

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Featured Article

Contents lists available at ScienceDirect

The American Journal of Surgery



journal homepage: www.elsevier.com/locate/amjsurg

Partial COVID-19 vaccination associated with reduction in postoperative mortality and SARS-CoV-2 infection



Nikhil K. Prasad^{a,b}, Brian R. Englum^a, Minerva Mayorga-Carlin^{a,b}, Douglas J. Turner^{b,a}, Shalini Sahoo^{a,b}, John D. Sorkin^{c,d}, Brajesh K. Lal^{a,b,*}

^a Department of Surgery, University of Maryland School of Medicine, Baltimore, MD, USA

^b Surgery Service, Veterans Affairs Medical Center, Baltimore, MD, USA

^c Baltimore Veterans Affairs Medical Center, Geriatric Research Education and Clinical Center, Baltimore, MD, USA

^d Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA

ARTICLE INFO

Keywords: COVID-19 Surgery Postoperative mortality Postoperative pneumonia Vaccination

ABSTRACT

Background: There are currently no data to guide decisions about delaying surgery to achieve full vaccination. *Methods:* We analyzed data from patients undergoing surgery at any of the 1,283 VA medical facilities nationwide and compared postoperative complication rates by vaccination status.

Results: Of 87,073 surgical patients, 20% were fully vaccinated, 15% partially vaccinated, and 65% unvaccinated. Mortality was reduced in full vaccination vs. unvaccinated (Incidence Rate Ratio 0.77, 95% CI [0.62, 0.94]) and partially vaccinated vs. unvaccinated (0.75 [0.60, 0.94]). Postoperative COVID-19 infection was reduced in fully (0.18 [0.12, 0.26]) and partially vaccinated patients (0.34 [0.24, 0.48]). Fully vaccinated compared to partially vaccinated patients, had similar postoperative mortality (1.02, [0.78, 1.33]), but had decreased COVID-19 infection (0.53 [0.32, 0.87]), pneumonia (0.75 [0.62, 0.93]), and pulmonary failure (0.79 [0.68, 0.93]). *Conclusions*: Full and partial vaccination reduces postoperative complications indicating the importance of any

Conclusions: Full and partial vaccination reduces postoperative complications indicating the important degree of vaccination prior to surgery.

1. Introduction

As of November 17, 2021, 58.9% of the population in the United States (US) was fully vaccinated while an additional 9.8% was partially vaccinated against COVID-19, having received only one of a two-dose vaccine.¹ Among vaccinated individuals in the US, vaccination has significantly lowered COVID-19 infection rates and adverse outcomes compared to unvaccinated individuals.² Real world data suggests that vaccination is associated with lower rates of hospital admission and mortality for COVID-19.3,4 The Pfizer-BioNTech and Moderna mRNA vaccines, both a two-dose regimen, were the first to gain FDA approval for use in the US.⁵ Based on antibody titres, the Centers for Disease Control and Prevention (CDC) have found that maximum protection against COVID-19 develops two weeks after the second dose.⁶ We have previously shown data that mRNA vaccines against SARS-CoV-2 are associated with reduced rates of postoperative COVID-19 and pulmonary complications.⁷ However, there are no data comparing the effectiveness of being fully vaccinated vs. partially vaccinated. Patients and surgeons have no guidance on whether the risks associated with

delaying surgical procedures are outweighed by the benefits of waiting the recommended two weeks after the second dose of vaccination to allow for maximum immune protection. This question is particularly important in the context of elective and urgent procedures. We hypothesized that any degree of vaccination would be protective against the known sequalae of COIVD-19 infection. We further hypothesized that being fully vaccinated would offer more protection than being partially vaccinated.

The Veterans' Health Administration (VA) provides care to more than nine million individuals throughout the US.⁸ We analyzed data from patients undergoing surgery (elective, urgent, and emergency) at any of the 1,283 VA medical facilities nationwide and compared post-operative complication rates among fully vaccinated, partially vaccinated, and unvaccinated, patients.

https://doi.org/10.1016/j.amjsurg.2022.03.038

Received 2 December 2021; Received in revised form 9 March 2022; Accepted 23 March 2022 Available online 8 April 2022 0002-9610/© 2022 Elsevier Inc. All rights reserved.

^{*} Corresponding author. Department of Surgery, University of Maryland, 22 South Greene Street, Baltimore, MD, 21201, USA. *E-mail address:* blal@som.umaryland.edu (B.K. Lal).

2. Methods

2.1. Participants and study design

We conducted a multicenter study of patients who underwent a surgical procedure at any of the 1,283 VA medical facilities nationwide between January 6, 2021 and May 5, 2021. Outcome data were collected through June 5, 2021, to allow at least 30 days of follow-up in all patients. We compared outcome measures in three groups of patients defined by their COVID-19 mRNA vaccine status: 1) fully vaccinated, 2) partially vaccinated, and 3) unvaccinated. The University of Maryland Institutional Review Board and the Baltimore VA Research and Development Committee reviewed and approved the study and waived the requirement for informed consent.

Vaccination status was defined as follows:

- 1. Fully vaccinated group. Patients who underwent surgery at least 14 days after receiving two full doses of a COVID-19 mRNA vaccine (Pfizer BioNTech or Moderna).
- 2. Partially vaccinated group. Per CDC standards, a second dose was not considered effective until two weeks had elapsed after the second dose.⁶ Thus, patients could fall within this partially vaccinated group if:
 - a. The first dose of the vaccine was administered less than 14 days before surgery and the second dose was administered after surgery or never at all, or
 - b. The first dose was administered at least 14 days before surgery and second dose any time after surgery or never at all, or
 - c. The first dose was administered at least 14 days before surgery and second dose less than 14 days before surgery
- 3. Unvaccinated group. Patients who did not receive any vaccination before surgery constituted the unvaccinated group.

2.2. Inclusion and exclusion criteria

The exposure for our primary analysis was vaccination status before undergoing elective, urgent or emergency surgery, resulting in a total of 3 groups (groups 1, 2 and 3 listed above). The exposure for our secondary analysis was also vaccination status, however the partially vaccinated group was divided into three distinct subgroups, resulting in a total of five groups (groups 1, 2a, 2b, 2c and 3 listed above).

Only one surgery per patient was included in the analysis: the first surgery after vaccination or the first surgery within our study period for unvaccinated patients. Patients receiving the single-dose Janssen vaccine and patients with a history of preoperative COVID-19 infection were excluded. Patients who had COVID-19 (i.e., SARS-CoV-2 infection) any time before surgery were excluded as were patients who had a positive test the day of surgery. COVID-19 was defined as a positive SARS-CoV-2 test result (by PCR or antigen testing) on the day of, or any time before surgery. Follow up for post-operative COVID infection started the day after the surgical procedure. Testing for SARS-CoV-2 was performed as per guidance issued by the VA National Surgery Office. Particularly early in the pandemic, and in the case of emergencies, we did not require that patients have a documented negative result to be included in our study, just that they not have a documented positive test. It is therefore possible, particularly early in the pandemic, that some of the patients included in our study had a prior asymptomatic COVID-19 infection. As a result, we cannot infer whether a patient had asymptomatic COVID, as asymptotic COVID patients are presumably less likely to test. We also excluded patients when data necessary for analysis was unknown, i.e., if they were missing data on race, BMI, CPT code, case urgency, or anesthesia type.

2.3. Data collection

Data were obtained from the VA Corporate Data Warehouse, VINCI

(VA Informatics and Computing Infrastructure), which stores all data entered into the VA's electronic medical record, known as CPRS (Computerized Patient Record System).⁹ The VA updates and continuously checks the data for accuracy in near real time, and supplements CPRS with external medical records whenever Veterans receive medical treatment outside the VA. Data obtained described the patient, the vaccine, the surgery, and the postoperative outcome. Patient data included age, sex, race (white, black, and other), ethnicity (Hispanic/Latino or not), body mass index (BMI), smoking status (current, former, or never), the American Society of Anesthesiologists (ASA) physical status classification,¹⁰ and medical comorbidities, defined by the International Classification of Disease 10th revision (ICD-10) codes. Pre-surgical comorbidity was quantified by the Elixhauser comorbidity index (ECI), a composite of 30 comorbidities existing within two years of the date of surgery.¹¹ Higher ECI values indicate a higher burden of comorbidities. Vaccine data included vaccine type and the date of administration of each dose. Data describing the surgery included the five-digit Current Procedural Terminology (CPT) code describing the procedure in its entirety, case urgency (elective, urgent, or emergency), and type of anesthesia used (general or other, a composite of sedation, spinal, epidural and local). The first two digits of the CPT code were then used to describe the organ system undergoing surgery.

2.4. Outcome measures

Our co-primary outcome measures were (1) all-cause mortality and (2) evidence of postoperative SARS-CoV-2 infection, defined as a positive SARS-CoV-2 PCR or antigen test after surgery. Our four secondary outcome measures included (1) pulmonary failure defined as a composite of need for mechanical ventilation, acute respiratory distress syndrome, or acute respiratory failure; (2) pneumonia; (3) arterial thrombotic complications defined as a composite of myocardial infarction, ischemic stroke, or arterial thrombosis; and (4) venous thromboembolic events defined as a composite of deep vein thrombosis or pulmonary embolism. The secondary outcome measures were identified by examining ICD-10 codes and post-surgery admission, discharge, outpatient, and transfer notes. ICD-10 and CPT codes were used to identify mechanical ventilation. For all outcome measures, events that occurred more than 30 days after the index procedure were ignored.

2.5. Statistical analysis

We compared the demographic, clinical, and procedural characteristics across the vaccination groups (fully vaccinated, partially vaccinated, and unvaccinated) using frequencies and percentages, means and standard deviations (SD), or medians and interquartile ranges (IQR), as appropriate. Comparisons of categorical data were performed using Pearson's χ^2 test. One-way analysis of variance (ANOVA) was used to compare normally distributed continuous data across the three vaccination groups, and Kruskal-Wallis one-way analysis of variance by rank (H test) was used for non-normally distributed continuous data.

Poisson regression was used to compare the postoperative complication rates in the three vaccination groups. We used six distinct models, each one with one of our two primary or four secondary outcome measures as the dependent variable. All models were adjusted for age, sex, BMI, ASA class, ECI, case urgency, CPT system, and use of general anesthesia. Adjusted incidence rate ratios (IRR) with 95% confidence intervals (CI) quantified differences in postoperative complication rates between vaccination groups. Adjusted rates for each outcome were calculated based on a composite patient that reflected the average value of all covariates.

A two-tailed p-value ≤ 0.05 was considered statistically significant. Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

The American Journal of Surgery 224 (2022) 1097-1102

3. Results

surgery, and 4,258 receiving it less than 14 days before surgery.

A total of 95,179 patients underwent surgery at the VA between January 6, 2021 and May 5, 2021 (Fig. 1). The 7,203 patients who tested positive for COVID-19 before surgery were excluded from this analysis, as well as 512 patients who received the single-dose Janssen vaccine, and 401 patients for whom data necessary for the analysis was unknown. Of the 87,063 patients who were included in the analysis, 17,117 (20%) were fully vaccinated prior to surgery, 13,455 (15%) were partially vaccinated, and 56,491 (65%) received no vaccine prior to surgery. Among the partially vaccinated patients, 4,680 received both doses before surgery, but their second dose was administered less than 14 days before surgery, with 4,517 receiving it at or beyond 14 days before

Compared to unvaccinated patients, both fully vaccinated and partially patients were more likely to be older (p < 0.001), male (p < 0.001), have a higher burden of comorbid conditions (higher ECI, p < 0.001), and undergo elective surgery (p < 0.001) (Table 1). Compared to partially and fully vaccinated patients, unvaccinated patients were more likely to be obese (p < 0.001). The distribution of surgical procedures was similar in the three groups. (Supplementary Fig. 1).

Multivariable models adjusted for age, sex, BMI, ASA class, ECI, case urgency, CPT system, and use of general anesthesia demonstrated that vaccination was associated with a significant reduction in mortality compared to unvaccinated patients, for both fully vaccinated (Incidence Rate Ratio, IRR 0.77 95% Confidence Interval, CI [0.62, 0.94]) and partially vaccinated patients (IRR 0.75 [0.60, 0.94]) (Table 2). Fully and

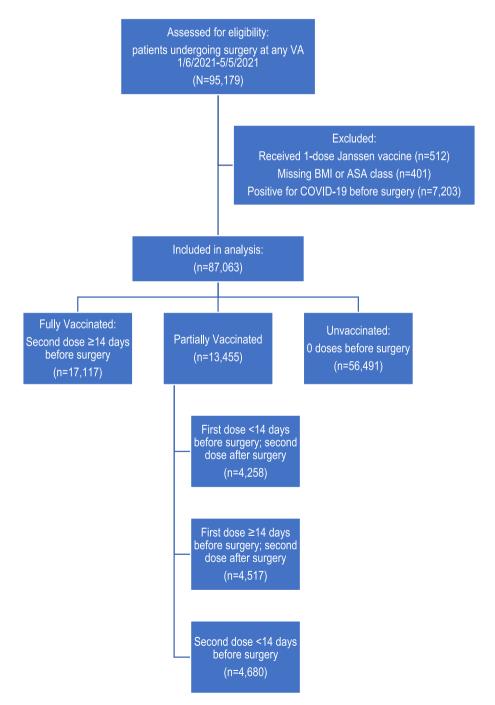


Fig. 1. Flowchart for patient selection of the analytic cohort.

Table 1

Demographic, clinical, and procedural characteristics of patients by COVID-19
vaccine group (unvaccinated, partially, or fully vaccinated).

	Unvaccinated	Vaccine Group	Fully Vaccinated	p-value
		Partially Vaccinated		
	N = 56,491	N = 13,455	N = 17,117	
Age, years (median [IQR])	64 [53, 72]	70 [62, 74]	72 [66, 76]	< 0.001
Sex (Male)	49,869 (88.3)	12,421 (92.3)	16,076 (93.9)	< 0.001
Hispanic or Latino Race	3,975 (7.3)	945 (7.2)	1,001 (6.0)	$< 0.001 \\ < 0.001$
White	40,477 (76.0)	9,657 (76.0)	12,548 (77.3)	
Black	11,517 (21.6)	2,785 (21.9)	3,364 (20.7)	
Other	1,292 (2.4)	267 (2.1)	322 (2.0)	
Body Mass Index (mean \pm SD)	30.0 ± 6.1	29.9 ± 6.1	29.7 ± 5.9	< 0.001
Underweight	749 (1.3)	160 (1.2)	210 (1.2)	
Normal weight	10,387 (18.4)	2,613	3,373	
0	10 001 (04 0)	(19.4)	(19.7)	
Overweight	19,291 (34.2)	4,650	6,071	
Obese	26,064 (46.1)	(34.6) 6,034	(35.5) 7,465	
ODESC.	20,004 (40.1)	6,034 (44.8)	(43.6)	
Smoking status		(11.0)	(10.0)	< 0.001
Current Smoker	12,469 (23.1)	2,578	2,793	20.001
	,,	(19.8)	(16.9)	
Former Smoker	23,224 (42.9)	6,273	8,457	
		(48.2)	(51.1)	
Never Smoker	18,397 (34.0)	4,159	5,317	
		(32.0)	(32.1)	
Elixhauser comorbidity index (median [IQR])	3 [0, 10]	6 [0, 13]	7 [0, 15]	< 0.001
General anesthesia	28,847 (51.1)	6,278	7,676	< 0.001
0		(46.7)	(44.8)	0.001
Case urgency	44.011 (70.0)	10.015	14 20 4	< 0.001
Elective	44,811 (79.3)	10,815	14,394	
Urgent	10 245 (10 1)	(80.4) 2 356	(84.1) 2.452	
Urgent	10,245 (18.1)	2,356 (17.5)	2,452 (14.3)	
Emergency	1,435 (2.5)	(17.3) 284 (2.1)	(14.3) 271 (1.6)	
ASA Class	_,	, (<u></u>)		< 0.001
I	913 (1.6)	58 (0.4)	46 (0.3)	
II	14,490 (25.7)	2,210	2,023	
		(16.4)	(11.8)	
III	36,243 (64.2)	9,780	12,935	
		(72.7)	(75.6)	
IV	4,817 (8.5)	1,399	2,101	
	00 (0 1)	(10.4)	(12.3)	
V Orange Constants	28 (0.1)	8 (0.1)	12 (0.1)	.0.001
Organ System ^a	2 6 97 (6 4)	1 066 (7 0)	1 404 (9 7)	< 0.001
Cardiovascular Gastrointestinal	3,627 (6.4)	1,066 (7.9) 2,227	1,484 (8.7) 2 464	
Gasuomestinai	10,753 (19.0)	(16.6)	2,464 (14.4)	
Integumentary	3,679 (6.5)	866 (6.4)	1,012 (5.9)	
Musculoskeletal	11,873 (21.0)	2,476	2,860	
	,	(18.4)	(16.7)	
Neurological	3,757 (6.7)	766 (5.7)	1,024 (6.0)	
Ophthalmological	8,754 (15.5)	2,713	4,100	
-		(20.2)	(24.0)	
Respiratory	2,581 (4.6)	579 (4.3)	679 (4.0)	
Urology	8,182 (14.5)	2,140	2,714	
		(15.9)	(15.9)	
Other	3,285 (5.8)	622 (4.6)	780 (4.6)	

ASA class, American Society of Anesthesiologists classification system for the assessment of a patient's pre-anesthesia medical co-morbidities. IQR, Inter-Quartile Range.

^a Organ system is defined by the first two digits of the CPT code.

partially vaccinated patients also had decreased rates of postoperative COVID-19 infection compared to unvaccinated patients (IRR 0.18 [0.12, 0.26] and 0.34 [0.24, 0.47], respectively), as well as decreased rates of pulmonary failure (IRR 0.67 [0.59, 0.76] and 0.84 [0.74, 0.95]). Compared to unvaccinated patients, a significant reduction in pneumonia was observed in fully vaccinated patients (IRR 0.77 [0.66, 0.90]), but not among partially vaccinated patients (IRR 1.02 [0.88, 1.20]). Although fully vaccinated patients had similar mortality (IRR 1.02 [0.78, 1.33]) and venous thrombotic events (IRR 0.84 [0.69, 1.02]) compared to partially vaccinated patients, they had a decreased rate of COVID-19 infections (IRR 0.53 [0.32, 0.87]), pneumonia (IRR 0.75 [0.62, 0.92]), pulmonary failure (IRR 0.79 [0.68, 0.93]), and arterial thrombotic complications (IRR 0.83 [0.71, 0.98]).

After dividing partially vaccinated patients into three sub-groups based on the number of doses received and the time between vaccination and surgery, we did not find consistent differences or a gradient in the effect size in postoperative death, pneumonia, pulmonary failure, arterial, or venous thrombotic complications (Supplementary Tables 1 and 2). However, a gradient could be appreciated in postoperative COVID-19 infection rates, with infection rates being highest among unvaccinated patients (0.81 infected per 100 procedures, 95% CI [0.64, 1.04]), lower across the partially vaccinated sub-groups, and lowest among fully vaccinated patients (0.14 infected per 100 procedures [0.09, 0.23], Supplementary Table 1). Going from unvaccinated to 1 dose <14 days before surgery, the decrease in COVID-19 infection was significant (IRR 0.60 [0.39, 0.94]); we also observed a significant decrease going from 1 dose <14 days before surgery to 1 dose \ge 14 days before surgery (IRR 0.35 [0.16, 0.80]); the other differences were numerically consistent though not statistically significant (Supplementary Table 2).

4. Discussion

This is the first report that compares the effectiveness of full versus partial COVID-19 mRNA vaccine dosage in preventing postoperative complications. Both fully and partially vaccinated patients have a lower risk of postoperative mortality, COVID-19 infection, and pneumonia compared to unvaccinated individuals. In addition, fully vaccinated individuals have a lower risk of COVID-19 infections, pneumonia, and pulmonary failure compared to partially vaccinated patients, but their risk of mortality is similar. These data indicate the value of receiving even partial vaccination prior to surgery, and they provide the first evidence-based guidance for patients and surgeons struggling to decide whether to postpone time-sensitive elective or urgent surgery to achieve fully vaccinated status.

There are at least three mechanisms by which vaccination might diminish the adverse effects of the Sars-CoV-2 infection. First, vaccination reduces the probability that a patient becomes infected with the Sars-CoV-2 virus. Second, by stimulating the immune system to produce neutralizing antibodies to the Sars-CoV-2 virus, vaccination can reduce the severity of COVID-19 if a patient develops the infection in the perioperative period. Third, major surgery, particularly surgery that includes general anesthesia, is known to suppress innate immune response to infective agents. Vaccination, by pre-conditioning the immune system to mount a vigorous response to Sar-CoV-2, may offset some of the immune suppression brought about by major surgery. Although full and partial vaccination may interact with these mechanisms in different ways, our study suggests that vaccination status should be considered when determining the timing of elective, and possibly urgent surgery.

We have previously reported significant elevations in mortality, reoperation, readmission, and pulmonary complications among individuals who test positive for COVID-19 in the postoperative period.¹² The reduction in postoperative COVID-19 infection shown in this report may be responsible for the lower mortality rate after a single dose of mRNA vaccine. These findings are corroborated by a recent report from the Israeli vaccination drive, in which a single dose of vaccine was 72%

Table 2

Primary and secondary outcomes stratified by vaccination status.

30-day Adverse Events	Unvaccinated (N = 56,491)		Partially Vaccinated (N $= 13,455$)		Fully Vaccinated (N = 17,117)		Fully Vaccinated vs. Unvaccinated		Partially Vaccinated vs. Unvaccinated		Fully Vaccinated vs. Partially Vaccinated	
	Events	Adjusted Rate (%) [95% CI]	Events	Adjusted Rate (%) [95% CI]	Events	Adjusted Rate (%) [95% CI]	IRR [95% CI]	p-value	IRR [95% CI]	p-value	IRR [95% CI]	p- value
All-cause Mortality	398	0.46 [0.35, 0.61]	92	0.35 [0.25, 0.49]	127	0.35 [0.26, 0.49]	0.77 [0.62, 0.94]	0.01	0.75 [0.60, 0.94]	0.01	1.02 [0.78, 1.33]	0.89
Postoperative COVID-19	420	0.81 [0.64, 1.04]	37	0.28 [0.18, 0.41]	26	0.14 [0.09, 0.23]	0.18 [0.12, 0.26]	<0.001	0.34 [0.24, 0.47]	<0.001	0.53 [0.32, 0.87]	0.01
Pneumonia	733	1.35 [1.15, 1.58]	205	1.38 [1.13, 1.69]	204	1.04 [0.85, 1.28]	0.77 [0.66, 0.90]	0.001	1.02 [0.88, 1.20]	0.76	0.75 [0.62, 0.92]	0.004
Pulmonary failure	1,306	1.82 [1.60, 2.08]	291	1.53 [1.29, 1.81]	298	1.22 [1.03, 1.44]	0.67 [0.59, 0.76]	<0.001	0.84 [0.74, 0.95]	0.008	0.79 [0.68, 0.93]	0.005
Arterial thrombotic complications	872	1.23 [1.04, 1.45]	277	1.35 [1.11, 1.64]	312	1.13 [0.93, 1.37]	0.92 [0.80, 1.05]	0.20	1.10 [0.96, 1.26]	0.17	0.83 [0.71, 0.98]	0.03
Venous thrombotic events	637	1.21 [1.03, 1.42]	193	1.39 [1.14, 1.70]	213	1.17 [0.96, 1.43]	0.97 [0.82, 1.13]	0.68	1.15 [0.98, 1.35]	0.09	0.84 [0.69, 1.02]	0.08

IRR, incidence rate ratio.

CI, confidence interval.

All estimates were calculated through multivariable Poisson regression models adjusted for age, sex, BMI, ASA class, ECI, case urgency, CPT system, and use of general anesthesia.

Pulmonary failure is a composite of mechanical ventilation, acute respiratory distress syndrome, and acute respiratory failure.

Arterial thrombotic complications include myocardial infarction, ischemic stroke, and arterial thrombosis.

Venous thromboembolic events include deep vein thrombosis and pulmonary embolism.

effective at reducing mortality after two weeks.³ Our sensitivity analysis showed a reduction in postoperative COVID-19 infections even in patients receiving the vaccine less than two weeks before surgery. This suggests that surgeons should consider offering vaccination during preoperative evaluation, even if they are unwilling to postpone surgery for four weeks to allow patients to achieve fully vaccinated status.

The relationship between the rate of postoperative COVID-19 infection and number of vaccine doses received in our surgical patients is consistent with recommendations from the Pfizer and Moderna clinical trials on non-surgical patients.^{13,14} Fully vaccinated patients (i. e. those who had received their second dose at least two weeks prior to surgery) had the lowest rates of pulmonary complications and COVID-19 infections. Partially vaccinated patients had partial protection, with pulmonary complication rates that were higher than fully vaccinated patients but lower than the unvaccinated. The higher incidence of pulmonary complications may be direct sequelae of COVID-19 infection, or an indirect opportunistic infection after long-term pulmonary damage from prior COVID-19. The dose response we found lends credibility to our findings. It is, however, important to note that even a single dose of vaccine reduced the rate of postoperative COVID-19 infection. This is in line with recent reports suggesting that, among individuals who have previously been infected with COVID-19, a single dose of vaccine induces a much stronger antibody response, and greater protection than those who have never been exposed to the virus.^{15–17}

In addition to confirming our previous report, which noted that two doses of mRNA vaccine were associated with a lower rate of pulmonary failure compared to no vaccination,⁷ the current report finds that being partially vaccinated is associated with reduction in the rates of pulmonary failure. Given the reduction in mortality rates associated with being partially vaccinated, it is possible that there are other systemic benefits to SARS-CoV-2 viral mRNA exposure through vaccination. COVID-19 can produce a severe systemic inflammatory response,^{18,19} which may be mitigated in part by even a single dose of vaccine.

We attempted to provide detailed information on the decreasing risk of postoperative complications as a function of time from initial vaccination dose to guide clinicians on when surgery might be safest when a time-sensitive procedure does not allow the four weeks needed to achieve full vaccination status. Unfortunately, limited numbers of events in these more granular groups did not permit for robust comparisons, and we will have to wait for future studies to provide insight on the benefits of waiting a specific number of weeks after initial vaccination to proceed to surgery.

Our analysis has several limitations. First, we were not able to obtain the causes of death in the patients we followed. This information might allow a better characterization of why patients in the non-vaccinated group had a higher mortality rate, but it does not negate the finding that full or partial vaccination status was associated with a reduction in all-cause mortality in patients undergoing surgery. Our study is not intended to be construed as the definitive body of work on this topic, however, the results can be used to guide future studies.

Our study is not a randomized clinical trial and as a result may be subject to unrecognized residual bias despite our use of statistical adjustment to account for differences between our three study groups. Concern about the potential presence of residual bias is applicable to every non-randomized observational study that has investigated the COVID-19 pandemic. Despite this concern we believe that our study makes an important contribution to our understanding of a disease that, given the known benefits of vaccination, precludes the conduct of randomized studies in which patients are randomized to receive, or not receive, SARS-CoV-2 vaccination.

Future studies will need to examine the impact of single-dose vaccines (Janssen) on surgical outcomes, as these patients were beyond the scope of the current study. Secondly, due to limited number of events, we were unable to analyze elective surgeries separate from emergency surgeries. However, we minimized the possibility of confounding by adjusting for ECI, ASA class, CPT system, and case urgency. Finally, this analysis relied on administrative data, which is influenced by patterns of coding within different institutions.

5. Conclusions

Our data show, at least for the variants that circulated early in the pandemic, in patients who undergo surgery, that one vaccination provides more protection against COVID-19 related adverse events than none, and two vaccinations provide more protection than one vaccination. Postoperative pulmonary complications and mortality are significantly reduced in patients fully or partially vaccinated before surgery, with fully vaccinated patients having the greatest protection. Our analysis of VA data provides support for two doses of presurgical SARS-CoV-2 vaccination and ideally waiting two weeks after the second dose before preforming surgery. Where possible, patients should be encouraged to receive one, and when possible two doses of COVID-19 vaccination prior to surgery. However, even a single dose of vaccine was associated with reduced rates of postoperative COVID-19 infection and mortality. These data will allow patients and surgeons to make an informed decision about delaying elective or urgent surgery to achieve full vaccination, but additional research is needed to more clearly define the risks and benefits of this critical choice. Despite the push by the CDC and Federal government, there remains a considerable reluctance to vaccine uptake. Data continues to show that vaccines are effective against emerging variants of COVID-19 among patients who undergo surgery. Until such time as a new study indicates otherwise, when surgeons think about the timing of surgery, they should incorporate this information into their decision-making process. Where possible, patients should be encouraged to receive one, and when possible two doses of COVID-19 vaccination prior to surgery. Additionally, due to the emergence of new variants, including delta and omicron and emerging information indicating the effects of first doses of vaccines are reduced after 6-8 months, health experts should still advocate for vaccination prior to surgeries.

Funding

Veterans Affairs awards HSRD C19-20-407, RRD RX000995 and CSRD CX001621, and NIH awards NS080168, NS097876 and AG000513 (BKL); National Institutes of Health awards AG028747, DK072488, and Baltimore VA Medical Centre GRECC (JDS); National Institutes of Health T32 AG00262 (NKP).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2022.03.038.

References

- Centers of Disease Control and Prevention. COVID-19 Vaccinations in the United States; 2021. Published online https://covid.cdc.gov/covid-data-tracker/#vacc inations.
- Moghadas SM, Vilches TN, Zhang K, et al. The impact of vaccination on Coronavirus disease 2019 (COVID-19) outbreaks in the United States. *Clin Infect Dis.* 2021;30. https://doi.org/10.1093/cid/ciab079. Published online January.
- Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med. 2021;24. https://doi.org/ 10.1056/NEJMoa2101765. Published online February.
- Torjesen I. Covid-19: first doses of vaccines in Scotland led to a substantial fall in hospital admissions. BMJ. 2021;372:n523. https://doi.org/10.1136/bmj.n523.
- FDA. Vaccines and Related Biological Products Advisory Committee December 10, 2020. Meeting Briefing Document- FDA; 2020.
- 6. When you've been fully vaccinated | CDC. https://www.cdc.gov/coronavirus/2 019-ncov/vaccines/fully-vaccinated.html; March 23, 2021.
- Prasad NK, Lake R, Englum BR, et al. COVID-19 vaccination associated with reduced post-operative SARS-CoV-2 infection and morbidity [published online ahead of print]. Ann Surg. 2021. https://doi.org/10.1097/SLA.00000000005176, 10.1097/SLA.00000000005176.
- 8. Veterans Affairs Health Administration. U.S. Department of Veterans Affairs. Published https://www.va.gov/health/; 2020. Accessed September 15, 2020.
- U.S. Department of Veterans Affairs. VA Informatics and computing infrastructure (VINCI) homepage. https://www.hsrd.research.va.gov/for_researchers/vinci/; 2018. Accessed September 28, 2020.
- Mayhew D, Mendonca V, Murthy BVS. A review of ASA physical status historical perspectives and modern developments. *Anaesthesia*. 2019;74(3):373–379. https:// doi.org/10.1111/anae.14569.
- Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11): 1130–1139.
- Prasad NK, Lake R, Englum BR, et al. Increased complications in patients who test COVID-19 positive after elective surgery and implications for pre and postoperative screening. *Am J Surg.* 2021. https://doi.org/10.1016/j.amjsurg.2021.04.005, 0(0).
- Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med; 2020. https://doi.org/10.1056/nejmoa2034577. Published online.
- Baden LR, El Sahly HM, Essink B, et al. *Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine*. N Engl J Med; 2021. https://doi.org/10.1056/nejmoa2035389. Published online.
- Manisty C, Otter AD, Treibel TA, et al. Antibody response to first BNT162b2 dose in previously SARS-CoV-2-infected individuals. *Lancet*. 2021;397:1057–1058. https:// doi.org/10.1016/S0140-6736(21)00501-8, 10279.
- Krammer F, Srivastava K, Alshammary H, et al. Antibody responses in seropositive persons after a single dose of SARS-CoV-2 mRNA vaccine. N Engl J Med. 2021;384 (14):1372–1374. https://doi.org/10.1056/nejmc2101667.
- Bradley T, Grundberg E, Selvarangan R, et al. Antibody responses after a single dose of SARS-CoV-2 mRNA vaccine. N Engl J Med. 2021;384(20):1959–1961. https://doi. org/10.1056/nejmc2102051.
- Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, transmission, diagnosis, and treatment of Coronavirus disease 2019 (COVID-19): a review. JAMA - J Am Med Assoc. 2020;324(8):782–793. https://doi.org/10.1001/jama.2020.12839.
- Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26(7):1017–1032. https://doi.org/10.1038/s41591-020-0968-3.