Title

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Authors

Aslam, Saima
Liu, Jinyuan
Sigler, Rachel
et al.

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COVID-19 vaccination is protective of clinical disease in solid organ transplant recipients

Saima Aslam[1], **Jinyuan Liu**[1], **Rachel Sigler**[1], **Rehan R. Syed**[1], **Xin M. Tu**[1], **Susan J. Little**[1], **Victor De Gruttola**[2]

[1]Division of Infectious Diseases and Global Public Health, University of California San Diego, La Jolla, CA

[2]Department of Biostatistics, Harvard TH Chan School of Public Health, Boston, MA

Abstract

Background: Clinical effectiveness of coronavirus disease 2019 (COVID-19) vaccination in solid organ transplant recipients (SOTR) is not well documented despite multiple studies demonstrating sub-optimal immunogenicity.

Methods: We reviewed medical records of eligible SOTRs at a single center to assess vaccination status and identify cases of symptomatic COVID-19 from 1/1/2021–8/12/2021. We developed a Cox proportional hazards model using date of vaccination and time since transplantation as a time varying covariate with age and gender as potential time-invariant confounders. Survival curves were created using the parameters estimated from the Cox model.

Results: Among 1904 SOTRs, 1362 were fully vaccinated (96% received mRNA vaccines) and 542 were either unvaccinated (n=470) or partially vaccinated (n=72). There were 115 cases of COVID-19, of which 12 occurred in fully vaccinated individuals. Cox regression with date of vaccination and time since transplantation as the time-varying co-variates showed that after baseline adjustment for age and sex, being fully vaccinated had a significantly lower hazard for COVID-19, hazard ratio = 0.29, 95% confidence interval (0.09, 0.91).

Conclusion: We found that 2-dose mRNA COVID-19 vaccination was protective of symptomatic COVID-19 in vaccinated vs. unvaccinated SOTRs.

Graphical Abstract

Corresponding Author: Saima Aslam, MD, MS, 4510 Executive Drive, MC 7745, San Diego, CA 92121, saslam@health.ucsd.edu, Twitter handle: @DocSaimaAslam.

Author Contribution Statement: SA –study design, data collection, analysis, interpretation of data, and manuscript writing; JL - analysis, interpretation of data, and manuscript writing; RS- data collection, interpretation of data, and manuscript writing; RRS- data collection, interpretation of data, and manuscript writing; XMT- analysis, interpretation of data, and manuscript writing; SJL- study design, interpretation of data, and manuscript writing; VDG- study design, analysis, interpretation of data, and manuscript writing. All authors have reviewed the final manuscript draft for publication.

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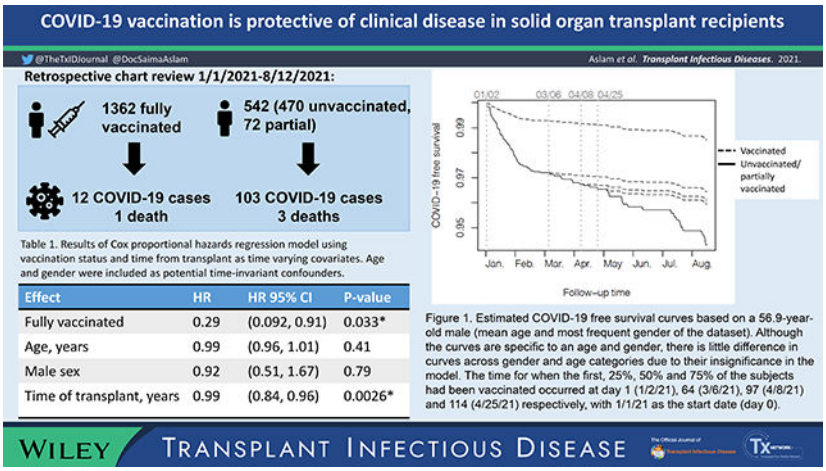
Disclosures:

SA – Consultant for Merck (honoraria paid), Gilead (honoraria paid), and BioMx (unpaid).

SL – Gilead (Research grant funding paid to institution).

Tweet: COVID-19 vaccination was associated with significantly lower hazard for symptomatic COVID-19 (HR 0.29, 95% CI 0.09, 0.91) among 1904 SOT recipients at a single center from 1/1/2021–8/12/2021.



Keywords

COVID-19 vaccine; solid organ transplant; clinical effectiveness; SARS-CoV-2

1. Introduction

Recent data demonstrate sub-optimal coronavirus disease 2019 (COVID-19) vaccine immunogenicity in solid organ transplant recipients (SOTR); however data on clinical effectiveness in this population remains sparse.[1] We recently published our experience using a transplant registry dataset that demonstrated clinical effectiveness of vaccination in SOTR with an incidence risk ratio of 0.19 when compared to unvaccinated SOTR.[2] Temporal confounding related to the early winter surge, late winter/spring decline, and summer resurgence of COVID-19 locally within San Diego County as well as varying times of vaccine eligibility for different groups may potentially have affected these results. The goal of the current study was to assess clinical effectiveness of symptomatic COVID-19 vaccination in SOTR over a longer duration of follow-up and to address confounding due to difference in onset of vaccine availability and the COVID-19 surge.

2. Methods:

We obtained institutional review board approval with a waiver of informed consent from the University of California San Diego (UCSD) Human Research Protections Program (IRB#210948XX) and retrospectively reviewed electronic medical records (EMR) of SOTRs that were alive in 2021 and followed by the UCSD transplant team for the study period 1/1/2021–8/12/2021. We excluded patients that had a COVID-19 diagnosis prior to the study period, and those who had not been seen within our medical system during the study period.

2.a. Medical record review:

We reviewed local records from UCSD as well as affiliated hospitals that were available through EMR review as well as any external scanned medical records in our system. Data was collected via manual chart review involving the EMR search function which searched

for not only within the UCSD chart but also other local providers in the system (called "careeverywhere"). This searched through medical notes, emergency room/ urgent care visits, as well as laboratory data. There is a chance that we missed some cases in patients that had an infection at an outside hospital that was not linked to our hospital's EMR and also were not followed up within UCSD during the study period. For this reason, we excluded patients that were not actively followed at UCSD and thus our chance of missing a diagnosis of COVID-19 is low. However, given that this study is retrospective in nature, some bias is expected. Vaccination status was captured from the medical record and included documented vaccination status for patients vaccinated within California and self-reports in the chart if vaccinated outside the state.

We abstracted the following data from the medical record– age, gender, type and date of transplant, type and date of COVID-19 vaccination, diagnosis of COVID-19 via polymerase chain reaction, and death. Fully vaccinated patients in the study had received either 2 doses of an mRNA vaccine (mRNA-1273, Moderna or BNT162b2, Pfizer-BioNTech) or a single dose of the Johnson and Johnson non-replicating viral vector vaccine (Ad26.COV2.S, Janssen); all patients had at least 2 weeks of follow-up from the date of last vaccination. Time at risk started from 1/1/2021 and the event of interest was COVID-19 diagnosis. Participants were censored at death. Follow-up ended for all participants on 8/12/21.

2.b. Statistical analysis:

Statistical analysis was conducted via R software and consisted of Cox proportional hazards modelling using date of vaccination and time since transplantation as time varying covariates. Age and gender were included in the model as potential time-invariant confounding factors; as such, their inclusion was not based on model fit. The target of analyses is the effect of vaccination on risk of developing COVID-19 and the impact of time since transplantation on this risk. Left truncation—which reflected varying chronologic times of eligibility for vaccination and hence of entering the set of participants at risk of COVID-19 and eligible for vaccination included in the Cox regression —was handled by allowing delayed entry into risk sets. The left truncation variable (TV) was set to be the time at which participants were first eligible for vaccination. Our analysis considered 4 different truncation conditions: 1) For patients with age greater than 65 years on 1/1/2021 who were transplanted at least 3 months prior (before 10/1/2020) there was no truncation. 2) For patients transplanted after 10/1/2020 but older than 65 years on 1/1/2021, the TV was set to be either 3 months after transplantation (kidney and heart recipients, as our transplant protocols recommended 3-month delay from transplant with thymoglobulin induction to vaccine eligibility) or 1 month after transplantation (lung and liver recipients, as our transplant protocols recommended 1 month delay from transplant to vaccine eligibility) depending on organ. 3) For patients younger than 65 years on 1/1/2021 who were transplanted before 10/1/2020, the TV was set to be set to be March 15 (date COVID-19 vaccination in California was opened up to patients with chronic medical conditions regardless of age) unless they turned 65 years of age between January 1 and March 15 2021, in which case, the TV was set to be their birth date. 4) For patients who were transplanted after 10/1/2021 and were younger than 65 years on 1/1/2021, TVs were calculated for both conditions 2) and 3), and the TV was set to be the later of the two times.

Survival curves were created using the parameters estimated from the Cox model. The plots represent men (most common gender) whose age is the mean age of the cohort and who were never/partially vaccinated or vaccinated on 4 different dates, as indicated in the plot. The reason for having multiple curves is that there is no single curve that can represent the experience of the vaccinated populations, given the varying times of vaccination. A smoothed estimate of the underlying hazard was also produced using the same R software.

3. Results:

Among 1904 SOTRs, 1362 were fully vaccinated (71.5%) and 542 were either unvaccinated (n=470, 24.7%) or partially vaccinated (n=72, 3.8%) by August 12, 2021. As noted in Table 1, the study cohort consisted of 1,224 men (64.3%), mean age 56.9 years (standard deviation, 13.9), and median time since last transplanted organ of 52.2 months (interquartile range, 22.3–115.4). Based on primary transplanted organ, the study cohort consisted of 347 (18.2%) heart, 186 (9.8%) lung, 551 (28.9%) liver, and 820 (43.1%) kidney transplant recipients. Almost 96% of vaccinated subjects received mRNA vaccines.

There were 115 cases of COVID-19 in the study period. Among these, 12 occurred in fully vaccinated individuals and 103 in unvaccinated or partially vaccinated individuals. There were 4 deaths in patients with COVID-19 of which one was in the vaccinated group.

3.a. Details of breakthrough COVID-19:

3.a.(i) Baseline characteristics: Among the 12 breakthrough cases, median age was 56 years (IQR 44–62.75), 11 (92%) were men, and median time from transplant was 33.9 months (IQR 10.6–54.9). Transplanted organs consisted of heart (1), heart-kidney (2), lung (1), liver (4) and kidney (4). Immunosuppression at the time of breakthrough infection consisted of tacrolimus (8, 66.7%), mycophenolate mofetil (5, 41.7%), prednisone (8, 66.7%), cyclosporine (3, 25%) and sirolimus (3, 25%). All breakthrough cases occurred in those that had received mRNA vaccines: 7 (58.3%) had received mRNA1273 (Moderna) and 5 (41.7%) had received the BNT 162b2 (Pfizer-BioNTech) vaccine; median days from second dose of vaccination to COVID-19 diagnosis was 89.5 days (IQR 63–116).

3.a.(ii) Clinical course: Eight patients presented with mild infection with symptoms of headache (5), upper respiratory tract symptoms of rhinorrhea, sore throat, nasal/sinus congestion (4), diarrhea (2), loss of taste and/ or smell (2), fever (3), cough (5), and fatigue and/or body aches (6). Of these, 7/8 were treated with casirivimab/imdevimab and had resolution of symptoms; one was admitted under observation due to fever and discharged a day later. One patient was outside the treatment window of 10 days for monoclonal antibody infusion and infection self-resolved without intervention.

Two patients had a moderate illness on presentation with cough and shortness of breath in one for which they were admitted with COVID-19 pneumonia (but did not become hypoxic), and the second was admitted with diarrhea but no respiratory symptoms. Both received remdesivir during the inpatient admission; the patient with subjective shortness of breath received a prednisone taper as well.

Two patients had severe clinical illness: One patient was a heart and kidney transplant recipient from 2017 who presented with cough, fever, and shortness of breath and required oxygen supplementation with nasal cannula at 2 liters/minute. He was diagnosed with COVID-19 pneumonia as well as pneumococcal bacteremia and pneumonia upon admission. He received casirivimab/imdevimab prior to admission and then remdesivir after admission as well as ceftriaxone for pneumococcal infection and was discharged home after 9 days of inpatient stay. The second patient with severe illness had received a liver transplant 10 months previously and initially presented with flu-like symptoms, fever, and postural dizziness. He refused monoclonal antibody infusion at initial diagnosis and later presented with cough and shortness of breath and received remdesivir, dexamethasone, and tociluzimab. He had progressive respiratory failure but refused ventilatory support and eventually died 27 days after diagnosis.

In summary, 5/12 (41.7%) breakthrough cases required hospitalization and 1/12 (8.3%) died. COVID-19 specific therapeutics consisted of casirivimab/imdevimab in 8/12 (66.7%), remdesivir in 4/12 (33.3%), steroids (dexamethasone, high dose prednisone) in 2/12 (16.7%), and tocilizumab in 1 (8.3%)

3.a.(iii): COVID-19 exposure: Five of the 12 patients (42%) had documented exposure to at least one household member with COVID-19. Vaccination status of contacts was not clearly documented in all cases; one contact with COVID-19 had a breakthrough infection following vaccination as well.

3.a.(iv): Epidemiology: Eight of the 12 (66.7%) had confirmed or probable delta variant infection as noted in the microbiology results section of the EMR. Four were confirmed via sequencing, and 4 were probable based on polymerase chain reaction testing for spike gene mutations; and 4 were not tested for variants of concern by the UCSD Microbiology laboratory.

3.b. Multivariable model:

Table 2 shows the results of Cox regression for estimation of the effect of time-varying vaccination, adjusted for age, sex and time of transplantation. Fully vaccinated participants had significantly lower hazard for COVID-19 (hazard ratio = 0.29; 95% confidence interval 0.09, 0.91). Longer time (in years) since transplantation reduced the hazard for COVID-19 (hazard ratio = 0.90; 95% confidence interval 0.84, 0.96). We did not find a significant difference in vaccine effect with time since transplantation in this model.

We note that the risk of COVID-19 decreased later in the winter and throughout the spring and early summer but rose in late summer (Supplementary Figure 1). Our Cox proportional hazards modelling accounts for the fact that vaccine uptake was lowest during the period of highest COVID-19 incidence.

3.c. Figure 1 displays the COVID-19 free survival curves that would apply to 5 different theoretical populations of men (most common gender) of age 56.9 years (mean age of participants). Age and gender had very little effect on the hazards, so these curves differ by a very small amount for participants with different demographic characteristics. The top curve

shows what we would expect (based on estimated parameters) for a population in which each member was vaccinated at the date of the first completed vaccination (Jan 2). The next curve (from the top) represents the expected experience of people who were all vaccinated on the date at which 25% of those ultimately vaccinated had received their vaccination. The next two curves are the same in principle but for the dates for which 50% and 75% were vaccinated. The bottom curve displays the expected experience of people who were never vaccinated (or partially vaccinated).

4. Discussion:

COVID-19 vaccination is the mainstay against developing symptomatic illness; however measurable immunogenicity following two doses of mRNA vaccines in SOTRs is sub-optimal.[1] Detectable antibodies against the SARS-CoV-2 spike and receptor binding domain increases following an additional third dose of mRNA vaccine in SOTRs from that observed after two doses, ranging between 55– 68%, though is still less than what is reported in the immunocompetent population.[3,4] Data on clinical effectiveness of COVID-19 vaccination in SOTRs is scarce. National registry data from the United Kingdom demonstrated reduction in death within 28 days of a COVID-19 diagnosis from 12.6% in unvaccinated to 7.7% in fully vaccinated SOTRs.[5] We previously demonstrated an almost 80% reduction in the incidence of COVID-19 at a single transplant center though were limited by using data from a local registry and the analysis did not address the potential confounding by chronologic time. i.e. the low rate of vaccination during the time of greatest COVID-19 incidence as well as varying vaccination eligibility criteria during the initial roll-out.

In the current paper, we reviewed individual medical records to assess both the COVID-19 vaccination status and diagnosis of COVID-19 and extended the follow-up period to August 12, 2021 to include almost 10 additional weeks when the SARS-CoV-2 delta variant was the predominant variant in California. Our findings of a 71% reduction in the hazard of COVID-19 in vaccinated individuals demonstrate the effectiveness of vaccination against COVID-19 in this vulnerable population. The COVID-19-free survival curves demonstrating the projected amount of reduction of symptomatic infection had patients been vaccinated at four time points during the study period underscore the magnitude of this effect.

Clinical effectiveness of vaccination in preventing symptomatic SARS-CoV-2 infection at the individual level may be impacted by external factors in addition to immunogenicity such as type of circulating SARS-CoV-2 variants. As the vaccination in our study was not randomly assigned, the vaccination status of members of individual patient's households may differ between study participants who were and were not vaccinated—creating a potential of confounding by indication. Such confounding may also arise from various behavioral factors of the index participant and of their contacts. More broadly the effectiveness of vaccine in preventing COVID-19 spread at the community level also depends on vaccination rates in the community. Assessing the relative impact of these individual factors on the clinical effectiveness of COVID-19 vaccination seen in our SOT population is beyond the scope of the current paper.

In general, COVID-19 related mortality in our dataset was low, 4/115 (3.5%). We have previously demonstrated relatively low COVID-19 related mortality in heart transplant recipients at our center as well when compared to other centers.[6] During the current study period, a variety of treatment options existed for COVID-19 such as widespread use of monoclonal antibodies early during the infection, [7] and use of remdesivir, steroids, and tocilizumab when indicated. Reduction in COVID-19 mortality of SOTRs has previously been demonstrated as the pandemic has progressed in a recent multicenter registry report as well.[8] Additionally, new oral antiviral agents that can be initiated early in the outpatient setting are on the horizon which may impact disease progression.[9,10]

Reduced vaccine effectiveness against any COVID-19 infection especially in high risk patients (health care workers, nursing home residents) has recently been reported and attributed to waning of antibody levels over time and increased rate of breakthrough infections with the delta variant.[11,12] We could not assess for this specifically in the current study as the follow-up duration following 2-dose vaccination was 131 days (4.4 months) and number of infections overall was low. We would, however, recommend that larger studies that combine information across multiple centers be used to investigate such effects.

It is important to note that almost half of the SOTRs with breakthrough COVID-19 had exposure to at least one household member with the illness. Thus, vaccination and other COVID-19 mitigation strategies (masking, social distancing, adequate ventilation among others) in household members remains an important tool to protect our immunocompromised patients and should be encouraged.

Limitations of this study include single center retrospective data collection, potential under-reporting of vaccination status and COVID-19 diagnosis, and possible additional time-varying confounding factors, as described above. Of note, the study assessed symptomatic COVID-19 as an endpoint and not all infections. We did not check serologies to assess for prior COVID-19 (though patients with a history of symptomatic COVID-19 prior to the study period were excluded) or the immunogenicity of vaccination. Additionally, the study was not designed to assess the impact of community vaccination rates and behavioral factors on vaccine effectiveness. Almost all patients received mRNA vaccination and thus the results are pertinent to mRNA vaccines only.

In conclusion, we demonstrate significant clinical effectiveness of COVID-19 vaccination in SOTRs when compared to unvaccinated/partially vaccinated SOTRs at a single center. However, clinical effectiveness in this population might remain sub-optimal compared to non-immunosuppressed population. With implementation of third dose vaccination, it will be important to assess the clinical effectiveness of such a strategy as well. We believe it remains vitally important to continue to emphasize COVID-19 vaccination in our transplant patients in addition to other mitigation strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement:

Data available on request due to privacy/ethical restrictions

Abbreviations:

(COVID-19)	coronavirus disease 2019
(CDC)	Centers for Disease Control
(EMR)	electronic medical records
(SOTR)	solid organ transplant recipients
(UCSD)	University of California San Diego

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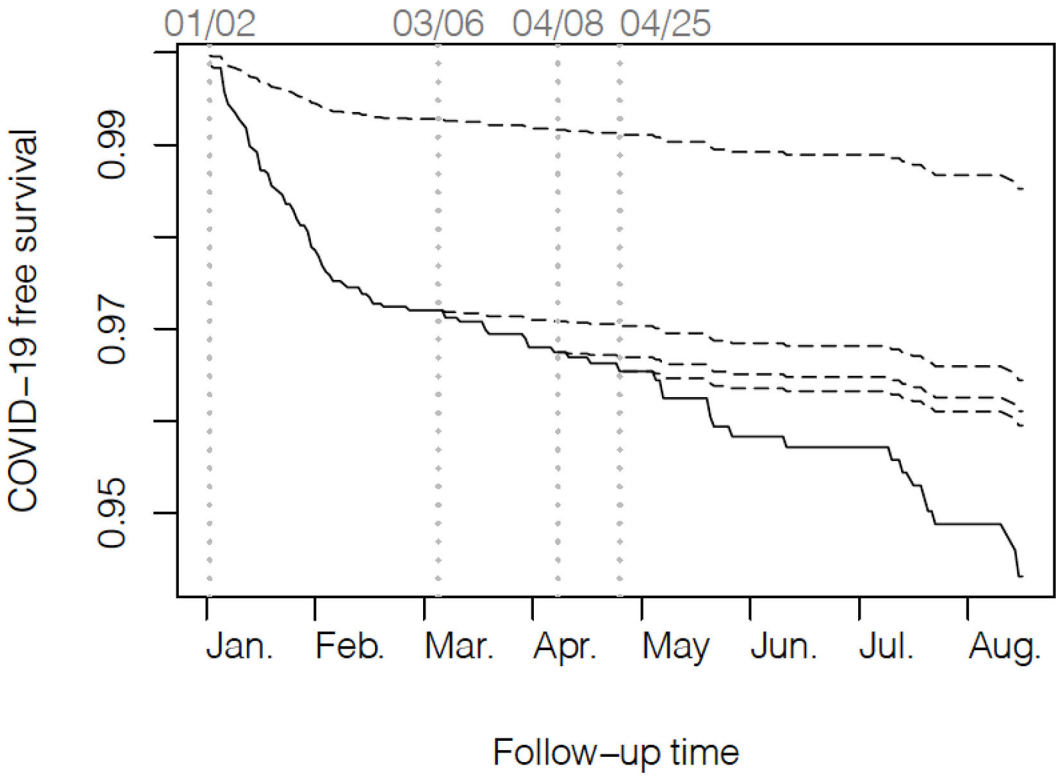

Figure 1.

Estimated COVID-19 free survival curves based on a 56.9-year-old male (mean age and most frequent gender of the dataset). Although the curves are specific to an age and gender, there is little difference in curves across gender and age categories due to their insignificance in the model. The time for when the first, 25%, 50% and 75% of the subjects had been vaccinated occurred at day 1 (1/2/21), 64 (3/6/21), 97 (4/8/21) and 114 (4/25/21) respectively, with 1/1/21 as the start date (day 0).

The top curve shows the expected COVID-19 free survival (based on estimated parameters) for a population of people all of whom were vaccinated at the date of the first vaccination (Jan 2). The next curve represents the expected experience of people who were all vaccinated at the date at which 25% of those ultimately vaccinated had received their vaccination. The next two curves are the same in principle but for dates when 50 and 75% were vaccinated. The bottom curve is the expected experience of people who were never vaccinated.

Table 1.

Baseline data of the study cohort. Patients with multi-organ transplant were categorized according to primary organ. NS is not significant.

	Vaccinated (N=1362)	Unvaccinated or partially vaccinated (N=542)	Univariate p-value
Mean age in years, SD	58.2 (13.4)	53.7 (14.7)	<0.001
Male sex, %	875 (64.2%)	349 (64.4%)	NS
Median time from transplant in months, IQR	50.8 (21.9– 112.8)	54.6 (24.8 – 119.9)	NS
Type of transplant, %			0.006
Heart	234 (17.2%)	113 (20.86%)	
Lung	150 (11.01%)	36 (6.64%)	
Liver	383 (28.12%)	168 (31%)	
Kidney	595 (43.69%)	225 (41.51%)	
Type of vaccine, %			
mRNA-1273, Moderna	783 (57.49%)		
BNT162b2, Pfizer-BioNTech	529 (38.84%)		
JNJ-78436735, Janssen	42 (3.08%)		
Unknown	8 (0.59%)		

Table 2.

Results of Cox proportional hazards regression model using vaccination status and time from transplantation as time varying covariates. Age and gender were included in the model as potential time-invariant confounding factors.

	Cox PH Model		
Effect	**HR**	**HR 95% CI**	**p**
Fully vaccinated	0.29	(0.092, 0.91)	0.033 *
Age (in years)	0.99	(0.96, 1.01)	0.41
Sex (Male vs. Female)	0.92	(0.51, 1.67)	0.79
Time of transplantation (in years)	0.90	(0.84, 0.96)	0.0026 **