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ORIGINAL ARTICLE

Effectiveness of first, second, and third COVID-19 vaccine doses in solid organ transplant recipients: A population-based cohort study from Canada

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Abstract

Limited data exists on the effectiveness of a third COVID-19 vaccine dose in solid organ transplant recipients. We conducted a population-based cohort study using linked healthcare databases from Ontario, Canada to answer this question. We included solid organ transplant recipients ($n = 12{,}842$) as of December 14, 2020, with follow-up until November 28, 2021. We used an extended Cox proportional hazards model with vaccination status, including BNT162b2, mRNA-1273, and ChAdOx1 vaccines, modeled as a time-dependent exposure. Individuals started in the unvaccinated category (reference) and could contribute person-time to first, second, and third doses. Over a median follow-up of 349 days, 12.7% ($n = 1632$) remained unvaccinated, 54.1% ($n = 6953$) received 3 doses, and 488 (3.8%) tested positive for SARS-CoV-2 (of which 260 [53.3%] had a clinically important outcome [i.e., hospitalization or death]). Adjusted vaccine effectiveness against infection was 31% (95% CI: 2, 51%), 46% (95% CI: 21, 63%), and 72% (95% CI: 43, 86%) for one, two, and three doses. Vaccine effectiveness against clinically important outcomes was 38% (95% CI: 4, 61%), 54% (95% CI: 23, 73%), and 67% (95% CI: 11, 87%). Vaccine effectiveness in solid organ transplant recipients is lower than the general population, however, vaccine effectiveness improved following a third dose.

KEYWORDS
clinical research / practice, infection and infectious agents – viral: SARS-CoV-2/COVID-19, solid organ transplantation, vaccine

Abbreviations: CCM, Case and Contact Management System; CIHI, Canadian Institute for Health Information; CORR, Canadian Organ Replacement Register; OHIP, Ontario Health Insurance Plan; RPDB, Registered Persons Database.

Kyla L. Naylor and Sang Joseph Kim contributed equally to this work.

1 | INTRODUCTION

Compared to the general population, solid organ transplant recipients may have increased morbidity and mortality from SARS-CoV-2 infection.[1–6] The introduction of the COVID-19 vaccine has significantly reduced morbidity and mortality in the general population.[7,8] However, solid organ transplant recipients take immunosuppressive drugs which may alter their immune response to vaccines.[9] Studies have shown reduced immunogenicity after two doses of the COVID-19 vaccine in solid organ transplant recipients, but significant improvement after three doses.[10,11] Several population-based studies have examined vaccine effectiveness against infection and severe outcomes after two doses of the COVID-19 vaccine, finding lower vaccine effectiveness estimates in solid organ transplant recipients compared to the general population.[12–14] For example, Callaghan et al., found that solid organ and islet transplant recipients with two vaccine doses had an increased risk of testing positive for SARS-CoV-2 and only the ChAdOx1 (not the BNT162b2) vaccine was associated with reduced mortality.[12] Bell et al., examined vaccine effectiveness in kidney transplant recipients and found that the vaccine effectiveness after two doses was 39% against infection and 40% against hospitalization.[13] In the general population, vaccine effectiveness estimates against infection and severe outcomes with two doses of the COVID-19 vaccine have been greater than 90% (pre-Omicron era),[8,15] with additional protection after three doses.[16,17] However, limited real-world data exist on the effectiveness of third doses of the COVID-19 vaccine in solid organ transplant recipients. Therefore, we conducted a population-based cohort study to evaluate this question in solid organ transplant recipients.

2 | MATERIALS AND METHODS

2.1 | Design and setting

Using linked administrative healthcare databases from Ontario, Canada held at ICES (ices.on.ca) we conducted a population-based cohort study. These datasets were linked using unique encoded identifiers and analyzed at ICES. ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. We reported this study following the reporting of studies conducted using observational routinely collected health data (RECORD) statement (Table S1).[18]

2.2 | Data sources

We used the Canadian Organ Replacement Register (CORR) and the Ontario Health Insurance Plan (OHIP) to identify solid organ transplant recipients. CORR collects information on all Canadians receiving a solid organ transplant while OHIP provides information on physician diagnostic and billing codes. Information on demographics and vital status was obtained from the Registered Persons Database (RPDB). We used the Canadian Institute for Health Information (CIHI) Discharge Abstract Database for information on diagnostic and procedural codes used during hospitalization, while CIHI Same Day Surgery provided information on same day surgeries. We obtained information on residing in a long-term care home from the Continuing Care Reporting System and from the Ontario Drug Benefits database. To obtain information on public health unit regions, we used postal codes and the Statistics Canada Postal Code Conversion File Plus (version 7B). We used 2016 census data to obtain information on the following social determinants of health (information obtained using dissemination areas and is at the ecological level): neighborhood income quintile, essential worker quintile (i.e., proportion employed as non-healthcare essential workers and therefore not able to work from home), persons per dwelling quintile (i.e., average number of people living in a dwelling), and self-identified visible minority quintile (i.e., proportion of the population identifying as a visible minority).

Information on all Ontario COVID-19 vaccinations are recorded in Ontario's centralized vaccination system, COVaxON. We identified recipients who were SARS-CoV-2-positive using the ICES-derived COVID-19 Integrated Testing Dataset which contains all available COVID-19 PCR results in Ontario and is derived from three data sources: the Ontario Laboratories Information System, distributed testing data from laboratories within the COVID-19 diagnostic network and the Case and Contact Management System (CCM). We used the CCM system (i.e., Ontario's central data repository for COVID-19 reporting in Ontario) to capture deaths and hospitalizations associated with a positive SARS-CoV-2 test result. See Table S2 for further details on databases and coding definitions used.

2.3 | Solid organ transplant recipients

We included individuals with a functioning solid organ transplant (i.e., kidney, heart, liver, lung, pancreas, and multiorgan transplants) from Ontario, Canada as of December 14, 2020 (first date that the COVID-19 vaccine was available in Ontario). Our databases capture solid organ transplants from the 1980s onwards. The cohort entry date (index date) was December 14, 2020, for all solid organ transplant recipients. We excluded recipients who died prior to the cohort entry date, aged <18 years, experienced graft failure (applicable to kidney transplant recipients only and defined as return to maintenance dialysis) prior to cohort entry, were not eligible for OHIP (i.e., were not a Canadian citizen or landed immigrant that lives most of the year in Ontario)[19] or tested positive for SARS-CoV-2 during the 90 days prior to cohort entry.

2.4 | COVID-19 vaccine

We included two mRNA vaccines (BNT162b2 [Pfizer-BioNTech] and mRNA-1273 [Moderna]) and an adenovirus vector vaccine (ChAdOx1

[Oxford-AstraZeneca]). On December 14, 2020, vaccine priority for mRNA vaccines in Ontario, Canada was initially given to healthcare workers, individuals aged ≥80 years, adults residing in congregate settings, and Indigenous communities.[20] On April 16, 2021, solid organ transplant recipients were prioritized to receive their first dose of the COVID-19 vaccine. Unlike the general population, it was recommended that the timing of the second dose for solid organ transplant recipients was not delayed (i.e., dosing interval on vaccine product monograph was followed). Therefore, it was recommended that the second dose be given 3 weeks after the first dose for BNT162b2, 4 weeks after for mRNA-1273 and 4–12 weeks after for ChAdOx1 nCoV-19. Solid organ transplant recipients who received ChAdOx1 nCoV-19 for their first dose could receive BNT162b2, mRNA-1273, or ChAdOx1 nCoV-19 as their second dose. Ontario stopped administrating the first doses of ChAdOx1 nCoV-19 on May 11, 2021,[21] and in June Canada's National Advisory Committee on Immunization recommended that if an individual received ChAdOx1 nCoV-19 as the first dose it was better to mix with an mRNA vaccine for the second dose.[22] On August 17, 2021, all solid organ transplant recipients became eligible for a third dose.[23] It was recommended in Ontario that individuals who received ChAdOx1 nCoV-19 for their first and second doses received an mRNA vaccine for their third dose.[24] For the third dose it was recommended that the full dose of mRNA-1273 (100 μg) or BNT162b2 (30 μg) be given.[25]

2.5 | SARS-CoV-2 infection and clinically important outcomes

Our primary outcome was PCR-confirmed SARS-CoV-2 infection. During the study period, there were no restrictions on receiving a SARS-CoV-2 test in solid organ transplant recipients. At the beginning of the study period (early 2021), B.1.1.7 (Alpha) was the dominant strain of SARS-CoV-2 and by July, B.1617.2 (Delta) became the dominant strain.[26] At the end of the study period (November 28, 2021) Omicron was estimated to represent <1% of SARS-CoV-2 positive test results in Ontario.[27]

Our secondary outcome was hospitalization or death associated with a positive SARS-CoV-2 test (i.e., clinically important outcomes). We captured clinically important outcomes in CCM which we supplemented with information from RPDB to identify deaths, defined as a positive SARS-CoV-2 test occurring in the 30 days prior to death. Whereas for hospitalizations, we supplemented CCM with information from CIHI and considered a COVID-19 related hospitalization as hospitalization with a positive SARS-CoV-2 test occurring in the 14 days prior or 3 days after hospital admission. Similar definitions have been used previously.[7]

2.6 | Statistical analysis

We defined continuous variables as medians (25th and 75th percentiles) and categorical variables as proportions. We used standardized differences to compare baseline characteristics between solid organ transplant recipients who received at least one dose of the COVID-19 vaccine during follow-up to individuals who remained unvaccinated, with a difference of >10% representing a meaningful difference.[28]

We used an extended Cox proportional hazards model with vaccination status as a time-dependent exposure. All individuals started follow-up in the unvaccinated category (reference) and could contribute person-time to all vaccine dose categories, including first, second, and third. Specifically, we considered individuals to be unvaccinated if they never received a COVID-19 vaccine or were within the 0- to 13-day interval after dose 1. We defined dose 1 as 14+ days after dose 1 until 13 days after dose 2, dose 2 as 14+ days after dose 2 until 13 days after dose 3, and dose 3 as 14+ days after dose 3. We calculated vaccine effectiveness using the formula (1 − hazard ratio) x 100. We censored at the time of non-COVID death or end of follow-up (November 28, 2021). We confirmed that the proportional hazards assumption was met for all variables included in the model using weighted Schoenfeld residuals. No meaningful departures from the proportionality assumption were observed. We also examined model fit and overfitting, noting no concerns.

We selected adjustment variables based on factors known to be associated with receiving a vaccine and being infected with SARS-CoV-2, clinical expertise, and considerations for model overfitting. Specifically, we adjusted for age, sex, public health unit region, number of SARS-CoV-2 tests in the 3 months prior to December 14, 2020 (0, 1, and ≥2), influenza vaccine in the 2019/20 or 2020/21 influenza season, solid organ transplant type (i.e., kidney, liver, lung, heart, pancreas, or multi-organ transplant), diabetes, chronic heart disease, major cancer, hypertension, chronic respiratory disease, SARS-CoV-2 infection in 90+ days prior to cohort entry (i.e., December 14, 2020), living in a long-term care residence, years since most recent transplant and several neighborhood-level variables (income [measured as quintiles], proportion of people working as a non-health essential worker [ranked into quintiles], persons per dwelling quintile, and self-identified visible minority quintiles). Adjustment for varying rates in SARS-CoV-2 infection in the community over time was not required as we had a closed cohort of transplant recipients with the calendar and study timescales being equivalent. As such, the extended Cox model automatically controls for different periods in the pandemic, comparing only people at the same point in time (e.g., recipient with 1 dose in July is compared to an unvaccinated recipient in July). Additionally, we included a geographic variable for public health unit region to control for differences in infection by geographic location. Finally, we did not observe any violations in the proportional hazards assumption for vaccine status, indicating no change in the relative effect during our study despite changes in community rates across different pandemic waves. From our previous unpublished vaccine effectiveness work, we found that the results of an extended Cox model on the calendar timescale, controlling for region and meeting the proportional hazards assumption offered comparable

results to the model where we adjusted for monthly community rates (in place of the region). Therefore, for our final model, we did not adjust for community rates, selecting the more parsimonious model, which also allowed us to attribute the degrees of freedom to other important covariates. We used variance inflation factors to assess for collinearity among confounders and noted no issues (i.e., all variance inflation factors <2).

Less than 1% of data was missing for the following variables: residence (missing imputed as urban), public health unit region (kept the missing category), and for income quintile, essential workers fifth, number of people per dwelling fifth, and self-identified visible minority fifth we imputed the middle category (i.e., category 3). Losses to follow-up are minimal in our data sources with only 0.5% emigrating from Ontario each year.[29] A two-sided P value of <0.05 was considered statistically significant and confidence intervals widths were not adjusted for multiple testing. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

2.7 | Additional analysis

Given studies in the general population suggest reduced vaccine effectiveness with the ChAdOx1 nCoV-19 adenovirus vector vaccine compared to mRNA vaccines,[30,31] in an additional analysis, we estimated the adjusted vaccine effectiveness by censoring individuals if they received the ChAdOx1 nCoV-19 vaccine (first or second dose) during follow-up.

3 | RESULTS

3.1 | Baseline characteristics

We included 12,842 solid organ transplant recipients (median age 57.7 years, 37.8% female) (Figure S1). Solid organ transplant types included kidney (*n* = 7539 [58.7%]), liver (*n* = 2903 [22.6%]), lung (*n* = 881 [6.9%]), heart (*n* = 844 [6.6%]), pancreas (*n* = 564 [4.4%]), and multi-organ (*n* = 111 [0.8%]). Compared to recipients who did not receive the COVID-19 vaccine (i.e., unvaccinated) during follow-up, recipients who received at least 1 dose were older (58 vs 56 years), more likely to be from the highest income quintile (19.5 vs 14.7%), received their transplant more recently (7 vs 8 years), and were more likely to have received the influenza vaccine (51.0 vs 23.2%) (Table 1).

3.2 | Vaccine effectiveness

During follow-up, 12.7% (*n* = 1632) of solid organ transplant recipients remained unvaccinated, 87.3% (*n* = 11 210) received at least one dose of COVID-19 vaccine with 1.8% (*n* = 235) receiving only one dose, 31.3% (*n* = 4022) receiving only two doses, and 54.1% (*n* = 6953) receiving 3 doses. The most common vaccine type for the first dose was BNT162b2 (*n* = 8667, 77.3%), followed by mRNA-1273 (*n* = 2035, 18.2%), and ChAdOx1 nCoV-19 (*n* = 508, 4.5%). Second dose vaccine types included BNT162b2 (*n* = 8364, 76.2%), mRNA-1273 (*n* = 2344, 21.4%), and ChAdOx1 nCoV-19 (*n* = 267, 2.4%). Among individuals who received two doses of the COVID-19 vaccine, the most common vaccine combination was receipt of two doses of BNT162b2 (69.4%) (Table S3a), the median time between the first and second dose was 28 days (23, 43) and 348 (3.2%) received mixed COVID-19 vaccines (e.g., ChAdOx1 nCoV-19 for first dose and BNT162b2 for second dose). Third dose vaccine types included BNT162b2 (*n* = 5773, 83.0%) and mRNA-1273 (*n* = 1180, 17.0%). Among individuals who received three doses of the COVID-19 vaccine, the most common vaccine combination was receipt of three doses of BNT162b2 (76.6%) (Table S3b) and the median time between the second and third dose was 133 days (116, 155).

Over a median follow-up of 349 days, 488 (3.8%) solid organ transplant recipients tested positive for SARS-CoV-2. Among recipients who tested positive, 260 (53.3%) had a clinically important outcome, of which 84 died (17.2%). Adjusted vaccine effectiveness against infection was 31% (95% CI: 2, 51%), 46% (95% CI: 21, 63%), and 72% (95% CI: 43, 86%) with one, two, and three doses, respectively. Adjusted vaccine effectiveness against clinically important outcomes was 38% (95% CI: 4, 61%), 54% (95% CI: 23, 73%), and 67% (95% CI: 11, 87%), respectively (Table 2). Table S4 provides the adjusted hazard ratios for risk factors for SARS-CoV-2 infection in solid organ transplant recipients.

Results did not meaningfully change when in an additional analysis we estimated the adjusted vaccine effectiveness censoring at receipt of the adenovirus vector vaccine ChAdOx1 nCoV-19 with effectiveness estimates against SARS-CoV-2 infection of 32% (95% CI: 3, 53%), 49% (95% CI: 25, 66%), and 71% (95% CI: 41, 86%) with one, two, and three doses, respectively. Vaccine effectiveness against clinically important outcomes was 41% (95% CI: 6, 63%), 59% (95% CI: 29, 76%), and 66% (95% CI: 10, 88%), respectively.

4 | DISCUSSION

In this study, we estimated the real-world vaccine effectiveness of a third COVID-19 vaccine dose in solid organ transplant recipients. We found that solid organ transplant recipients had a considerably lower vaccine effectiveness against clinically important outcomes (54%) after two doses compared to the general population. However, a third dose improved vaccine effectiveness against infection (72%) and clinically important outcomes (67%). Our results suggest that while COVID-19 vaccine effectiveness in solid organ transplant recipients is lower compared to the general population, effectiveness notably improves after three doses.

Our vaccine effectiveness estimates were considerably lower compared to the general population. It is not surprising that vaccine effectiveness is reduced in solid organ transplant recipients given these patients are taking immunosuppressive agents which alter the

TABLE 1 Baseline characteristics for solid organ transplant recipients by vaccination status

Characteristic	Solid organ transplant recipients (*N* = 12842)	≥1 dose COVID-19 vaccine (*N* = 11, 210)	Unvaccinated (*N* = 1632)	Standardized difference[a]
Age, years	60 (49, 68)	60 (50, 68)	57 (45, 67)	**0.17**
18-<40	1605 (12.5)	1318 (11.8)	287 (17.6)	**0.16**
40–65	6960 (54.2)	6080 (54.2)	880 (53.9)	0.01
>65	4277 (33.3)	3812 (34.0)	465 (28.5)	**0.12**
Female	4860 (37.8)	4261 (38.0)	599 (36.7)	0.03
Neighborhood income quintile[b]				
1 (low)	2709 (21.1)	2261 (20.2)	448 (27.5)	**0.17**
2	2624 (20.4)	2303 (20.5)	321 (19.7)	0.02
3 (middle)	2639 (20.5)	2302 (20.5)	337 (20.6)	0.00
4	2447 (19.1)	2161 (19.3)	286 (17.5)	0.05
5 (high)	2423 (18.9)	2183 (19.5)	240 (14.7)	**0.13**
Rural[c]	1459 (11.4)	1283 (11.4)	176 (10.8)	0.02
Time since transplant, years	7 (3, 13)	7 (3, 13)	8 (4, 14)	**0.11**
Number of transplants[d]				
1	11,718 (91.2)	10,232 (91.3)	1486 (91.1)	0.01
2	1015 (7.9)	883 (7.9)	132 (8.1)	0.01
≥3	109 (0.8)	95 (0.8)	14 (0.9)	0.01
Long-term care residence	56 (0.4)	50 (0.4)	6 (0.4)	0
Prior SARS-CoV-2 infection (infection occurred between March 2020 and September 2020)[e]	45 to 49 (0.4)	44 (0.4)	1 to 5 (0.1 to 0.3)	0.02–0.07
Chronic heart disease[f]	4114 (32.0)	3635 (32.4)	479 (29.4)	0.06
Hypertension[f]	10,378 (80.8)	9117 (81.3)	1261 (77.3)	0.10
Diabetes[f]	6308 (49.1)	5522 (49.3)	786 (48.2)	0.02
Chronic respiratory disease[f]	4128 (32.1)	3636 (32.4)	492 (30.1)	0.05
Major cancer[g]	2124 (16.5)	1865 (16.6)	259 (15.9)	0.02
Public health unit region				
Central East	876 (6.8)	755 (6.7)	121 (7.4)	0.03
Central[h] West	2571 (20.0)	2264 (20.2)	307 (18.8)	0.04
Durham	613 (4.8)	533 (4.8)	80 (4.9)	0.00
Eastern	934 (7.3)	859 (7.7)	75 (4.6)	**0.13**
North	737 (5.7)	656 (5.9)	81 (5.0)	0.04
Ottawa	1045 (8.1)	949 (8.5)	96 (5.9)	0.10
Peel	1164 (9.1)	979 (8.7)	185 (11.3)	0.09
South West	1661 (12.9)	1436 (12.8)	225 (13.8)	0.03
Toronto	2360 (18.4)	1994 (17.8)	366 (22.4)	**0.11**
York	881 (6.9)	785 (7.0)	96 (5.9)	0.04
Number SARS-CoV-2 tests in past 3 months				
0	10,462 (81.5)	9120 (81.4)	1342 (82.2)	0.02
1	1510 (11.8)	1343 (12.0)	167 (10.2)	0.06
≥2	870 (6.8)	747 (6.7)	123 (7.5)	0.03
2019–2020 and/or 2020–21 influenza vaccine	6097 (47.5)	5719 (51.0)	378 (23.2)	**0.60**
Essential workers fifth (%)[i,j]				
1 (0–28.4)	2458 (19.1)	2217 (19.8)	241 (14.8)	**0.13**

TABLE 1 (Continued)

Characteristic	Solid organ transplant recipients (*N* = 12842)	≥1 dose COVID-19 vaccine (*N* = 11, 210)	Unvaccinated (*N* = 1632)	Standardized difference[a]
2 (28.4–37.0)	2645 (20.6)	2333 (20.8)	312 (19.1)	0.04
3 (37.0–43.6)	2704 (21.1)	2374 (21.2)	330 (20.2)	0.02
4 (43.6–50.3)	2555 (19.9)	2208 (19.7)	347 (21.3)	0.04
5 (50.3–100)	2406 (18.7)	2013 (18.0)	393 (24.1)	**0.15**
Number (range) of people per dwelling fifth[i]				
1 (0–2.1)	2703 (21.0)	2341 (20.9)	362 (22.2)	0.03
2 (2.2–2.4)	2399 (18.7)	2121 (18.9)	278 (17.0)	0.05
3 (2.5–2.6)	1773 (13.8)	1566 (14.0)	207 (12.7)	0.04
4 (2.7–3)	2973 (23.2)	2596 (23.2)	377 (23.1)	0.00
5 (3.1–5.7)	2919 (22.7)	2520 (22.5)	399 (24.4)	0.04
Self-identified visible minority fifth (%)[i,k]				
1 (0–2.2)	2205 (17.2)	1967 (17.5)	238 (14.6)	0.08
2 (2.2–7.3)	2267 (17.7)	2018 (18.0)	249 (15.3)	0.07
3 (7.3–18.3)	2357 (18.4)	2086 (18.6)	271 (16.6)	0.05
4 (18.3–42.6)	2702 (21.0)	2342 (20.9)	360 (22.1)	0.03
5 (42.6–100)	3237 (25.2)	2732 (24.4)	505 (30.9)	**0.15**

Note: Data are presented as n (%) or median (25th and 75th percentile).

[a]Standardized differences measure the difference between groups divided by the pooled standard deviation; a value >10% is a meaningful difference between the unvaccinated and vaccinated groups. Bold standard differences denote a meaningful difference (i.e., >10%).

[b]Income presented as quintiles of average neighborhood income.

[c]Rural is defined as living in an area with a population < 10000.

[d]Includes the transplant that entered the individual into the cohort. Therefore, everyone has at least 1 transplant.

[e]In accordance with ICES policy of suppressing cell sizes <6, numbers presented as ranges.

[f]Comorbidities assessed prior to index date.

[g]Major cancer is defined as a composite of lung/bronchi, colon/rectum, breast, pancreas, prostate, leukemia, non-Hodgkin lymphoma, liver, ovarian, and esophageal. Evidence of major cancer was assessed in the 5-years prior to index date.

[h]Public Health Unit region was missing for <1% of recipients. Missing data were imputed to the Central West Region.

[i]Sum of values will not equal the column total due to missing data which was <1%.

[j]Ranges in brackets represent the proportion of people in a given area working as non-healthcare essential workers (e.g., sales, transport, agriculture, manufacturing).

[k]Ranges in brackets represent the proportion of people in a given area who self-identified as a visible minority.

immune response.[9] Studies in the general population have found vaccine effectiveness estimates against infection and clinically important outcomes of ~90%[8,15] after two doses of the COVID-19 vaccine compared to our estimate of 46% against infection and 54% against clinically important outcomes.

In contrast to our results, a study from the United Kingdom found that transplant recipients with two vaccine doses had an increased risk of testing positive for SARS-CoV-2 and only the ChAdOx1 (not the BNT162b2) vaccine was associated with reduced mortality.[12] In contrast, we found that both two and three vaccine doses reduced infection and severe outcomes in our population where >97% received an mRNA vaccine. The United Kingdom study did not have data on third doses. Potential reasons for differences in results between our study and the aforementioned study,[7] include different methodology (e.g., we used a Cox model treating vaccination status as a time-dependent exposure and we had different adjustment variables) and different follow-up time. Bell et al., examined vaccine effectiveness after two doses of the COVID-19 vaccine in kidney transplant recipients finding effectiveness was 39% against infection and 40% against hospitalization.[13] These estimates were lower than our vaccine effectiveness estimates against infection (46%) and against clinically important outcomes (i.e., hospitalization or mortality) (54%). Our estimates might be slightly higher for several reasons, including we allowed for other solid organ transplant types in addition to kidney, we used different methodology and we adjusted for several variables (vs. their analysis was unadjusted).

Similar to the general population and immunogenicity studies in the solid organ transplant population,[10,11] we found that a third dose improved vaccine effectiveness against infection (72%) and clinically important outcomes (67%). However, these estimates were lower compared to the general population. For example, Spitzer

TABLE 2 Unadjusted and adjusted hazard ratios and vaccine effectiveness estimates of COVID-19 vaccines (BNT162b2, mRNA-1273, and ChAdOx1 nCoV-19) against laboratory-confirmed SARS-CoV-2 infection and clinically important outcomes (hospitalization or death) between December 14, 2020, and November 28, 2021, in solid organ transplant recipients from Ontario, Canada

	Rate per 100000 person-days	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio[a] (95% CI)	Unadjusted vaccine effectiveness[b] % (95% CI)	Adjusted vaccine effectiveness[a,b] % (95% CI)
SARS-CoV-2 Infection[c]					
Unvaccinated	17.7	Reference	Reference	Reference	Reference
One vaccine dose	11.2	0.67 (0.47, 0.95)	0.69 (0.49, 0.98)	33 (5, 53)	31 (2, 51)
Two vaccine doses	4.8	0.55 (0.38, 0.81)	0.54 (0.37, 0.79)	45 (19, 62)	46 (21, 63)
Three vaccine doses	3.5	0.24 (0.12, 0.48)	0.28 (0.14, 0.57)	76 (52, 88)	72 (43, 86)
Clinically important outcomes (composite of hospitalization or death)[c]					
Unvaccinated	9.3	Reference	Reference	Reference	Reference
One vaccine dose	6.9	0.69 (0.44, 1.08)	0.62 (0.39, 0.96)	31 (−8, 56)	38 (4, 61)
Two vaccine doses	2.3	0.57 (0.34, 0.96)	0.46 (0.27, 0.77)	43 (4, 67)	54 (23, 73)
Three vaccine doses	2.0	0.37 (0.14, 0.97)	0.33 (0.13, 0.89)	63 (3, 86)	67 (11, 87)

Abbreviation: CI, confidence interval.

[a]Model was adjusted for age, sex, public health unit region, number of SARS-CoV-2 tests in the 3 months prior to December 14, 2020 (0,1, ≥2), influenza vaccine in the 2019/20 or 2020/21 influenza season, solid organ transplant type (i.e., kidney, liver, lung, heart, pancreas, or multi-organ transplant), diabetes, chronic heart disease, major cancer, hypertension, chronic respiratory disease, SARS-CoV-2 infection in 90+ days prior to cohort entry (i.e., December 14, 2020), living in a long-term care residence, years since most recent transplant and several neighborhood-level variables (income [measured as quintiles], proportion of people working as a non-health essential worker [ranked into quintiles], persons per dwelling quintile, and self-identified visible minority quintiles).

[b]Vaccine effectiveness was calculated using the formula: (1 − hazard ratio) × 100.

[c]Vaccine categories: one vaccine dose: 14+ days after dose 1 until 13 days after dose 2; two vaccine doses: 14+ days after dose 2 until 13 days after dose 3; three vaccine doses: 14+ days after dose 3.

et al., compared healthcare workers who received two doses of the BNT162b2 vaccine to individuals who received three doses, finding an adjusted hazard ratio against SARS-CoV-2 infection of 0.07 (95% CI: 0.02 to 0.2).[17]

Information on the vaccine effectiveness after three doses of the COVID-19 vaccine in the solid organ transplant population is particularly important with only 54% of solid organ transplant recipients in our study receiving a third dose and only 28% of the United States population receiving a booster dose.[32] Given our results suggest increased vaccine effectiveness with a third dose there is an urgent need to develop strategies to increase booster dose uptake in this immunocompromised population.

The limitations of our study deserve to mention. First, our study did not include information on vaccine effectiveness during the Omicron surge. However, preliminary research in the general population suggests that vaccine effectiveness for Omicron-associated clinically important outcomes is still high with three doses suggesting that our results for clinically important outcomes in solid organ transplant recipients will also hold in the Omicron era.[33,34] Second, our vaccine effectiveness estimates had relatively wide confidence intervals; however, our vaccine effectiveness point estimates showed a clear graded increase from unvaccinated to three doses. Third, at the time of analysis we did not have data available on fourth doses. In Ontario, solid organ transplant recipients became eligible for fourth doses in mid-December 2021; however, to date, fourth dose uptake has been relatively low compared to second dose uptake highlighting the importance of understanding the vaccine effectiveness after three doses as many solid organ transplant recipients may opt to not receive the fourth dose. Fourth, we had incomplete information on immunosuppression medication. Fifth, we did not have the power to present vaccine effectiveness estimates by vaccine type (e.g., BNT162b2 versus mRNA-1273) or by solid organ transplant type (e.g., lung versus kidney). Some research suggests vaccine effectiveness might be higher with mRNA-1273 compared to BNT162b2.[35,36] Sixth, we may have missed some SARS-CoV-2 infections that were captured using rapid antigen tests. However, this number is likely low with widespread access to PCR testing during the study period, the administration of confirmatory PCR tests at Ontario transplant centers, and PCR testing upon admission to the hospital (regardless of the reason for admission). Last, like all observational studies examining vaccine effectiveness, our study may have some residual confounding (e.g., unmeasured differences in mask use and social distancing). For example, on September 22, 2021, Ontario introduced a vaccine certificate system, restricting air and rail travel, entrance to bars, gyms, restaurant, and sporting events to individuals with two doses of vaccine, which may have resulted in an increased exposure risk among vaccinated individuals.

We conclude that while the vaccine effectiveness achieved is not as marked as the general population, campaigns to increase booster

dose uptake in the solid organ transplant population are needed since vaccine effectiveness against clinically important outcomes notably improved following a third dose.

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DISCLOSURE

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. Dr. Knoll has received investigator-initiated research grants from the Canadian Institutes of Health Research. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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