose prior to the September 22, 2021 FDA recommendation for additional booster doses for nonimmunocompromised patients, suggesting that in real-world practice that such patients had been (self) designated as immunocompromised for the purposes of COVID-19 vaccinations.

Next, we analyzed vaccination rates using a more restrictive approach, defining vaccine eligibility according to FDA authoriza-

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Figure 1 Antispike antibody titers following mRNA-1273, BNT-162b2, and Ad26.COV2.S vaccines in patients with lung cancer. (A-C) Quantitative SARS-CoV-2 spike IgG/A/M antibody concentration in U/mL of serum for 242 patients with lung cancer following initial complete vaccination series for SARS-CoV-2 stratified by initial vaccine type (A), type of systemic therapy received within 90 days of first vaccine dose (B) and by tumor stage (C); IO, immunotherapy; TKI, tyrosine kinase inhibitor. (D) Immunogenicity following third vaccine doses for 53 patients with lung cancer who received mRNA-based initial vaccine series (mRNA-1273 and BNT-162b2) and underwent repeat serologic testing after third vaccine dose.

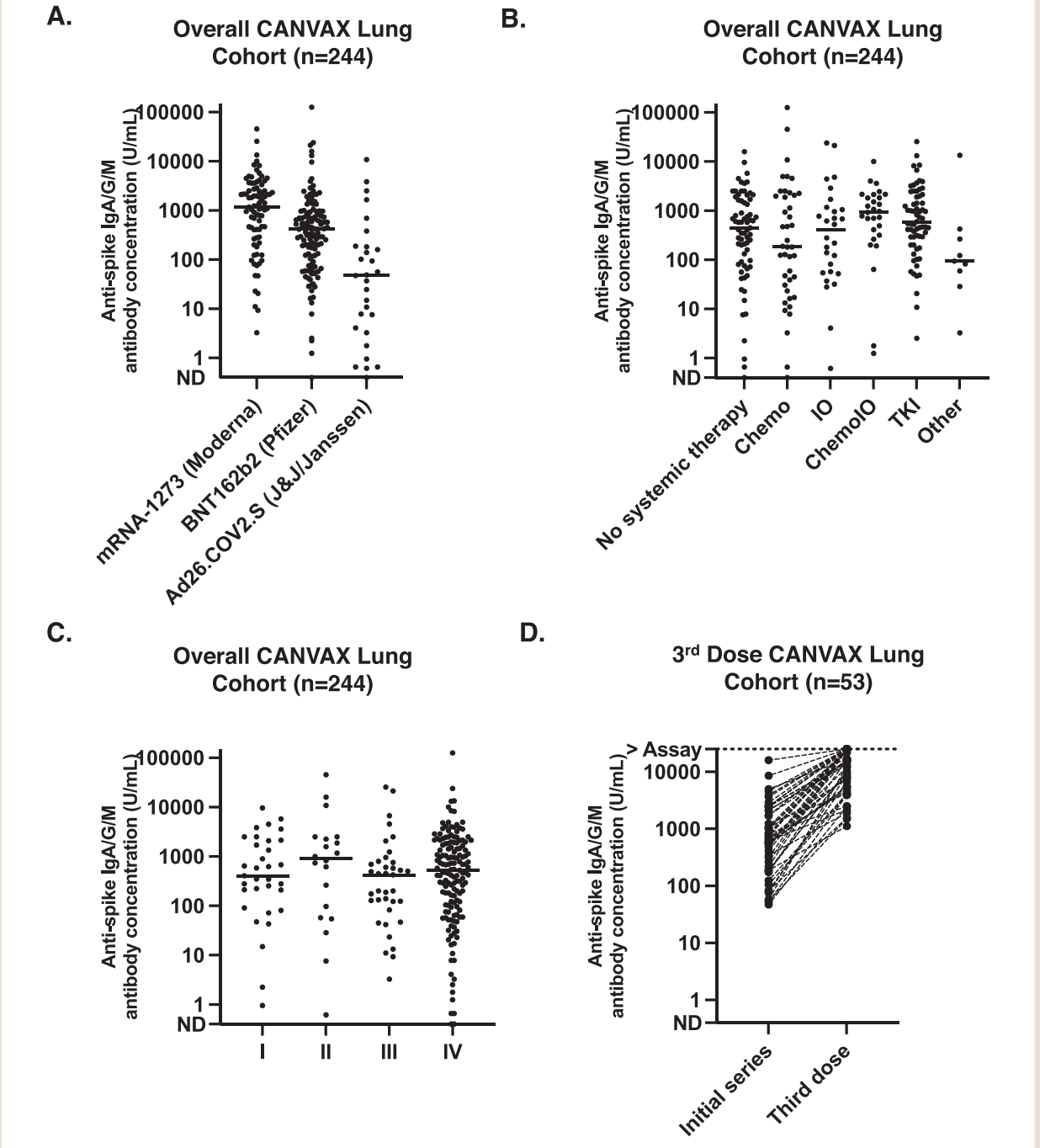

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Table 1 Demographics and Clinical Information

Total N		242
Characteristic		
Age, median (range)		68 (19-90)
Sex, No. (%)		
	Female	139 (57)
	Male	103 (43)
Ethnicity, No. (%)	Hispanic/Latinx	1 (0)
	Not Hispanic/Not Latinx	215 (89)
	Unavailable	26 (11)
Race, No. (%)	American Indian	1 (0)
	Asian	18 (8)
	Black	3 (1)
	Native Hawaiian / Pacific Islander	1 (0)
	Unavailable	9 (4)
	White	210 (87)
Tobacco use, No. (%)	Current	12 (5)
	Former	150 (62)
	Never	78 (32)
	Unknown	2 (1)
Cancer Stage, No. (%)	I	33 (14)
	II	20 (8)
	III	37 (15)
	IV	152 (63)
Histologic subtype, No. (%)	Adenocarcinoma	181 (75)
	Squamous	18 (7)
	Small cell	16 (7)
	Large cell neuroendocrine	3 (1)
	Thymic cancer	7 (3)
	Mesothelioma	3 (1)
	Unknown	14 (6)
No. prior therapies, median (range)[a]		1 (0-8)
Molecular genotype, No. (%)	KRAS	28 (12)
	ALK	22 (9)
	EGFR	55 (22)
	MET	6 (2)
	RET	7 (3)
	ROS1	5 (2)
	BRAF	3 (1)
	HER2	3 (1)
	Other/unknown	114 (47)
Initial vaccination window (Within 90 d of first vaccine dose)		
Systemic therapy, No. (%)[b]	Chemotherapy	66 (27)
	Immune checkpoint inhibitor	36 (15)
	Chemotherapy-immunotherapy	31 (13)
	Tyrosine kinase inhibitor	76 (31)
	Other	14 (6)
	No systemic therapy	69 (28)
Radiation therapy		49 (20)
Cancer-related surgery		20 (8)
Vaccine type		
Initial vaccine series, No. (%)	mRNA-1273 (Moderna)	86 (35)
	BNT162b2 (Pfizer)	128 (53)
	Ad26.COV2.S (J&J/Janssen)	28 (12)

[a] Relative to the initial vaccination window.
[b] 28% of patients (n = 69) received >1 line of therapy during the initial vaccination window.

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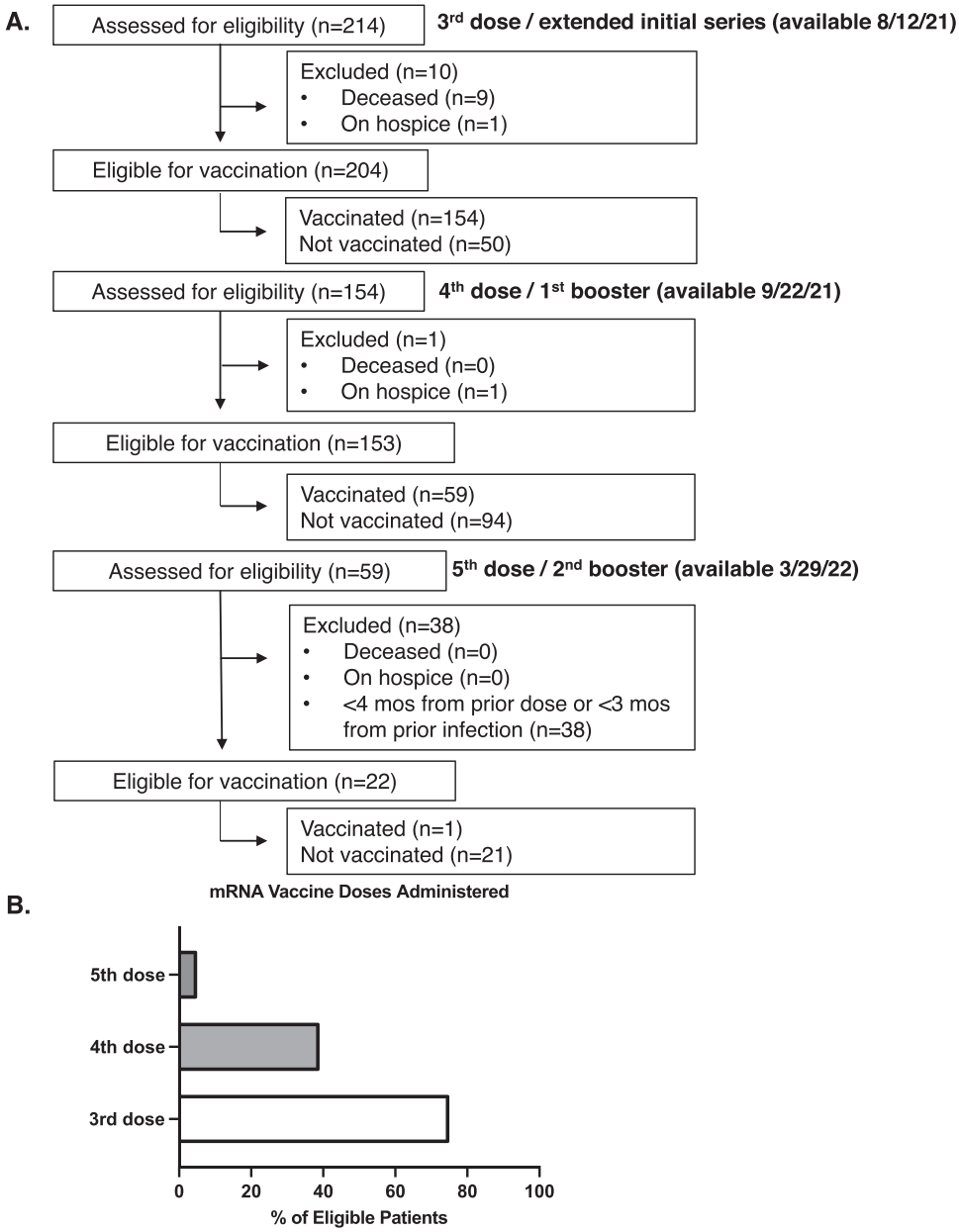
Figure 2 Rates of administration of recommended additional doses of SARS-CoV-2 vaccines following initial vaccination series with mRNA-based vaccines (mRNA-1273 and BNT-162b2). (A) Consort diagram outlining patient eligibility within defined cohort. Eligibility dates utilized for third (August 2, 2021), fourth (September 22, 2021), and fifth (March 29, 2022) vaccine doses determined based on FDA emergency use authorization and associated CDC press releases as detailed in Supplemental Table 1. (B) Rates of administration of additional vaccine doses among eligible patients. Data cutoff July1, 2022.



tions on September 22, 2021, and March 29, 2022. Under this approach, patients with lung cancer would have been eligible for a maximum of only 4 total doses prior to data cut-off. Using these parameters for our analysis and excluding patients who received a third additional dose prior to September 22, 2021, we found that 64% (n = 85) of eligible patients received a third dose and 36% (n = 28) of eligible patients received the fourth recommended dose (Supplemental Figure 3).

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Serial Antibody Testing and Breakthrough SARS-CoV-2 Infections in Vaccinated Cohort

Of 55 patients in our cohort who underwent repeat antispike antibody measurements within 10 to 90 days following additional vaccine doses, all demonstrated an increase in antispike titer (Figure 1D; Supplemental Figure 1D). Median antispike antibody titer following additional vaccine dose was 13,276 U/mL (range 110-25000). Of our 242-patient cohort, there were 40 documented SARS-CoV-2 infections since the beginning of the SARS-CoV-2 pandemic (Supplemental Table 2). Of these, 83% (n = 33) occurred following the initial vaccination series and were considered breakthrough infections (Supplemental Figure 4). All but 4 breakthrough infections occurred >90 days following the most recent vaccine dose. Eighty-one percent (n = 27) of patients with breakthrough SARS-CoV-2 infections experienced documented symptoms during infection, 9% (n = 3) were hospitalized for their infections, and one patient died of complications related to SARS-CoV-2 infection (Supplemental Table 2).

Discussion

To our knowledge, this is among the largest cohorts investigating SARS-CoV-2 vaccination in patients with thoracic malignancies. Building upon our prior pan-cancer analysis,[10] we demonstrated that factors specific to patients with thoracic malignancies such as tumor histology, genotype, and stage did not significantly affect antispike antibody responses. Among patients who had repeat serologic testing following additional vaccine doses, antispike antibody levels rose in all patients. While sample size precluded formal comparisons between antispike titers and breakthrough infections, only 9% of vaccinated individuals with thoracic malignancies were hospitalized with COVID-19. This suggests that patients who received the initial vaccination series were largely protected from serious COVID-19 infection regardless of clinical factors.

Despite accumulating evidence of the importance of vaccination in this patient population, we found a dramatic decrease in adherence to the vaccination schedule with each subsequent recommended dose—even when using variable definitions of vaccine eligiblity. Among recipients of 3 or more vaccine doses, most received their last vaccine >6 months prior to the data cutoff. While rates of vaccination were lower than expected, they appear to be higher than those observed in the general population.[13] Reasons for declining vaccine administration rates are not known, though limited press coverage of recent public health announcements and confusion over messaging may have contributed. Indeed, in a recent survey of healthy adults, only approximately half reported awareness of bivalent COVID-19 booster availability.[14] Safety concerns from patients, changes in health status, or prior breakthrough infections may also be affecting patients' decisions about pursuing additional doses. It is noteworthy that despite lower than anticipated vaccination adherence, rates of hospitalization and subsequent mortality due to COVID-19 in our population were lower than those observed in initial reports early in the pandemic, suggesting that even the initial vaccination series provides important protection. Nonetheless, given the limited follow-up duration of this study and the potential for waning immunity, emphasis should continue to be placed on ensuring that patients are up-to-date on vaccination recommendations while prospective studies determine the optimal number and frequency of vaccinations.

One limitation of our study is that self-reporting of subsequent vaccine doses was not required per protocol. It is therefore possible that we did not capture complete vaccination records for all patients. To address this possibility, we used a combination of available patient-reported data and a review of electronic medical records, including access to local pharmacy vaccination records. We also acknowledge that reporting the rate of administration of additional vaccine doses among eligible patients assumes shared definitions of immunocompromised status and consistent adherence to changing public health recommendations. In order to address this limitation, we have included in our analysis a calculation of the vaccine uptake rate both assuming and excluding eligibility for the initial dose for immunocompromised patients (August 2021; Supplemental Table 1). In clinical practice, patients with active malignancy have been largely designated as "immunosuppressed" for the purpose of vaccine eligibility; however, even with our more conservative approach to the analysis, we still found a substantial drop off in vaccination rates.

Subsequent to our analysis, novel bivalent mRNA boosters have been recommended for all individuals aged 12 and over after completion of primary series and/or booster doses of monovalent vaccines. This is in the context of emerging data demonstrating low neutralization of more recent Omicron subvariants even among individuals with prior infection and updated vaccination with monovalent booster doses.[15] Therefore, our observation of declining booster vaccine uptake despite clinical benefit following the initial vaccine series highlights an urgent need for providers to counsel patients about public health guidance and the availability of heterologous vaccines for the broadest possible protection.

CRediT authorship contribution statement

Catherine B. Meador: Conceptualization, Investigation, Data curation, Formal analysis, Writing – original draft. **Vivek Naranbhai:** Conceptualization, Investigation, Data curation, Formal analysis, Writing – review & editing. **Grace Hambelton:** Data curation. **Julia Rivera:** Data curation. **Christopher S. Nabel:** Data curation, Writing – review & editing. **Rebecca Lewinsohn:** Data curation. **Mustafa Sakhi:** Data curation. **Alejandro B. Balazs:** Conceptualization, Funding acquisition, Writing – review & editing. **A. John Iafrate:** Conceptualization, Funding acquisition, Writing – review & editing. **Justin F. Gainor:** Conceptualization, Funding acquisition, Writing – review & editing.

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Disclosure

JFG has consulted and/or had advisory roles for Agios, Amgen, Array BioPharma, Blueprint Medicines Corporation, BMS, Genentech, Gilead Sciences, Jounce Therapeutics, Lilly, Loxo Oncology, Merck, Mirati, Silverback Therapeutics, Sanofi, GlydeBio, Moderna Therapeutics, Oncorus, Regeneron, Takeda, Theravance; has an immediate family member who is an employee with equity in Ironwood Pharmaceuticals; and has received Honoraria from Merck, Novartis, Pfizer, and Takeda; and research funding from Adaptimmune, ALX Oncology, Array BioPharma, AstraZeneca, Blueprint Medicines Corporation, BMS, Genentech, Jounce Therapeutics, Merck, Novartis, and Tesaro. CSN receives royalties from ThermoFisher (formerly Life Technologies) and Cambridge Epigenetix and has stock ownership in Opko Health. The remaining authors have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2023.01.007.

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