Protection by vaccines and previous infection against the Omicron variant of SARS-CoV-2

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SUMMARY

Effectiveness of vaccines and post-infection immunity against the Omicron variant of SARS-CoV-2 is significantly lower than against the Delta variant. The probability of a severe outcome is substantially lower for the Omicron variant compared to Delta.

ABSTRACT

Background. The Omicron variant of SARS-CoV-2 evades immunity conferred by vaccines and previous infections.

Methods. We used a Cox proportional hazards model and a logistic regression on individual-level population-wide data from the Czech Republic to estimate risks of infection and hospitalization, including severe states.

Results. A recent ($\leq$ 2 months) full vaccination reached VE 43% (95% CI: 42-44) against infection by Omicron compared to 73% (CI: 72-74) against Delta. A recent booster increased VE to 56% (CI: 55-56) against Omicron infection compared to 90% (CI: 90-91) for Delta. The VE against Omicron hospitalization of a recent full vaccination was 45% (95% CI: 29-57), with a recent booster 87% (CI: 84-88). The VE against the need for oxygen therapy due to Omicron was 57% (CI: 32-72) for recent vaccination, 90% (CI: 87-92) for a recent booster. Post-infection protection against Omicron hospitalization declined from 68% (CI: 68-69) at $\leq$ 6 months to 13% (CI: 11-14) at $>$ 6 months after a previous infection. The OR for Omicron

relative to Delta was 0.36 (CI: 0.34-0.38) for hospitalization, 0.24 (CI: 0.22-0.26) for oxygen, and 0.24 (CI: 0.21-0.28) for ICU admission.

Discussion. Recent vaccination still brings substantial protection against severe outcome for Omicron.

Keywords. Covid-19; post-infection immunity; vaccine effectiveness; SARS-CoV-2; Omicron variant; hospitalization.

INTRODUCTION

The B.1.1.529 (Omicron) variant of SARS-CoV-2 was first detected in South Africa in November 2021, immediately designated a variant of concern by the WHO [1], and thereafter seen to spread quickly throughout most of the world. This rapid spread was at least in part brought about by a degree of immune evasion due to a large number of mutations in the viral S-protein, which led to changes in epitopes recognised by antibodies elicited by vaccination or previous infection [2]. Together with non-pharmacological interventions, such as face masks, distancing, ventilation of interior spaces testing and isolating, vaccination is among the most effective means of individual and collective protection from the impacts of the pandemic. The immune evasion by the Omicron variant thus caused concern and led to a lot of interest in both laboratory and real-life epidemiological data that could accurately measure this phenomenon.

Since 27 December 2020 the inhabitants of the Czech Republic have been receiving Covid-19 vaccines, the largest number vaccinated with the mRNA vaccine BNT162b2 (Pfizer/BioNTech), followed by mRNA-1273 (Moderna), and the adenovirus-based vector vaccines ChAdOx1 nCoV-19 (AstraZeneca) and Ad26.CoV2.S (Johnson&Johnson) [3]. By the end of our study period on 13 February 2022, 68% of the population had

a complete vaccination and 39% received a booster dose [3]

The first case of the Omicron variant in the Czech Republic was detected at the end of November 2021, its proportion of recorded cases rapidly rose and by 10 January 2022 it became the dominant variant (Fig. 1). An increasing number of infections among fully vaccinated and re-infections indeed suggests that immune evasion poses a significant risk to further Covid-19 development [3].

In this study, we estimate how the protection due to vaccination or previous SARS-CoV-2 infection against Covid-19 infection, hospital admission, oxygen therapy and ICU admission varies in relation to the virus variant and time elapsed for the entire population of the Czech Republic.

METHODS

Study population and data sources

The analyses are based on data from the Czech National Information System of Infectious Diseases (ISID), which includes records of all individuals tested positive for SARS-CoV-2 in the Czech Republic since the beginning of Covid-19 pandemic, including children [4]. This database is overseen by the Czech Ministry of Health and operated by the Institute of Health Information and Statistics of the Czech Republic. Data are routinely collected in compliance with Czech legal regulations (Act on the Protection of Public Health). The Director of the Institute of Health Information and Statistics of the Czech Republic has granted that there is no need for ethical approval of the retrospective analyses presented in this paper.

The ISID database collects demographic data (age, sex and region of residence), dates of vaccination, including the vaccine types for each dose, and dates of in-

fection and potential reinfection, hospitalization including treatment type, and the date of potential death with Covid-19. The data recorded in the study period include information on whether the infection is caused by the Omicron, Delta, some other variant, or that a variant discrimination was not performed, see Figure 1. The information on the variant is based on results of multiplex PCR or viral genome sequencing, which are available only for a subset of all PCR-positive cases. The variants were identified using the definition of viral S-protein mutations according to ECDC [5]; the algorithm was tailored to multiplex PCR kits used in the Czech Republic in collaboration with the National Institute of Public Health and the National Reference Laboratory [6]. Additional information on deaths from any cause comes from the Death Certificate System; these data are used for censoring purposes only.

Study endpoints

We studied four types of events: (i) SARS-CoV-2 infection defined as a PCR-confirmed positive test of any type of sample regardless of the presence of symptoms, (ii) hospital admission of a person who tested positive on a PCR test within two weeks after the confirmed infection or earlier, (iii) use of any type of oxygen therapy (nasal oxygen, noninvasive ventilation, invasive mechanical ventilation, high-flow nasal oxygen, and extracorporeal membrane oxygenation) and (iv) admission to ICU during the hospitalization. All events were related to the date of infection report.

We examined events during the two month period from 7 December 2021 to 13 February 2022, during which Delta and Omicron switched dominance in the Czech Republic (Fig. 1).

Statistical analysis

A Cox regression with time-varying covariates was applied to estimate hazard ratios (HRs) for the outcomes of interest separately for each viral variant. In these analyses, the infections by the variant other than the examined one and the infections lacking variant assignment were censored at the time of infection. Analogously to [7] we used calendar time instead of time from event occurrence as the time scale. Thus the time course of individual cases was modelled by means of "switching" dummy variables, corresponding to the development of the immune status after vaccination or past infection in 61-day periods for vaccination and 121-day periods for the time from the last infection. The control variables include age group and sex.

The protection provided by vaccine (vaccine effectiveness) or previous infection is calculated by comparing hazards of the vaccinated and/or immunized individuals to those of the "control group" – those who have not been vaccinated and infected so far and subtracted from 1 using the equation:

$$\mathit{Protection}\,(\mathrm{VE}) = 1 - \frac{\mathrm{Hazard}_{\mathrm{protected}}}{\mathrm{Hazard}_{\mathrm{unprotected}}}. \tag{1}$$

Further we examine the post-infection immunity by estimating hazard ratios of infection of previously unvaccinated individuals in relation to time elapsed from the infection.

By using calendar time we were able to incorporate automatically the changing conditions of the epidemic, including non-pharmacological measures, seasonal effects, the ratio of discriminated samples, and the proportion of the virus variant, as all of these phenomena can be included in the underlying baseline hazard function.

To examine the probabilities of hospitalization, oxygen therapy and ICU admission for an infected individual, we use the logistic regression with the event of interest as

the outcome and with immunity status at the time of infection, age group and sex as the covariates. We compare the probabilities of the outcome for both variants by means of the dummy corresponding to the virus variant.

All calculations were performed using the R software. The algorithm used to transform data from the database into the package command inputs was coded in C++. See Supplementary material 1 for details.

RESULTS

Protection against infection

First we looked at the protection conferred by vaccination or a previous infection against a new infection, since the protection against infection represents the potential to protect other risk groups in the population. The protection after vaccination against the Omicron variant reached 43% (95% CI 42-44) shortly after completing the full vaccination scheme, falling to 9% (95% CI 8-10) after more than two months. This protection increased to 56% (95% CI 55-56) shortly after receiving a booster dose, followed by a decline to 21% (95% CI 19-23) after more than two months. These numbers strongly contrast with the protection against the Delta variant, which was consistently higher at 73% (95% CI 72-74), 57% (95% CI 56-58), 90% (95% CI 90-91) and 82% (95% CI 79-84), respectively. Similar degrees of protection against infection are conferred also by post-infection immunity: 68% (95% CI 68-69) shortly after a previous infection (2-6 months); a positive test during the first two months after an infection is not considered a reinfection by definition) and 13% (95% CI 11-14) after six months for Omicron, versus 95% (95% CI 94-96) shortly after infection, and 83% (95% CI 82-84) after six months for Delta (Figure 2). Based on the past prevalence of viral variants, it can be expected that the infections older

than 6 months were mostly due to the original Wuhan, D614G and Alpha variants, while the more recent ones were predominantly due to Delta. As we show in the Supplementary material 2, Sections 11 and 12, explicit accounting for the vaccine type (BNT162b2 by Pfizer/BioNTech and mRNA-201273 by Moderna) gave values of effectiveness comparable with the analyses of pooled data reported here in the main text.

We had enough data to examine all the combinations in which a previous infection preceded vaccination. As expected, protection declined with time elapsed from the previous infection or vaccination (Table 1). Regarding protection against the Delta variant, any combination provided $\geq 95\%$ protection against infection (Table 1). This protection remained quite high also against Omicron when the previous infection was recent, falling to lower values for an older previous infection, but even then the protection was significantly higher than that provided by a vaccination or previous infection alone (Table 1). We also analysed cases when a vaccination preceded an infection followed by a re-infection. In the case of re-infections caused by Delta, against which the achieved protection was generally high at 96% (90-98%), the exact order of events did not appear to matter. For re-infections caused by Omicron, against which protection is generally lower, the cases where a previous infection followed a vaccination appeared to provide a higher level of protection than the inverse sequence: protection provided by the Full 2+/Inf 6− combination was 89% (95% CI 88-91) as compared to 86% (95% CI 85-88) for the Inf 6−/Full 2+ one.

A finer grained analysis of temporal dynamics of immunity waning after a previous infection was then conducted specifically for individuals that were previously infected but remained non-vaccinated. Against Omicron, the protection was estimated as 69% (95% CI 68-69) for 2-6 months after previous infection, 48% (95% CI 46-50) for 7-10 months, 34% (95% CI 33-35) for 11-14 months, and 17% (95% CI 15-18)

for 14 and more months after previous infection. For Delta, on the contrary, these numbers were 93% (95% CI 91-94), 91% (95% CI 90-92), 86% (95% CI 85-86), and 79% (95% CI 77-81), respectively.

Protection against hospitalization

A qualitatively similar pattern yet quantitatively consistently higher protection is seen against hospitalization, a need for oxygen therapy, and a need for intensive care (Table 2). For example, a recent booster dose provides 86% protection against hospitalization, 90% against a need for oxygen therapy, and 83% against a need for intensive care when infected by the Omicron variant. Moreover, all combinations of previous infection and vaccination present in our data appear to provide nearly complete protection against Omicron as regards hospitalization (Table 3) as well as oxygen therapy or intensive care (often no cases have been observed for such situations, see Supplementary material 2, Sec. 7–10).

Risk of a severe outcome for Omicron vs. Delta

Finally, our logistic regression analyses show that once infected, the odds ratio is 0.36 (0.34-0.38) for hospitalization with Omicron relative to Delta; 0.24 (0.22-0.26) for a need of oxygen therapy with Omicron relative to Delta; and 0.24 (0.21-0.28) for a need of intensive care with Omicron relative to Delta. Moreover, once hospitalized, the odds ratio is 0.44 (0.39-0.49) for a need of oxygen therapy with Omicron relative to Delta; and 0.64 (0.52-0.72) for a need of intensive care with Omicron relative to Delta (see Supplementary material 2, Sec. 15–19 for further details).

DISCUSSION

Our data support the existing evidence that the Omicron variant of SARS-CoV-2, to a significant extent, evades both the post-vaccination and post-infection immunity [2, 8–11]. The VE levels of all the vaccines used in the Czech Republic are lower for Omicron compared to Delta. As we previously observed with Alpha and Delta [12], the protection against infection by the Omicron variant wanes over time too. However, a booster vaccine dose provides robust and lasting, or slowly waning, protection against hospitalization, the need for oxygen therapy and intensive care. The combined post-infection and post-vaccination immunity is the most protective regardless of the exact sequence of events, suggesting that the best protective strategy before a coming wave is to vaccinate all individuals, whether previously vaccinated or with a previous Covid-19 infection.

We are aware of the complicated interpretation of the hospitalization data for the Omicron wave: the very high basic reproduction number R_0 of this variant [13] translated into the very high prevalence of infection in the population at the peak of the epidemic wave; and a much higher proportion of hospitalized patients with Covid-19 as a concomitant finding rather than the reason for admission. We therefore analysed separately the need for oxygen therapy and ICU admission as a more relevant measure of severe outcomes due to the Omicron infection.

Compared to the Delta variant, the protection provided by the post-infection or post-vaccination immunity is lower against the Omicron variant but at the same time the Omicron variant appears less severe than the Delta variant and the odds ratio for oxygen therapy or ICU admission both approximately equal about one quarter compared to the Delta variant.

A common limitation of studies like ours is the fact that only a certain proportion of infections is reported (ascertainment rate). We believe this phenomenon does not

significantly affect our estimates of vaccine effectiveness, assuming that the ascertainment rate is the same for the vaccinated and the unvaccinated alike and we have no evidence to the contrary. A potentially low ascertainment rate could also distort our estimates of the protection by the post-infection immunity; in particular, if there had been many undetected individuals with post-infection immunity in the control group, the infection risk of the virgin population would have been underestimated and, consequently, the protection by infection underestimated as well. Our results should be interpreted in terms of reported infections only.

In all of our analyses we used age and sex as control variables; however, with some caution they can also be understood as risk factors. In this respect, our results generally confirm the common knowledge that the risk of various severe outcomes grows exponentially with the person's age – this is clearly illustrated by the linear increase of log-hazard ratios for both variants (see Supplementary material 2, Sec. 5–19). The age-related risk of (re-)infection, on the other hand, appears to be the highest for children and people in the productive age. This pattern is more pronounced for the Omicron variant. However, it is not clear to what extent the pattern is caused by behavioral causes and/or the current epidemic situation rather than biological causes.

Notes

Data sharing. Data reported in this study and used for the analyses are not public. De-identified individual-level data are available to the scientific community. Requests, together with a short description of their analysis proposals, should be submitted to the Institute of Health Information and Statistics of the Czech Republic (`www.uzis.cz/index-en.php`) where they will be assessed based on relevance and scientific merit.

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Potential conflicts of interest All authors: No reported conflicts.

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Table 1: Protection due to various combinations of past infection preceding vaccination *against infection* for the *Omicron* and the *Delta* variants of the SARS-CoV-2 virus. Infection in recent 6 months is denoted as Inf 6− and older Inf 6+, completed vaccination scheme is denoted Full 2− for completion in recent 2 months and Full 2+ for older completion, analogously for booster. In parentheses, 95% confidence intervals (CI) are given.

VOC	*Infection*	*Vaccination*			
		Booster 2−	Full 2−	Booster 2+	Full 2+
Omicron	Inf 6−	92% (89-94%)	82% (75-87%)	82% (72-89%)	86% (85-88%)
	Inf 6+	74% (73-75%)	77% (76-78%)	48% (45-52%)	45% (44-46%)
Delta	Inf 6−	95% (66-99%)	100% no case	100% no case	97% (94-98%)
	Inf 6+	98% (98-99%)	98% (97-98%)	94% (89-97%)	96% (95-96%)

Table 2: Vaccine effectiveness and protection provided by post-infection immunity against a need for hospitalization, oxygen therapy, or intensive case, for the Omicron and Delta variants of the SARS-CoV-2 virus. In parentheses, 95% confidence intervals (CI) are given.

Vaccination	*Hospitalization*		*Oxygen therapy*		*Intensive care*	
or infection	Omicron	Delta	Omicron	Delta	Omicron	Delta
Full 2−	45% (29-57%)	73% (69-76%)	57% (32-72%)	82% (76-87%)	58% (3-82%)	84% (72-91%)
Full 2+	29% (21-37%)	77% (76-79%)	32% (20-43%)	82% (80-83%)	37% (12-55%)	86% (83-88%)
Booster 2−	86% (84-88%)	97% (97-98%)	90% (87-92%)	98% (98-98%)	83% (75-89%)	98% (97-99%)
Booster 2+	79% (75-82%)	96% (94-97%)	85% (80-88%)	97% (95-98%)	60% (37-74%)	97% (92-99%)
Inf 6−	73% (55-84%)	100% (no case)	81% (40-94%)	100% (no case)	83% (0-98%)	100% (no case)
Inf 6+	66% (54-75%)	94% (91-96%)	88% (72-94%)	98% (95-99%)	66% (15-86%)	97% (90-99%)

Table 3: Protection due to various combinations of past infection preceding vaccination *against hospitalization* for the *Omicron* and the *Delta* variant of the SARS-CoV-2 virus. Infection in recent 6 months is denoted as Inf 6− and older Inf 6+, completed vaccination scheme is denoted Full 2− for completion in recent 2 months and Full 2+ for older completion, analogously for booster. In parentheses, 95% confidence intervals (CI) are given.

VOC	*Infection*	*Vaccination*			
		Booster 2−	Full 2−	Booster 2+	Full 2+
Omicron	Inf 6−	100% no case	100% no case	71% (0-96%)	93% (49-99%)
	Inf 6+	95% (78-99%)	94% (77-95%)	90% (64-98%)	73% (78-99%)
Delta	Inf 6−	100% no case	100% no case	100% no case	100% no case
	Inf 6+	99% (99-100%)	97% (91-99%)	98% (85-100%)	98% (98-100%)

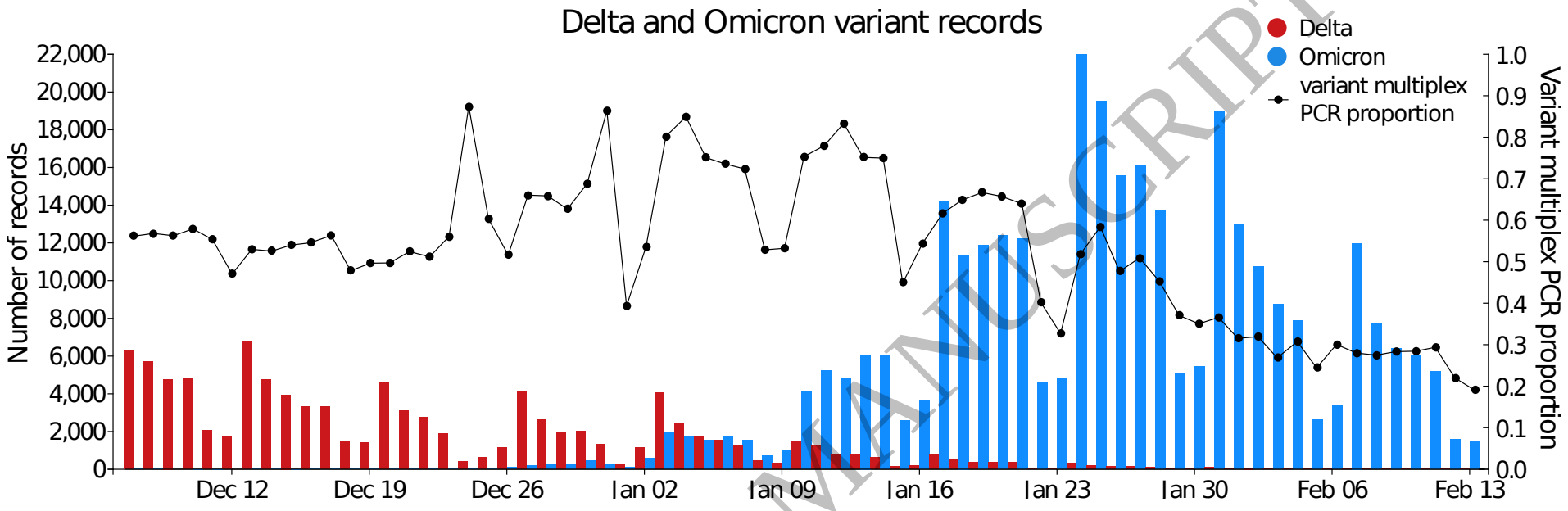

Figure 1: Number of recorded cases with assigned Delta (red) and Omicron (blue) variant and the proportion of PCR positive tests (black) tested for viral variants using multiplex PCR.

Figure

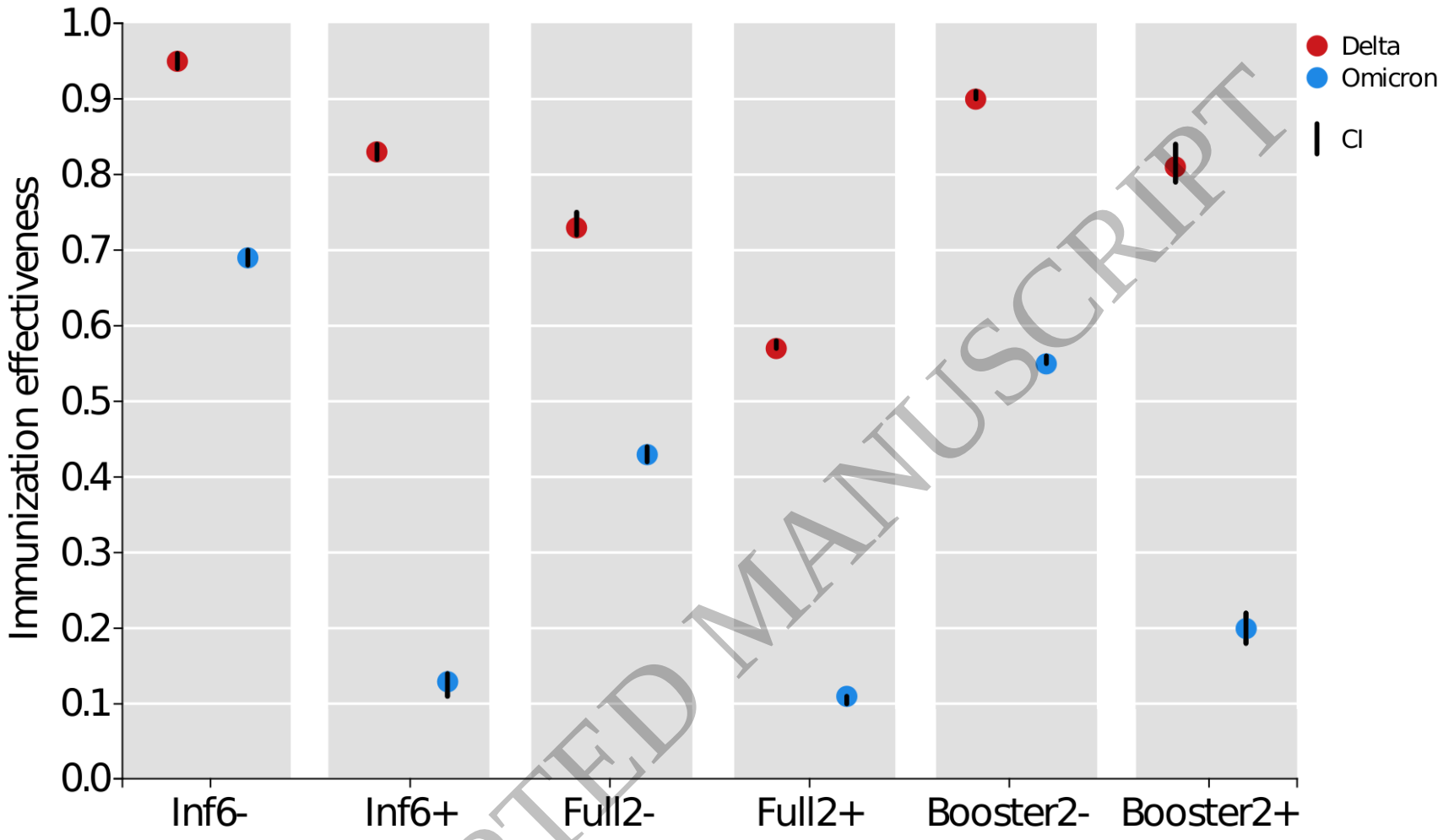

Figure 2: Protection provided by vaccination or previous infection against infection by the Omicron and Delta variants of the SARS-CoV-2 virus. Inf6-, previous infection ≤ 6 months ago; Inf6+, previous infection > 6 months ago; Full2-, complete vaccination ≤ 2 months ago; Full2+, complete vaccination > 2 months ago; Booster2-, booster dose ≤ 2 months ago; Booster2+, booster dose > 2 months ago. Point estimates of protection with 95% CI are shown.