Impact of SARS-CoV-2 vaccination and booster on COVID-19 symptom severity over time in the COVID-OUT trial

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Short title:
COVID-19 Boosters Reduce Symptoms

Abstract:

Background: SARS-CoV-2 vaccination has decreasing protection from acquiring any infection with emergence of new variants; however, vaccination continues to protect against progression to severe COVID-19. The impact of vaccination status on symptoms over time is less clear.

Methods: Within a randomized trial on early outpatient COVID-19 therapy testing metformin, ivermectin, and/or fluvoxamine**,** participants recorded symptoms daily for 14 days. Participants were given a paper symptom diary allowing them to circle the severity of 14 symptoms as none (0), mild (1), moderate (2), or severe (3). This is a secondary analysis of clinical trial data on symptom severity over time using generalized estimating equations comparing those unvaccinated, SARS-CoV-2 vaccinated with primary vaccine series only, or vaccine-boosted.

Results: The parent clinical trial prospectively enrolled 1323 participants, of whom 1062 (80%) prospectively recorded some daily symptom data. Of these, 480 (45%) were unvaccinated, 530 (50%) were vaccinated with primary series only, and 52 (5%) vaccine-boosted. Overall symptom severity was least for the vaccine-boosted group and most severe for unvaccinated at baseline and over the 14 days (P<0.001). Individual symptoms were least severe in the vaccine-boosted group including: cough, chills, fever, nausea, fatigue, myalgia, headache, and diarrhea, as well as smell and taste abnormalities. Results were consistent over delta and omicron variant time periods.

Conclusions: SARS-CoV-2 vaccine-boosted participants had the least severe symptoms during COVID-19 which abated the quickest over time.

Keywords: COVID-19; SARS-CoV-2; vaccine; symptoms

Clinical Trial Registration: ClinicalTrials.gov: NCT04510194

Introduction

SARS-CoV-2 vaccination reduces the propensity to progress to severe coronavirus disease 2019 (COVID-19); however, there has been waning effectiveness against protection from any SARS-CoV-2 infection.[1-3] Those who are vaccinated with breakthrough COVID-19 illness anecdotally are reported to have less severe disease.

This analysis compared symptom severity among vaccinated, boosted, and unvaccinated participants in a phase 3 outpatient Covid treatment trial. We assessed the longitudinal change in symptom severity over 2-weeks for 14 symptoms recommended by the U.S. Food and Drug Administration (FDA) to be captured in clinical trials.[4] We assessed the differences in symptom severity over time by vaccination status across the alpha, delta and omicron waves.

Methods

Study Design

We assessed a prospective cohort of participants who participated in a randomized clinical trial testing early outpatient treatment for COVID-19 in the United States. The COVID-OUT trial was a phase 3, randomized, double-blinded placebo-controlled clinical trial using a three-by-two factorial design (ClinicalTrials.gov: NCT04510194).[5] The trial originally opened on Dec 30, 2020 testing metformin versus placebo and was expanded to a 3x2 partial factorial design to include 1) metformin, immediate-release titrated over 6 days to 1,500 mg per day; 2) ivermectin median dose of 430 mcg/kg per day for 3 days; 3) fluvoxamine, 50 mg twice daily for 14 days; 4) metformin and ivermectin; 5) metformin and fluvoxamine, or 6) placebo. Manufacturers provided identically matched placebos. To maintain the blind, participants assigned to the placebo arm in the factorial portion of the trial received two matched placebos, and those assigned to a monotherapy arm also received a second placebo. Trial enrollment was completed on January 28, 2022. Long-term follow-up continues through January 2023 .

Eligibility Criteria

Eligibility criteria included age 30 to 85 years, body mass index (BMI) criteria for overweight or obesity ($\geq$ 25 kg/m^2 or $\geq$ 23 kg/m^2 if self-identifying as Asian or Latinx background), and documented confirmed SARS-CoV-2 infection and <7 days of symptoms. Pregnant women were eligible. Major exclusion criteria included current hospitalization, immunocompromised status, liver disease (Child-Pugh B or C), current alcohol abuse, advanced kidney disease with an estimated glomerular filtration rate of < 45 ml/min/1.73 m^2, unstable congestive heart failure, bipolar disorder, allergy to a study medicine, and specific medication exclusions due to drug-drug interactions. Refer to ClinicalTrials.gov (NCT04510194) for a detailed list of eligibility criteria.

Ethics

All participants provided informed consent to participate in the parent trial. The COVID-OUT trial was an investigator-initiated clinical trial at six participating institutions. The Advarra central institutional review board-approved protocol MET29324.

Procedures

We provided participants with a paper daily diary that consisted of a symptom survey on which they could circle symptom severity daily for 14 days. Fourteen different symptoms were assessed daily in accordance with September 2020 FDA guidance on assessing COVID-related symptoms in clinical trials.[4] Ten of these symptoms were based on "COVID-19 specific" symptoms as defined by the U.S. Council of State and Territorial Epidemiologists' clinical case definition of: cough, shortness of breath, subjective fever, fatigue, myalgia, sore throat, chills, headache, loss of smell, and loss of taste.[6] The four additional symptoms that were later considered to be non-specific were: rhinorrhea, nausea, diarrhea, and vomiting.[6]

Participants self-graded the severity of their cough, shortness of breath, subjective fever, fatigue, myalgia, sore throat, chills, headache, rhinorrhea, and nausea as none (0 points), mild (1 point), moderate (2 points), or severe (3 points). Loss of smell and loss of taste were graded as: same as usual (0 points), less than usual (1 point), or no taste / no smell (2 points). Vomiting and diarrhea were graded daily as none (0 points), 1-2 times (1 point), 3-4 times (2 points), and $\geq$ 5 times (3 points). After 14 days, participants' written diaries were mailed in pre-addressed return envelopes to the University of Minnesota and entered into the study database.

Statistical Analysis:

A total symptom severity score was calculated as the summation of each of the 14 graded symptoms.[4] Additionally, a modified total symptom score was *a priori* proposed (prior to data analysis) based on the 8 Covid-specific symptoms as per the U.S. clinical case definition,[6] excluding loss of taste or smell, recognizing these may take longer to recover; these two symptoms were thus presented individually. We grouped participants based on vaccination status at study baseline (i.e. time of enrollment): 1) unvaccinated; 2) vaccinated with primary vaccine series (i.e. 2 doses mRNA vaccine or 1 dose of adenovirus Ad26.COV2.S vaccine); or 3) vaccinated with booster (hereafter "booster" group). We also categorized trial enrollment into three periods corresponding to the alpha wave (June 18, 2021 or earlier), delta wave (between June 19 and December 19, 2021), and omicron wave (December 20, 2021 or later).

Symptom severity over time was evaluated using generalized estimating equations (GEEs) assuming a first-order autoregressive (AR1) working correlation matrix. The GEE model treated time as a factor and included a factorial time by vaccination status interaction, allowing for differential associations between vaccination status and symptom severity across the 14 days. Subgroup analyses were carried out for the three variant waves. Sensitivity analyses were carried out that further adjusted for participant age, assigned sex at birth, and study drugs. The primary statistical signficance test evaluates pairwise differences in the average

symptom severity scores across the 14 day period among the vaccination status categories. All analyses were conducted using R version 4.1 with statistical significance evaluated at the two-sided 0.05 alpha level.

Results:

The parent clinical trial prospectively enrolled 1323 participants in the primary, modified intent-to-treat analysis cohort, of whom 1062 (80%) prospectively returned daily symptom log data on at least one day. Overall, 89.6% (952/1062) of participants provided 14 days of data, 8.7% (92/1062) with 8-13 days of symptom data, and 2.7% (29/1062) with 1-7 days of symptom data. The analysis cohort includes all participants who provided a daily symptom log on at least one day and excludes those who did not provide any daily symptom logs. The median age of participants was 47 years (interquartile range, 38 to 55 years), the median body mass index was 30 kg/m^2 (interquartile range, 27 to 34 kg/m^2), 56% were women (6% of whom were pregnant), and 55% were vaccinated (9% of whom were boosted). Demographics of the unvaccinated (n=480), vaccinated (n=530), and vaccine-boosted (n=52) groups are presented in **Table 1**. Cumulative enrollment by vaccination status is presented in **Figure S1.** The median time from primary series vaccination to trial enrollment was 196 days [IQR: 146 to 240 days] with 10% enrolling in 90 days or less and 31% in 180 days or less. The median time from booster to trial enrollment was 37 days [IQR: 11 to 74 days] with 86% enrolling in 90 days or less and 12% in 180 days or less.

When assessing the total symptom score, there were clear differences at baseline by vaccination status. By 14 days, most participants who were not hospitalized experienced a resolution of their symptoms. Those unvaccinated had the greatest severity of total overall symptoms, followed by those vaccinated with a primary series only, and then the vaccine-boosted group with the lowest symptoms (**Figure 1** and **Table S1**). Average symptom severity across the 14 day study period was 1.2 points lower (95%CI, 0.6 to 1.8 points; P<0.001) among vaccinated participants compared with unvaccinated participants, and 3.0 points lower (95%CI, 2.1 to 3.9 points; P<0.0001) among boosted participants compared with unvaccinated participants (**Figure 1** and **Table S5a**).

These trends were consistent during the enrollment periods corresponding to the alpha and delta waves, though during the omicron wave the reduced symptom severity between vaccinated only and unvaccinated participants vanished (**Figure 2** and **Tables S5a**). During the delta time period, primary series vaccinated participants had an average over time of 2.0 points lower (95%CI, 1.3 to 2.7 points; P<0.0001) on total symptom severity compared with unvaccinated participants, which reflects a 24% relative reduction (6.5 versus 8.5 points) in symptom severity. Vaccine boosted participants had an average over time of 3.5 points lower (95%CI, 2.2 to 4.8 points; P<0.0001) compared with unvaccinated participants during delta variant time period, which reflects a 41% relative reduction (5.0 versus 8.5 points) in symptom severity. During the omicron time period, there was no difference between primary vaccine series vs unvaccinated participants with an average

of 0.7 points higher score in vaccinated participants (95%CI, -0.4 to 1.9 points; P=0.21). However, the vaccine boosted group maintained less severe symptoms with an average over 14 days of 1.6 points lower (95%CI, 0.4 to 2.8 points; P=0.007) as compared to unvaccinated participants during omicron.

Analyses adjusted for potential confounding factors including age, assigned sex at birth, study drugs, and pandemic variant period did not substantively alter the observed associations between vaccination status and symptom severity overall (**Table S6a)**. The statistical significance of the boosted versus unvaccinated comparison during the omicron period remained for the covid-19 specific symptoms, but not for all symptoms (**Table S6a - S6b)**. Symptom severity was higher in females and younger participants, and highest during the delta period and lowest during the omicron period (**Figures S2 – S4** and **Tables S2 – S4**).

In assessing individual symptoms, some symptoms were of similar severity between groups while others markedly differed, being most severe in the unvaccinated and the least severe in the vaccine-boosted group (**Figures 3 and 4**). Symptoms that differed across the three vaccine groups included: cough, chills, fever, nausea, fatigue, myalgia, headache, and diarrhea, as well as smell, and taste abnormalities (P<.05). In all cases the vaccine-boosted group had the least severe symptoms over time.

Discussion

In this prospective observational cohort nested within a clinical trial, we observed substantially lower subjective symptom severity among those who had received a vaccine booster as compared to those who were vaccinated with a primary series only or unvaccinated. Those who had received a vaccine booster had significantly lower severity of initial symptoms and symptoms over time during acute COVID-19 infection compared to unvaccinated participants. We observed a marked, statistically significant difference between those who had received a vaccine booster as compared with only the primary vaccine series (i.e. 2 doses mRNA vaccine or 1 dose of adenovirus Ad26.COV2.S vaccine); this reinforces the benefits of a booster vaccine in adults after approximately 5-6 months from primary SARS-CoV-2 vaccination.

The observational nature of this study is a limitation. Because the trial completed enrollment in January 2022, 4 months after vaccine boosters were widely available, these data are limited in understanding the durability of boosters against symptom severity. The study population comes from a large randomized trial of U.S adults over age 30 years with a body mass index of $\geq$ 25 kg/m^2 (i.e. overweight or obese) who were enrolled predominantly during 2021 with a majority of persons infected with the SARS-CoV-2 delta variant or omicron variant. These data are most generalizable to this population and could differ with future variants.

Overall, these data strongly support the impact of SARS-CoV-2 vaccine boosters on diminishing SARS-CoV-2 disease severity and symptoms. Vaccine protection from any SARS-CoV-2 infection wanes over time, in part due to new variants propagated by immune escape,[2, 3] yet the vaccine-booster was strongly associated with less severe symptoms at baseline as well as over 14-days of illness, even when adjusting for viral variants. SARS-CoV-2 vaccination, with the development of a primed immune response, is likely the best

single prophylatic treatment for COVID-19 to prevent clinical deterioration and decrease symptoms. With vaccination or survival of prior infection, COVID-related mortality becomes less of a concern; however, the morbidity of symptoms does remain a concern. Symptoms such as loss of sense of smell or taste affect quality of life. Vaccine-boosters appear to be the single best strategy to ameliorate symptom severity.

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Potential Conflicts:

Authors report no potential conflicts of interest.

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Table 1. Cohort demographics overall and by vaccination status.

	Overall N = 1,062	No Vaccine N = 480	Vaccinated only N = 530	Vaccine-Boosted N = 52
Age, years	47 (38, 55)	46 (38, 54)	47 (39, 56)	52 (37, 64)
Female	56% (591)	58% (279)	53% (279)	63% (33)
Race				
Native American	2.0% (21)	2.1% (10)	1.9% (10)	1.9% (1)
Asian	3.8% (40)	2.7% (13)	4.5% (24)	5.8% (3)
Hawaiian or Pacific Islander	0.6% (6)	0.2% (1)	0.9% (5)	0% (0)
Black or African American	6.4% (68)	5.8% (28)	6.2% (33)	13% (7)
White	85% (904)	87% (417)	84% (445)	81% (42)
Other/Declined	4.8% (51)	5.0% (24)	4.9% (26)	1.9% (1)
Hispanic Ethnicity	11% (114)	9.0% (43)	13% (69)	3.8% (2)
Body Mass Index, kg/m^2	30.0 (26.9, 34.3)	30.0 (26.9, 33.7)	29.8 (26.7, 34.6)	29.8 (27.4, 33.4)
BMI $\geq$ 30 kg/m^2	50% (530)	51% (245)	49% (259)	50% (26)
Cardiovascular disease	28% (294)	24% (117)	30% (159)	35% (18)
Diabetes	2.1% (22)	1.9% (9)	1.9% (10)	5.8% (3)
Symptom duration on study drug initiation, days	4.7 (1.8)	4.7 (1.9)	4.8 (1.8)	4.4 (2.0)
Symptom duration $\leq$ 4 days	47% (490)	48% (228)	45% (232)	61% (30)
Unknown duration	25	9	13	3
Variant time period				
Alpha	12% (132)	21% (103)	5.5% (29)	0% (0)
Delta	65% (694)	59% (285)	72% (382)	52% (27)
Omicron	22% (236)	19% (92)	22% (119)	48% (25)
Insurance Status				
Private	65% (688)	60% (286)	69% (368)	65% (34)
Medicare	7.9% (84)	6.9% (33)	7.5% (40)	21% (11)
Medicaid	14% (146)	17% (83)	11% (57)	12% (6)
No insurance	12% (124)	14% (69)	10% (54)	1.9% (1)
Unknown	1.9% (20)	1.9% (9)	2.1% (11)	0% (0)
Randomized to Study Drug*				
Metformin	50% (527)	48% (229)	51% (270)	54% (28)
Ivermectin	32% (341)	32% (152)	33% (173)	31% (16)
Fluvoxamine	25% (261)	22% (108)	27% (141)	23% (12)

Data displayed are median (interquartile range) or n (%).

*Percentages will not add up to 100% because the trial used a 3 x 2 factorial design.

Figure Legends

Figure 1. COVID-19 symptom severity score over 14 days by SARS-CoV-2 vaccination status

This line graph presents the expected symptom severity score and 95% confidence interval on study days 1 through 14 for the unvaccinated group in red, the vaccinated with a primary series group in blue, and the vaccinated with a primary series and boosted group in black. The upper panel presents the composite symptom severity score of 14 symptoms, as suggested by FDA.[4] The lower panel presents the composite score for 8 Covid-19 specific symptoms only, as defined by CDC clincial case defintion.[6] Expected scores and confidence intervals are from a GEE model assuming a first order autoregressive working correlation matrix with a factorial time by vacciation status interaction. Overall effect p-values reflect a joint Wald test for a difference in symptom score by vaccine status across days 1 through 14. Vaccination is associated with symptom severity over time (P<.001) with boosted participants having the lowest expected symptom severity.

Figure 2. COVID-19 symptom severity score over 14 days by SARS-CoV-2 vaccination status during three distinct enrollment periods corresponding to the alpha, delta and omicron waves.

This plot shows the average total symptom score (95% CI) over the 14-day follow-up period by vaccination status and variant wave. Fitted values were obtained separately for each SARS-CoV-2 variant period (alpha, delta, omicron) using a generalized estimating equation assuming a first order autoregressive working correlation matrix and including a factorial interaction between day and vaccination status. The purpose of this analysis was to account for the potential confounding effects of viral variant on the association between total symptom score and vaccination status.

Figure 3. Notable Symptoms differing by SARS-CoV-2 vaccination status

Figure 4a. Loss of Smell by SARS-CoV-2 Vaccination Status over time

Figure 4b. Loss of Taste by SARS-CoV-2 Vaccination Status over time

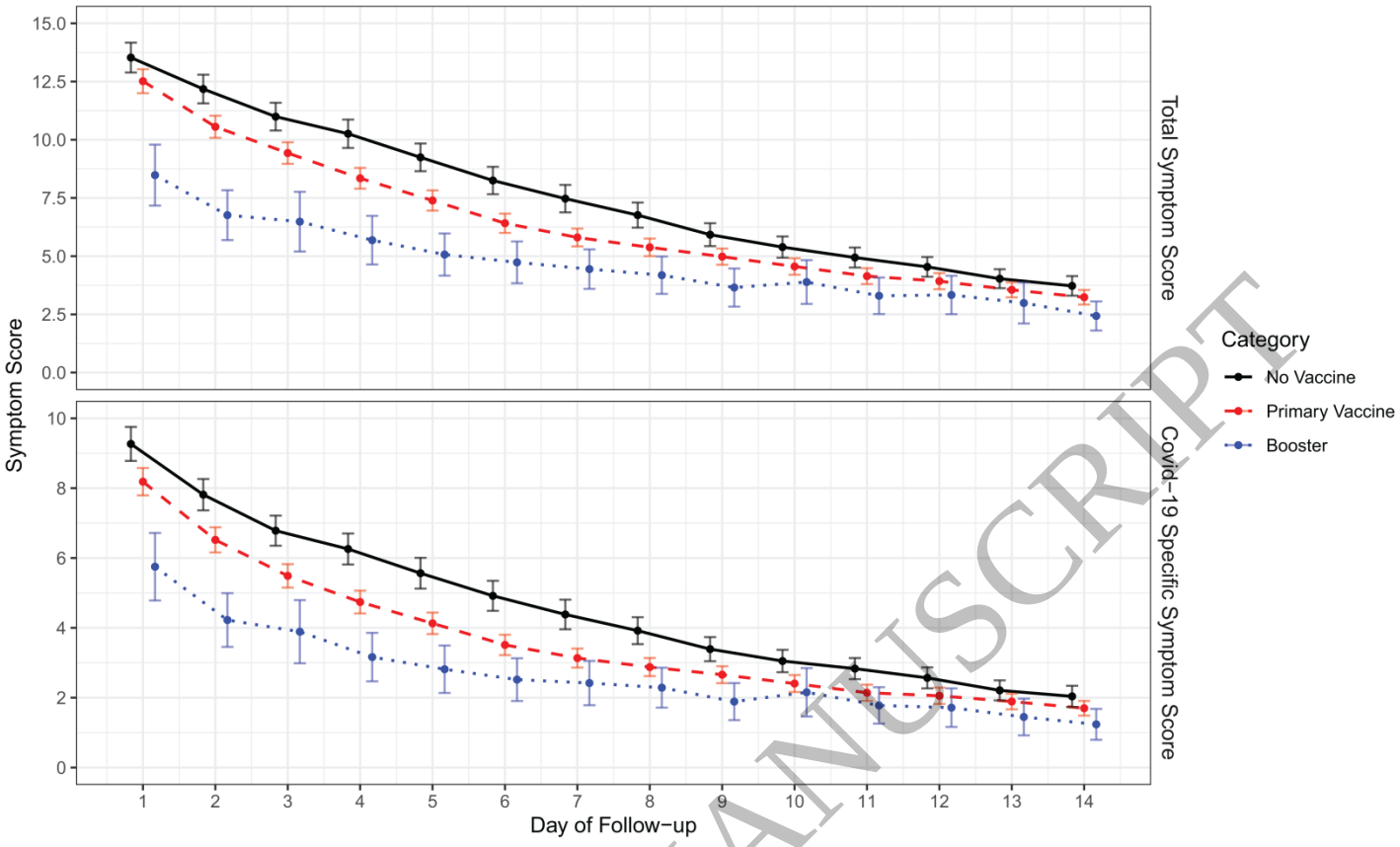

Figure 1
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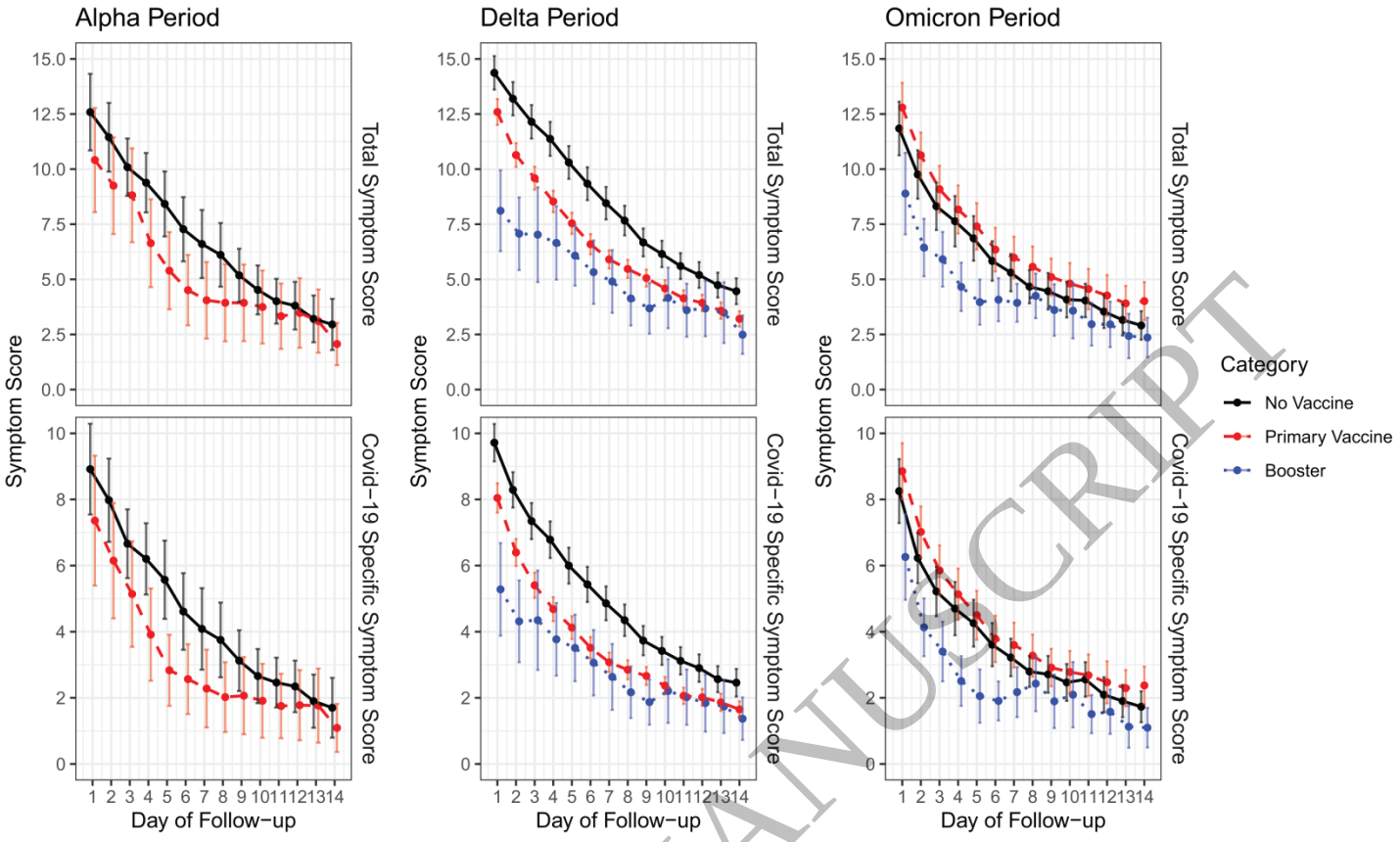

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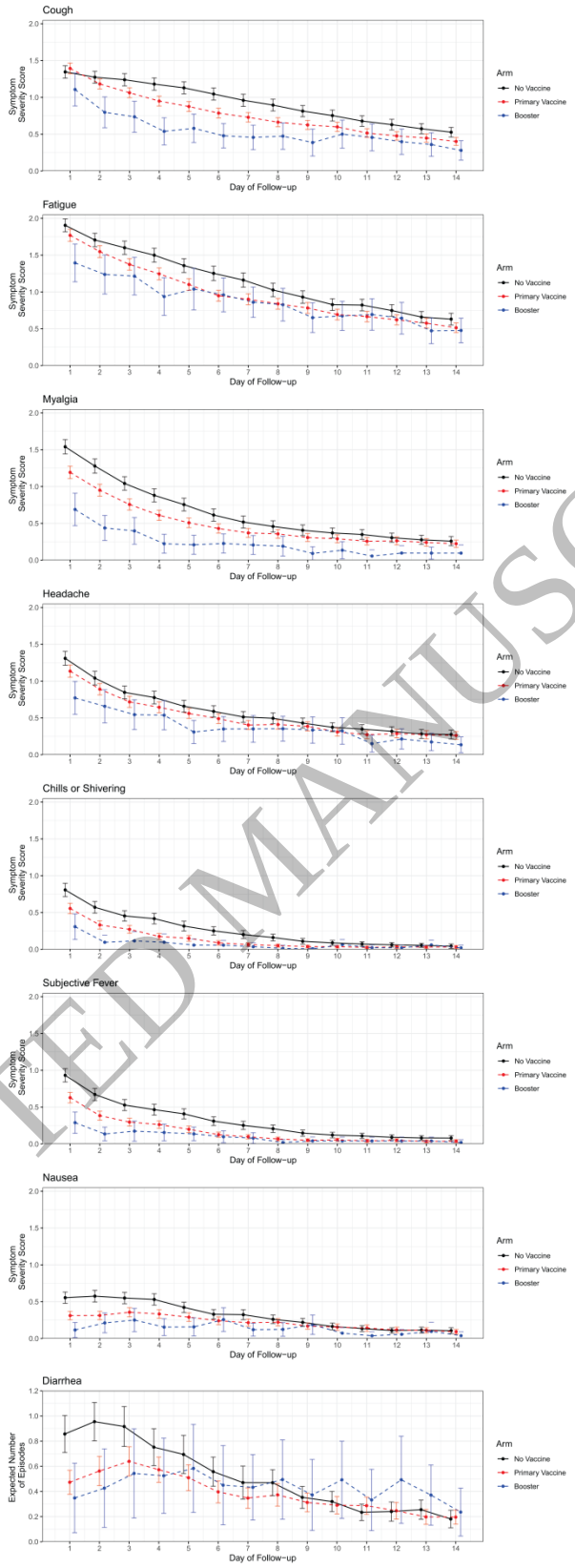

Figure 3
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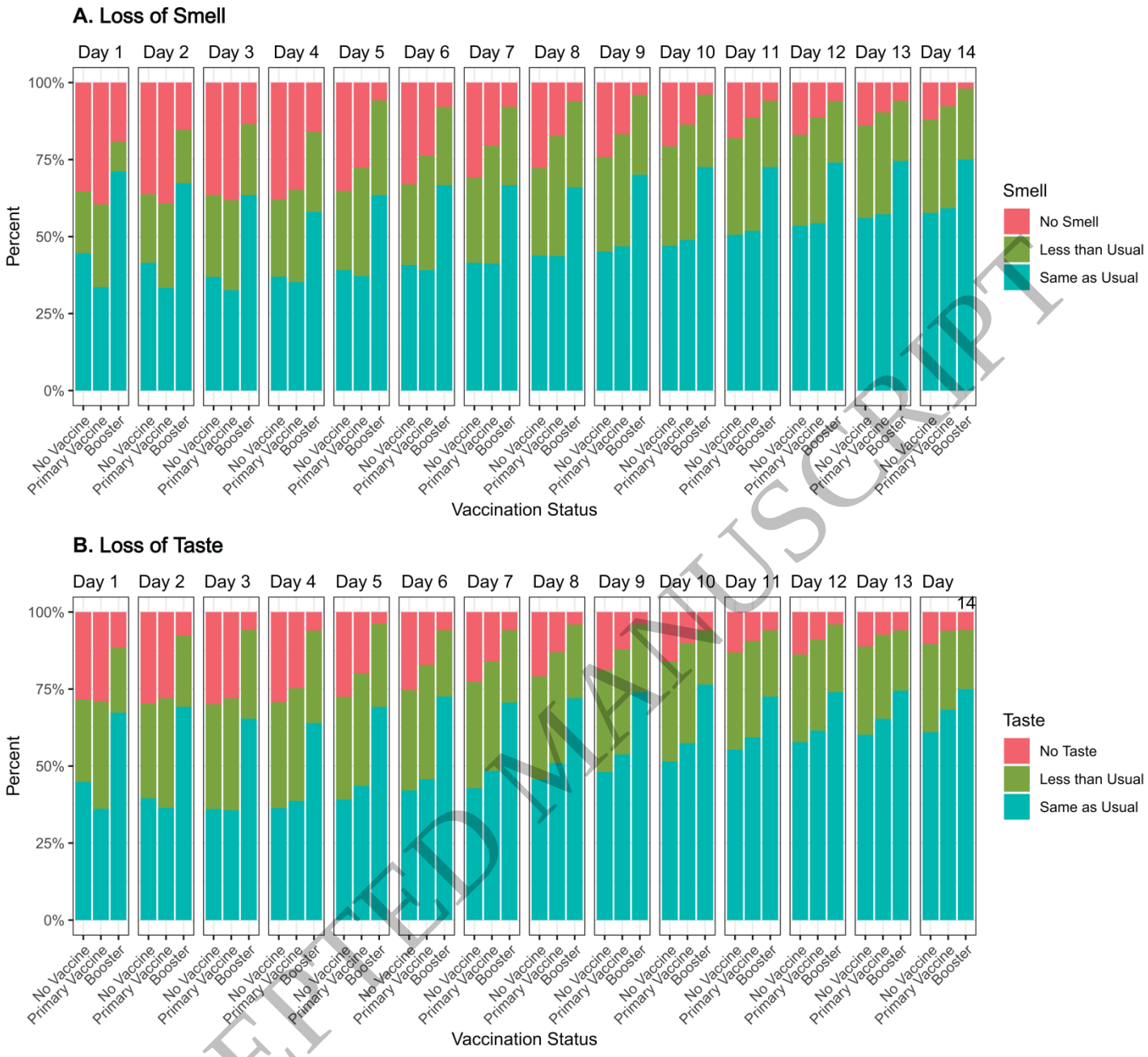

Figure 4
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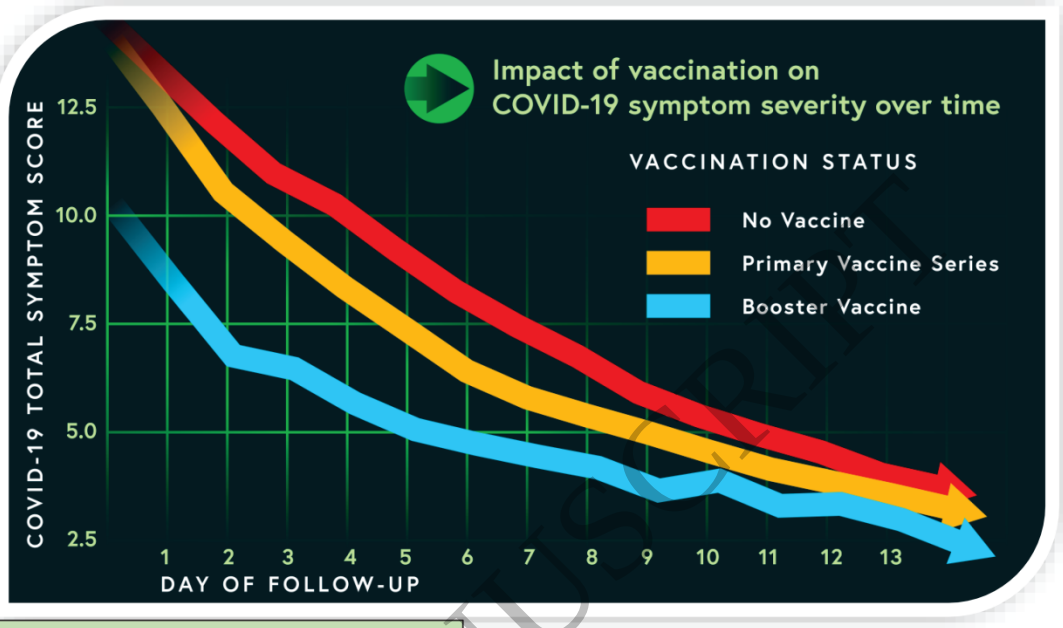
Impact of SARS-CoV-2 vaccination and booster on COVID-19 symptom severity over time

Population

Adults 30-85 years old with overweight or obesity enrolled in an outpatient Covid-19 trial.

Methods

- Secondary data analysis of Covid-Out trial data
- 1062 participants recorded 14 symptoms daily
- Total symptom severity score calculated
- Secondary analysis compared Symptoms among:
  - no vaccine (n=480 (45%);
  - primary vaccine series (N=530 (50%)
  - primary vaccine series + booster. N=52 (5%)



Key Findings

Covid-19 symptoms were least severe at baseline and subsided most quickly in boosted individuals.

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Graphical Abstract
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