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COVID-19 Severity and Waning Immunity After up to 4 mRNA Vaccine Doses in 73 608 Patients With Cancer and 621 475 Matched Controls in Singapore
A Nationwide Cohort Study

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 + **Supplemental content**

IMPORTANCE Despite patients with cancer being at risk of poor outcomes from COVID-19, there are few published studies for vaccine efficacy in this group, with suboptimal immunogenicity and waning vaccine efficacy described in small studies being a concern.

OBJECTIVE To assess the incidence rate of severe COVID-19 disease outcomes associated with the number of vaccine doses received and the waning of protection over time.

DESIGN, SETTING, AND PARTICIPANTS A prospective multicenter observational cohort study was carried out over 2 time periods (September 15, 2021, to December 20, 2021 [delta wave], and January 20, 2022, to November 11, 2022 [omicron wave]) predominated by SARS-CoV-2 delta and omicron variants, respectively. Overall, 73 608 patients with cancer (23 217 active treatment, 50 391 cancer survivors) and 621 475 controls matched by age, sex, race and ethnicity, and socioeconomic status were included.

EXPOSURE Vaccine doses received, from zero to 4 doses, and time elapsed since last vaccine dose.

OUTCOMES Competing-risk regression analyses were employed to account for competing risks of death in patients with cancer. Main outcomes were incidence rate ratios (IRRs) of COVID-19 infection, hospitalization, and severe disease (defined as requirement for supplemental oxygen, intensive care, or death). The IRRs stratified by time from last vaccine dose served as indicators of waning of vaccine effectiveness over time.

RESULTS The mean (SD) age of actively treated patients with cancer, cancer survivors, and controls were 62.7 (14.7), 62.9 (12.6), and 61.8 (14.7) years, respectively. Of 73 608 patients with cancer, 27 170 (36.9%) were men; 60 100 (81.6%) were Chinese, 7432 (10.1%) Malay, 4597 (6.2%) Indian, and 1479 (2.0%) were of other races and ethnicities. The IRRs for the 3-dose and 4-dose vs the 2-dose group (reference) for COVID-19 hospitalization and severe disease were significantly lower during both the delta and omicron waves in cancer and control populations. The IRRs for severe disease in the 3-dose group for active treatment, cancer survivors, and controls were 0.14, 0.13, and 0.07 during the delta wave and 0.29, 0.19, and 0.21 during omicron wave, respectively. The IRRs for severe disease in the 4-dose group during the omicron wave were even lower at 0.13, 0.10 and 0.10, respectively. No waning of vaccine effectiveness against hospitalization and severe disease was seen beyond 5 months after a third dose, nor up to 5 months (the end of this study's follow-up) after a fourth dose.

CONCLUSION This cohort study provides evidence of the clinical effectiveness of mRNA-based vaccines against COVID-19 in patients with cancer. Longevity of immunity in preventing severe COVID-19 outcomes in actively treated patients with cancer, cancer survivors, and matched controls was observed at least 5 months after the third or fourth dose.

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M ore than 500 million cases of COVID-19 have been
confirmed worldwide[1] since it was declared as a pan-
demic by the World Health Organization on March
11, 2020.[2] Effective vaccines for COVID-19, mainly using the
viral surface spike protein as an antigenic target,[3,4] have been
especially important for immunocompromised patients in-
cluding patients with cancer, who are at increased risk of se-
vere disease and poor outcomes from COVID-19.[5-8] However,
evidence of suboptimal immunogenicity and waning immu-
nity following vaccination in immunocompromised patients[9-12]
has prompted the urgent need for booster vaccination espe-
cially in this vulnerable population.

Various retrospective studies confirmed the clinical effi-
cacy of COVID-19 vaccination in reducing rates of sympto-
matic infection and severe disease.[13-15] Although the clinical
effectiveness of a third vaccine dose has been demonstrated
in the general population,[16] data in immunocompromised
patients have been limited to small studies of postvaccina-
tion seroconversion, both for an initial 2-dose series[17,18] as well
as a third dose.[19-24] Furthermore, there is a paucity of evi-
dence of the time course of waning immunity in both immu-
nocompromised and healthy individuals to guide optimal in-
tervals for booster vaccination. As the COVID-19 pandemic
progresses, representative data of waning immunity is cru-
cial to guide policy in protecting the general population and
vulnerable subgroups.

In Singapore, patients with cancer were first excluded
from the initial rollout of vaccines to the general public from
February 2021[25] as part of national vaccination efforts based
on safety considerations, but were subsequently made eli-
gible from July 2021 (eFigure 1 in Supplement 1).[26] Following
the implementation of a third vaccine dose, patients with can-
cer on active treatment were prioritized to receive it as early
as 2 months following the second dose, compared with the eli-
gibility of the general public to receive it only after 5 months.[27]
More recently, up to a fifth dose has been made available to
the general population, with vulnerable subgroups of pa-
tients including those immunocompromised through cancer
treatment being prioritized. Four vaccines are currently ap-
proved for use in Singapore[28] based on efficacy demon-
strated in randomized clinical trials; the mRNA-based
BNT162b2 Comirnaty (Pfizer-BioNTech)[29] and mRNA-1273
Spikevax (Moderna)[30] vaccines, protein subunit-based vac-
cine NVX-CoV2373 Nuvaxovid (Novavax),[31] and inactivated
virus-based vaccine CoronaVac (Sinovac).[32]

To address the limited studies of the clinical effective-
ness of vaccines among patients with cancer, this article as-
sesses vaccine effectiveness and waning of effectiveness of up
to 4 doses of COVID-19 vaccines among a nation wide sample
of patients with cancer compared with the general popula-
tion.

Methods

Setting and Study Population

This multicenter cohort study was conducted by Singapore's
Ministry of Health, and includes all patients on follow-up in

Key Points

Question How effective is COVID-19 vaccination in patients with
cancer in protecting against severe disease and does protection
wane over time?

Findings In this nationwide cohort study including 73 608
patients with cancer and 621 475 matched controls, third and
fourth vaccine doses were associated with incremental protection
in both groups. No significant decrease in protection against
severe disease was observed 5 months after the third and fourth
vaccine dose.

Meaning Each booster COVID-19 vaccine dose was associated
with significant clinical protection in patients with cancer, lasting
at least 5 months in actively treated patients with cancer and
cancer survivors, underscoring the benefit of boosters.

the public health care system for a diagnosis of cancer across
the 3 tertiary cancer institutions in Singapore; the National
Cancer Centre Singapore (NCCS), National University Cancer
Institute, Singapore (NCIS), and Tan Tock Seng Hospital (TTSH).
Most patients received the mRNA-based vaccines BNT162b2
and mRNA-1273 administered in national vaccination centers
in the community and health care institutions. Patients with
COVID-19 acquired outside Singapore or prior to the study
period were excluded to improve comparability between the
study and control populations.

Study Design

This study was conducted to support policy decision-making
and evaluation of public health responses to COVID-19 under
the Infectious Disease Act and was exempted from ethics re-
view and written informed consent. Relevant parameters were
extracted from national database records maintained as part
of Singapore's national pandemic response efforts. Patient char-
acteristics were collected prospectively and outcomes of
COVID-19 infection were predefined prior to commencement
of this study; these include baseline demographics (age, sex,
race and ethnicity, and socioeconomic status as indicated by
residence), cancer treatment at the time of study, number and
dates of mRNA-based COVID-19 vaccine doses received,
COVID-19 infection and date of infection, and COVID-19–
associated hospitalization, requirement for supplemental
oxygen, requirement for intensive care, and death. Patients
administered zero or 1 vaccine dose were considered as "un-
vaccinated/partially vaccinated," 2 doses as "fully vacci-
nated," and 3 or 4 doses as "boosted."

Our analysis was further stratified according to the pre-
vailing COVID-19 variant and time periods of infection waves
in Singapore, determined retrospectively. The study popula-
tion included patients with cancer over 2 separate time periods;
September 15, 2021, to December 20, 2021, corresponding to
the wave of infections predominated by the SARS-CoV-2 delta
variant (delta wave), and January 20, 2022, to November 11,
2022, predominated by the SARS-CoV-2 omicron variant (omi-
cron wave). For each study period, data collected was locked
after the last day stipulated, December 15, 2021, for the delta
wave and November 11, 2022, for the omicron wave. Five con-
trols from the general population matched by age, sex, race and

ethnicity, and socioeconomic status (based on type of residence) from national database records were included for every patient in the study population for comparison.

Vaccination status was categorized according to the number of vaccine doses administered; zero/single dose, 2 doses, 3 doses, and 4 doses. In the cancer cohort, patients receiving active treatment (chemotherapy, immunotherapy, targeted therapy) and no treatment (cancer survivors) were analyzed separately. Incidence of COVID-19 infections and vaccination rates in the study population were compared with the general population. Incidence rate ratios (IRRs) for COVID-19 infection, hospitalizations, and severe disease (defined as requirement for supplemental oxygen, intensive care, or death) by vaccination status were calculated for the cancer cohort and matched controls, as were IRRs over time for fully vaccinated and boosted patients as indicators of waning vaccine effectiveness. Patients who received non–mRNA-based vaccines were excluded from these analyses. Cases and controls were categorized by time elapsed since the last vaccine dose (8-59 days, 60-149 days, and more than 150 days) for analysis on waning vaccine effectiveness. For calculations of IRRs to assess statistical significance, 95% confidence intervals are reported.

Statistical Analysis

Using methods previously described by Bar-On et al[16] and with further reference to Zhang et al,[33] competing-risk regressions taking into account competing risks of non–COVID-19–related deaths were performed to estimate relative risks for comparison across vaccination status categories. Analyses were set up on a person-day basis, adjusted for the covariates of age, sex, race and ethnicity, prior infection with COVID-19 before the study period, and socioeconomic status. Weekly dummy date variables were included to control for varying force of infection across time. Exponentiated coefficients of competing-risks regression were derived and IRRs calculated, with lower IRR values indicating better vaccine efficacy compared with designated reference groups. Fully vaccinated patients were the reference for comparisons of vaccine effectiveness across patients of different vaccination status. Poisson regressions controlling for the same covariates were conducted for comparison.

To further improve the robustness of results, we conducted calendar time-scale Cox regressions following Lund et al,[34] with and without accounting for competing risks of non–COVID-19 deaths. Similar covariates were included in these Cox regressions. For waning of vaccine effectiveness, fully vaccinated patients within 8 to 59 days were the reference group in the delta phase, whereas boosted patients within 8 to 59 days were the reference group in the omicron phase for better comparability. The IRRs for patients were grouped by number of vaccine doses received (zero/single-dose, 2-dose, 3-dose, and 4-dose groups), with lower IRRs being reflective of decreased incidence of patients with corresponding COVID-19–related outcomes of infection, severe disease, or hospitalization.

Data analysis was carried out in STATA statistical software (StataCorp LP, version 17). $P<.05$ was considered statistically significant.

Results

Characteristics and Vaccination Rates in the Study Population

Overall, 73 608 individual patients with cancer (23 217 receiving active treatment and 50 391 cancer survivors) with 621 475 matched controls from the general population were included across the delta and omicron waves (baseline characteristics shown in **Table 1**). Cumulative incidence of COVID-19 infections among actively treated patients with cancer, cancer survivors, and matched controls over delta and omicron waves is shown in eFigure 2 in Supplement 1. The total observed person-days and incidence rate per million person-days is shown in eTable 1 in Supplement 1. In the general population, 84.8% received at least 2 doses of mRNA-based vaccine by the end of the study period. There were 2.6% who received non–mRNA-based vaccines, and are excluded from comparative analyses focusing on mRNA-based vaccination rates in subsequent sections of this study. Rates of vaccination across the delta and omicron waves are reflected in **Table 2**.

At the start of the delta wave, more cancer survivors (86.5%, $P < .001$) and slightly less of those receiving active treatment (74.1%, $P < .001$) were fully vaccinated or boosted compared with the general population (75.3%). As national policy prioritized vaccinations and boosters for immunocompromised patients, increasing numbers receiving active cancer treatment (91.1%, $P < .001$) and cancer survivors (93.2%, $P < .001$) were fully vaccinated or boosted compared with the general population (78.8%) by the end of the delta wave on December 20, 2021. Moving into the omicron wave, the proportion of fully vaccinated patients continued to remain significantly higher in the active treatment (92.0%, $P < .001$) and cancer survivors (93.6%, $P < .001$) cohorts compared with the general population (79.1%).

Booster fourth doses were made available in the later half of the omicron wave. By the end of the omicron wave on November 11, 2022, significantly higher proportions of patients in the active cancer (24.7%) and cancer survivor (31.6%) groups had received a fourth dose compared with the general population (12.5%, $P < .001$). As of the end of this study, 401 (0.54%) of the patients with cancer and 0.15% of the general population had received a fifth vaccine dose, with the numbers too small for any significant analyses to be performed.

Incidence Rate Ratios

The IRRs for patients grouped by number of vaccine doses received (zero/single-dose, 2-dose, 3-dose, and 4-dose groups) are shown in **Table 3**. During both the delta and omicron waves, IRRs for COVID-19 infection were not significantly higher in the zero/single-dose group in active treatment, cancer survivors, and control cohorts compared with the 2-dose group. This is likely owing to nationwide implementation of vaccination-differentiated safe management measures, which imposed significant restrictions on social activities for unvaccinated or partially vaccinated (zero/single-dose) patients in an effort to limit transmission of COVID-19. The IRRs for COVID-19 hospitalization in the zero/single-dose group are not shown because its

Table 1. Characteristics of Study and Control Populations

Characteristic	0/1 Doses			2 Doses			3 Doses			4 Doses		
	Active treatment	Cancer survivors	Controls	Active treatment	Cancer survivors	Controls	Active treatment	Cancer survivors	Controls	Active treatment	Cancer survivors	Controls
Sex, No. (%)												
Female	727 (61.8)	927 (55.5)	18 865 (52.5)	2286 (59.9)	2949 (56.8)	32 857 (58.7)	9303 (67.4)	20 142 (64.5)	257 162 (65.5)	2907 (65.7)	7197 (58.5)	81 765 (59.7)
Male	450 (38.2)	743 (44.5)	17 095 (47.5)	1533 (40.1)	2244 (43.2)	23 124 (41.3)	4496 (32.6)	11 079 (35.5)	135 398 (34.5)	1515 (34.3)	5110 (41.5)	55 209 (40.3)
Age, y, No. (%)												
0-17	6 (0.5)	34 (2.0)	280 (0.8)	6 (0.2)	38 (0.7)	307 (0.5)	5 (0)	56 (0.2)	688 (0.2)	0	4 (0)	3 (0)
18-29	10 (0.8)	25 (1.5)	266 (0.7)	67 (1.8)	149 (2.9)	1956 (3.5)	211 (1.5)	1070 (3.4)	12 484 (3.2)	10 (0.2)	10 (0.1)	74 (0.1)
30-39	31 (2.6)	60 (3.6)	743 (2.1)	133 (3.5)	320 (6.2)	3526 (6.3)	526 (3.8)	1936 (6.2)	24 027 (6.1)	25 (0.6)	21 (0.2)	208 (0.2)
40-49	95 (8.1)	150 (9.0)	2487 (6.9)	361 (9.5)	567 (10.9)	6811 (12.2)	1700 (12.3)	4447 (14.2)	58 153 (14.8)	91 (2.1)	178 (1.4)	1843 (1.3)
50-59	234 (19.9)	241 (14.4)	5944 (16.5)	784 (20.5)	903 (17.4)	12 788 (22.8)	3175 (23.0)	6505 (20.8)	86 511 (22.0)	790 (17.9)	1895 (15.4)	23 327 (17.0)
60-69	407 (34.6)	372 (22.3)	10 745 (29.9)	1216 (31.8)	1245 (24.0)	14 238 (25.4)	4353 (31.5)	8282 (26.5)	109 174 (27.8)	1627 (36.8)	4077 (33.1)	47 092 (34.4)
70-79	278 (23.6)	454 (27.2)	9046 (25.2)	916 (24.0)	1222 (23.5)	10 031 (17.9)	2986 (21.6)	6309 (20.2)	73 686 (18.8)	1331 (30.1)	3865 (31.4)	41 643 (30.4)
≥80	116 (9.9)	334 (20.0)	6449 (17.9)	336 (8.8)	749 (14.4)	6324 (11.3)	843 (6.1)	2616 (8.4)	27 837 (7.1)	548 (12.4)	2257 (18.3)	22 784 (16.6)
Race and ethnicity, No. (%)												
Chinese	923 (78.4)	1300 (77.8)	27 777 (77.2)	2980 (78.0)	4161 (80.1)	43 042 (76.9)	10 908 (79.0)	25 316 (81.1)	314 693 (80.2)	3744 (84.7)	10 768 (87.5)	118 474 (86.5)
Malay	152 (12.9)	165 (9.9)	4179 (11.6)	503 (13.2)	585 (11.3)	7805 (13.9)	1684 (12.2)	3204 (10.3)	43 443 (11.1)	354 (8.0)	785 (6.4)	9731 (7.1)
Indian	81 (6.9)	160 (9.6)	3114 (8.7)	256 (6.7)	374 (7.2)	4356 (7.8)	907 (6.6)	2076 (6.6)	26 485 (6.7)	208 (4.7)	535 (4.3)	6067 (4.4)
Others	21 (1.8)	45 (2.7)	890 (2.5)	80 (2.1)	73 (1.4)	778 (1.4)	300 (2.2)	625 (2.0)	7939 (2.0)	116 (2.6)	219 (1.8)	2702 (2.0)
Residence, No. (%)												
Public (1-3 room)[a]	395 (33.6)	556 (33.3)	11 798 (32.8)	1111 (29.1)	1541 (29.7)	17 407 (31.1)	3305 (24.0)	7172 (23.0)	90 354 (23.0)	983 (22.2)	2938 (23.9)	32 534 (23.8)
Public (4-5 room)[a]	614 (52.2)	810 (48.5)	18 049 (50.2)	2172 (56.9)	2727 (52.5)	31 166 (55.7)	8209 (59.5)	17 738 (56.8)	226 921 (57.8)	2388 (54.0)	6335 (51.5)	71 684 (52.3)
Private[a]	133 (11.3)	235 (14.1)	4968 (13.8)	431 (11.3)	740 (14.2)	5728 (10.2)	1914 (13.9)	5402 (17.3)	63 724 (16.2)	936 (21.2)	2735 (22.2)	29 533 (21.6)
Others	35 (3.0)	69 (4.1)	1145 (3.2)	105 (2.7)	185 (3.6)	1680 (3.0)	371 (2.7)	909 (2.9)	11 561 (2.9)	115 (2.6)	299 (2.4)	3223 (2.4)
COVID-19, No. (%)												
Infected[b]	453 (38.5)	684 (41.0)	3681 (10.2)	2287 (59.9)	3380 (65.1)	41 815 (74.7)	5977 (43.3)	14 428 (46.2)	164 212 (41.8)	532 (12.0)	1697 (13.8)	15 725 (11.5)
Hospitalized	253 (21.5)	354 (21.2)	1492 (4.1)	705 (18.5)	699 (13.5)	4919 (8.8)	888 (6.4)	993 (3.2)	6246 (1.6)	67 (1.5)	144 (1.2)	992 (0.7)
Severe disease[c]	67 (5.7)	145 (8.7)	646 (1.8)	105 (2.7)	171 (3.3)	1162 (2.1)	100 (0.7)	183 (0.6)	1128 (0.3)	9 (0.2)	23 (0.2)	147 (0.1)
Death[d]	22 (1.9)	53 (3.2)	241 (0.7)	23 (0.6)	35 (0.7)	242 (0.4)	13 (0.1)	21 (0.1)	128 (0)	0	3 (0)	18 (0)
Total, No. (%)	1177 (100)	1670 (100)	35 960 (100)	3819 (100)	5193 (100)	55 981 (100)	13 799 (100)	31 221 (100)	392 560 (100)	4422 (100)	12 307 (100)	136 974 (100)

[a] Type of residence was used as an indicator of socioeconomic status.

[b] Significant differences were observed for incidence of COVID-19 infection between the active treatment (P < .001) and cancer survivors (P < .001) groups compared with controls.

[c] Significant differences were observed for incidence of severe disease between those in the active treatment (P < .001) and cancer survivor (P < .001) groups compared with controls. Severe disease was defined as COVID-19 infection with resulting need for supplemental oxygen, intensive care admission, or death.

[d] Significant differences were observed for death from COVID-19 between the active treatment (P < .001) and cancer survivors (P < .001) groups compared with controls.

interpretation is confounded by national health care protocols mandating inpatient treatment of unvaccinated or partially vaccinated patients with confirmed COVID-19 infection regardless of disease severity.

Table 2. Vaccination Rates in Patients With Cancer and the General Population

Vaccine doses received	Start of delta wave (September 15, 2021), No. (%)			End of delta wave (December 20, 2021), No. (%)		
	Patients with cancer			Patients with cancer		
	Active treatment	Cancer survivors	General population	Active treatment	Cancer survivors	General population
0 doses	3527 (15.2)	4258 (8.4)	885 274 (21.1)	1030 (4.4)	1487 (3.0)	762 264 (18.2)
1 dose (mRNA-based)	2273 (9.8)	1973 (3.9)	91 946 (2.2)	384 (1.7)	398 (0.8)	15 615 (0.4)
2 doses (mRNA-based)	17 212 (74.1)	43 559 (86.4)	3 152 609 (75.3)	11 874 (51.1)	18 959 (37.6)	1 910 481 (45.6)
3 doses (mRNA-based)	3 (0)	5 (0)	204 (0)	9283 (40.0)	28 020 (55.6)	1 393 995 (33.3)
4 doses (mRNA-based)	0	0	0	0	0	77 (0)
Non-mRNA	203 (0.9)	596 (1.2)	59 186 (1.4)	647 (2.8)	1527 (3.0)	106 787 (2.5)
Total	23 217 (100)	50 391 (100)	4 189 219 (100)	23 217 (100)	50 391 (100)	4 189 219 (100)
	Start of omicron wave (January 20, 2022), No. (%)			End of omicron wave (November 11, 2022), No. (%)		
0 doses	921 (4.0)	1334 (2.6)	666 187 (15.9)	721 (3.1)	1102 (2.2)	492 199 (11.7)
1 dose (mRNA-based)	263 (1.1)	282 (0.6)	97 341 (2.3)	203 (0.9)	189 (0.4)	33 865 (0.8)
2 doses (mRNA-based)	9323 (40.2)	12 979 (25.8)	1 244 467 (29.7)	2206 (9.5)	2293 (4.6)	318 529 (7.6)
3 doses (mRNA-based)	12 033 (51.8)	34 196 (67.9)	2 070 688 (49.4)	13 467 (58.0)	28 749 (57.1)	2 687 293 (64.1)
4 doses (mRNA-based)	0	0	105 (0)	5729 (24.7)	15 908 (31.6)	522 294 (12.5)
Non-mRNA	678 (2.9)	1600 (3.2)	110 431 (2.6)	891 (3.8)	2150 (4.3)	135 039 (3.2)
Total	23 217 (100)	50 391 (100)	4 189 219 (100)	23 217 (100)	50 391 (100)	4 189 219 (100)

Table 3. Incidence and Risk of COVID-19 by Unvaccinated or Partially Vaccinated, Fully Vaccinated, and Boosted Populations

Vaccine doses	COVID-19 incidence (95% CI)			COVID-19 hospitalization (95% CI)			COVID-19 severe disease (95% CI)		
	Active treatment	Cancer survivors	Controls	Active treatment	Cancer survivors	Controls	Active treatment	Cancer survivors	Controls
Delta wave									
0 or 1 dose	0.64 (0.50-0.82)	0.92 (0.75-1.13)	0.28 (0.26-0.30)	1.57 (1.18-2.10)	2.80 (2.16-3.62)	0.99 (0.88-1.11)	3.37 (1.92-5.91)	9.37 (6.34-13.84)	2.51 (2.12-2.96)
2 doses	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
3 doses	0.37 (0.29-0.48)	0.34 (0.29-0.40)	0.26 (0.25-0.28)	0.24 (0.15-0.38)	0.23 (0.16-0.33)	0.14 (0.11-0.17)	0.14 (0.03-0.59)	0.13 (0.05-0.33)	0.07 (0.05-0.12)
Omicron wave									
0 or 1 dose	0.71 (0.59-0.87)	0.73 (0.63-0.85)	0.40 (0.37-0.44)	NA[a]	NA[a]	NA[a]	1.85 (0.99-3.47)	1.56 (1.02-2.39)	0.82 (0.62-1.08)
2 doses	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
3 doses	0.91 (0.86-0.97)	0.91 (0.86-0.96)	0.91 (0.88-0.93)	0.45 (0.40-0.52)	0.27 (0.24-0.32)	0.29 (0.27-0.32)	0.29 (0.20-0.42)	0.19 (0.14-0.26)	0.21 (0.18-0.25)
4 doses	0.78 (0.70-0.88)	0.80 (0.74-0.87)	0.85 (0.81-0.88)	0.24 (0.18-0.33)	0.15 (0.12-0.19)	0.21 (0.18-0.25)	0.13 (0.06-0.31)	0.10 (0.06-0.17)	0.10 (0.07-0.15)

[a] Incidence ratio ratios for COVID-19 hospitalization not shown because interpretation was confounded by mandatory inpatient treatment of unvaccinated or partially vaccinated patients with confirmed COVID-19 infection.

Despite lower COVID-19 infection rates for the zero/single-dose compared with the 2-dose group, these patients had significantly higher rates of severe COVID-19 disease during the delta wave in both the active treatment (IRR, 3.86) and cancer survivor (IRR, 10.07) groups. In addition, the IRR for severe COVID-19 disease for the zero/single-dose group during the omicron wave was also higher in both the active treatment (1.85) and cancer survivor cohorts (1.56), although this did not reach statistical significance in the active treatment cohort. This highlights the increased vulnerability of patients with cancer to adverse outcomes from COVID-19, with risk of severe disease further compounded in the absence of vaccination.

The 3-dose group was significantly protected from COVID-19 hospitalization and severe disease in both cancer and control groups, with lower IRRs compared with the 2-dose group across both the delta and omicron waves. Compared with controls, higher IRR was observed against severe COVID-19 disease in the active treatment cohort during both the delta (IRR, 0.14 vs 0.07) and omicron (IRR, 0.27 vs 0.18) waves, whereas the cancer survivor cohort had similar IRRs to controls (IRR, 0.13 vs 0.07 during the delta wave, 0.18 vs 0.18 during the omicron wave).

During the omicron wave, numerically lower IRRs against severe disease in the 4-dose compared with the 3-dose groups were suggestive of additional protection conferred by a fourth

Figure. Waning of Vaccine Effectiveness Across the Delta and Omicron Waves
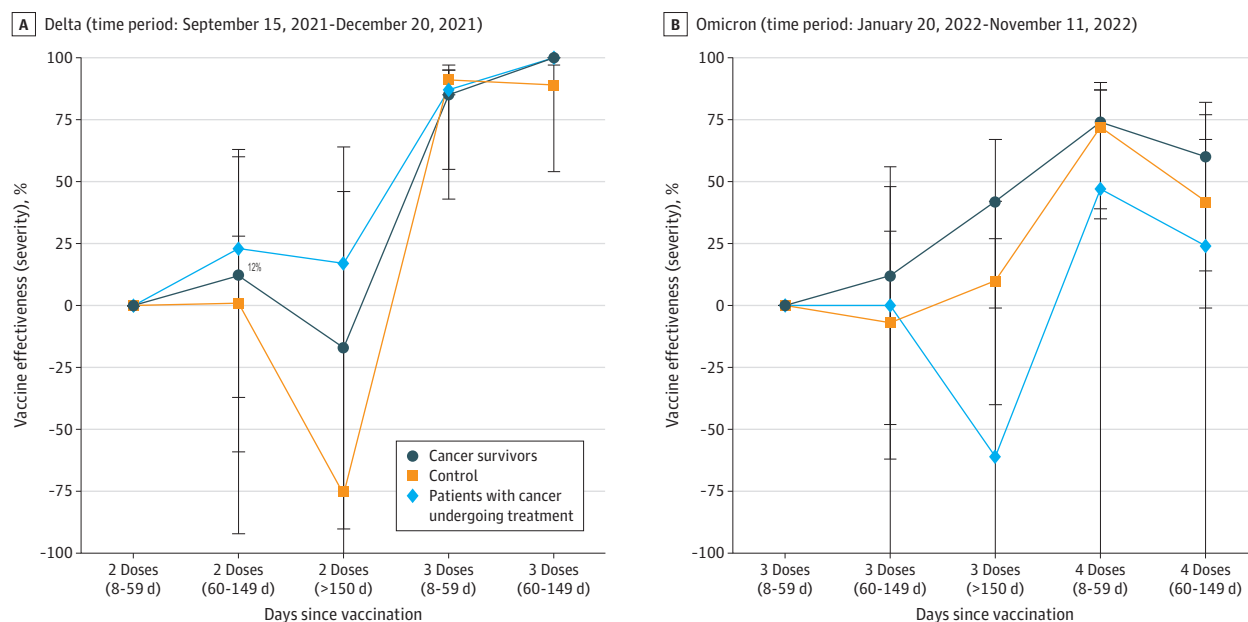
A, Shows the delta period; and B, the omicron period for the waning of vaccine effectiveness against severe COVID-19 with reference to 2 doses (8 to 59 days) and 3 doses (8 to 59 days), respectively. No significant waning was observed. The whiskers show the 95% CIs.

dose. In particular, the IRR for severe disease was significantly lower during infection 8 to 59 days after the fourth dose compared with 8 to 59 days after the third dose (eTable 2 in Supplement 1), suggesting a fourth dose provides additional protection.

For the outcome of COVID-19 hospitalization, IRRs were significantly lower in the 4-dose vs the 3-dose group in the active treatment (0.24 vs 0.45), cancer survivor (0.15 vs 0.27), and control groups (0.21 vs 0.29), suggesting a fourth vaccine dose may confer additional protection against COVID-19 infection necessitating hospitalization, regardless of cancer and treatment status.

Waning of Vaccine Effectiveness

The overall trends in waning of vaccine effectiveness are depicted in the **Figure**. During the delta wave, no significant waning of vaccine effectiveness following 2 doses was observed in the active treatment and cancer survivor cohorts against COVID-19 hospitalization and severe disease, which is more remarkable given the significant waning demonstrated in the control group from 150 days postvaccination (eTable 2 in Supplement 1). Although no significant waning following third dose was observed, numbers were small during the delta wave, which limits interpretation of results.

During the omicron wave, no significant waning of vaccine effectiveness following 3 doses was observed against COVID-19 hospitalization and severe disease in both the cancer and control cohorts, despite waning effectiveness against COVID-19 infection shown. The incidence of COVID-19 outcomes 8 to 59 days after the third dose was used as the reference.

Following the fourth dose, no significant waning of vaccine effectiveness was observed across all outcomes from 60 days postvaccination. However, small numbers may limit interpretation of these results, given only 0.2% of patients in the 4-dose group manifested the outcome of severe disease.

Sensitivity and Additional Analyses

Additional analyses, including Poisson regressions (eTables 3, 4, 5, and 6 in Supplement 1), calendar-time scale Cox regressions with and without incorporating competing risks (eTables 7, 8, 9, and 10 in Supplement 1), and regressions using time since last dose as a continuous variable (eTable 11 in Supplement 1) were run and compared with results derived from our primary competing risks regression methodology, demonstrating similar trends.

Adjusted absolute incidence rates per million person-days (eTables 1 and 12 in Supplement 1) were lower during the delta wave for the 3-dose compared with the 2-dose group for COVID-19 severe disease in the active treatment (5 vs 29), cancer survivor (4 vs 21), and control (2 vs 20) groups. The same was observed during the omicron wave for the 4-dose compared with the 3-dose group (active treatment, 21 vs 29; cancer survivors, 17 vs 21), though not in the control group (11 vs 11).

Discussion

To our knowledge, this study is the first to demonstrate clinical vaccine effectiveness of up to 4 doses of mRNA-based vaccines against COVID-19 in actively treated patients with can-

cer and cancer survivors, and matched noncancer controls at a population level. In addition, few other studies have longitudinally correlated the time from the last vaccination to clinical outcomes of COVID-19 infection in patients with cancer at a representative population level.[35]

High vaccination rates likely accounted for the low COVID-19 mortality observed among patients with cancer in Singapore reported in our study compared with prevailing case-fatality rates.[36] Vaccination-differentiated management measures directed toward reducing exposure of unvaccinated and partially vaccinated patients may have resulted in lower infection rates, although higher incidence of severe disease was still observed in unvaccinated and partially vaccinated individuals. This persisted into the omicron wave, despite the variant being associated with decreased severity compared with preceding variant strains.[37-42]

The findings of this cohort study provide evidence that patients receiving a third vaccine dose derive additional protection against severe infection from both the delta and omicron variants, consistent with results from previous studies.[16,43-48] Between September 15, 2021, to November 11, 2022, of the total 4 756 102 doses administered to the study population, 4 462 301 (93.8%) were monovalent mRNA vaccines, 76 247 (1.6%) were bivalent mRNA vaccines and the remaining 217 554 (4.6%) were non-mRNA vaccines. Significant risk reduction of severe COVID-19 with a third dose was shown in actively treated patients with cancer, although to a lesser extent compared with matched controls. Patients infected more than 150 days after their third dose did not show significantly higher risk of hospitalization and severe disease compared with those infected before 60 days, suggesting a sustained protective effect. Singapore began administering the fourth dose 5 months following the third, being among the first in the world to do so.[49] After a fourth vaccine dose, the risk reduction of hospitalization and severe disease during the omicron wave was even greater. This suggests that an approach of boosting at regular intervals may be an effective measure against successive waves of COVID-19.

Strengths and Limitations

This study was first limited by its design as a cohort study because results may be subject to confounding variables that could not be controlled for. Second, rates of hospitalization could have been confounded by national health care protocols mandating inpatient admission and evaluation for patients with cancer with confirmed COVID-19 infection regardless of disease severity. Third, we were unable to control for individual behaviors affecting seeking of medical care and COVID-19 infection risk. These limitations were addressed by defining severity with the clinical end point of COVID-19 infection requiring supplemental oxygen, intensive care admission, or resulting in death, which may be extrapolated widely to other countries and settings. Finally, we were not able to perform regression analyses according to the time elapsed from last treatment in cancer survivors.

Nevertheless, our study has several strengths. First, the study included all cancer patients receiving follow-up in tertiary public institutions, making the sample highly representative of the population. Second, matched controls from the general population allowed us to better isolate the mediating effect of cancer history and active cancer treatment on COVID-19 infection and severity. In this respect, using competing risk regressions in our methodology accounted for the effects of competing comorbidities, a significant consideration in patients with cancer, without introducing unnecessary bias in the results from censoring patients with non–COVID-19 related adverse outcomes. Third, analysis was based on accurate and comprehensive records collected as part of Singapore's national pandemic response efforts, mitigating missed outcomes and loss to follow-up. Fourth, as primarily mRNA-based monovalent vaccines were administered to the Singapore population during the study period, there was minimal confounding of vaccine efficacy results due to differential efficacy from different COVID-19 vaccines. Finally, the study reports data on clinical population-based efficacy of a fourth vaccine dose, both in immunocompromised cohorts of patients with cancer with or without active treatment and the general population.

Conclusions

The results of this cohort study provide evidence of the benefit of early vaccination and administration of booster vaccine doses against COVID-19 in patients with cancer, especially in conferring protective effects of vaccination against adverse outcomes of COVID-19. The findings also provided insight into the longevity of vaccine-mediated protection against clinical infection outcomes in both immunocompromised patients with cancer with or without active treatment and the general population. As the world moves toward living with COVID-19, evidence of the booster third and fourth vaccine dose and efficacy in overcoming waning immunity is imperative to guide the optimum protection for our most vulnerable patients.

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