FAST TRACK

Waning of vaccine effectiveness against moderate and severe covid-19 among adults in the US from the VISION network: test negative, case-control study

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ABSTRACT

OBJECTIVE

To estimate the effectiveness of mRNA vaccines against moderate and severe covid-19 in adults by time since second, third, or fourth doses, and by age and immunocompromised status.

DESIGN

Test negative case-control study.

SETTING

Hospitals, emergency departments, and urgent care clinics in 10 US states, 17 January 2021 to 12 July 2022.

PARTICIPANTS

893 461 adults (≥18 years) admitted to one of 261 hospitals or to one of 272 emergency department or 119 urgent care centers for covid-like illness tested for SARS-CoV-2.

MAIN OUTCOME MEASURES

The main outcome was waning of vaccine effectiveness with BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) vaccine during the omicron and delta periods, and the period before delta was dominant using logistic regression conditioned on calendar week and geographic area while adjusting for age, race, ethnicity, local virus circulation, immunocompromised status, and likelihood of being vaccinated.

RESULTS

45 903 people admitted to hospital with covid-19 (cases) were compared with 213 103 people with covid-like illness who tested negative for SARS-CoV-2 (controls), and 103 287 people admitted to emergency department or urgent care with covid-19 (cases) were compared with 531 168 people with covid-like illness who tested negative for SARS-CoV-2. In the omicron period, vaccine effectiveness against covid-19 requiring admission to hospital was 89% (95% confidence interval 88% to 90%) within two months after dose 3 but waned to 66% (63% to 68%) by four to five months. Vaccine effectiveness of three doses against emergency department or urgent care visits was 83% (82% to 84%) initially but waned to 46% (44% to 49%) by four to five months. Waning was evident in all subgroups, including young adults and individuals who were not immunocompromised; although waning was more noticeable in people who were immunocompromised. Vaccine effectiveness increased among most groups after a fourth dose in whom this booster was recommended.

CONCLUSIONS

Effectiveness of mRNA vaccines against moderate and severe covid-19 waned with time after vaccination. The findings support recommendations for a booster dose after a primary series and consideration of additional booster doses.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Studies of the BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) covid-19 vaccines suggest that their effectiveness decreases over time and increases with an additional dose

How this pattern has varied with the dominant variant and number of vaccine doses, or by age group, immunocompromise status, and vaccine product is, however, not known

WHAT THIS STUDY ADDS

Among US adults of all ages, protection provided by either mRNA vaccine against moderate and severe covid-19 waned after primary vaccination, increased markedly after a third dose, and then waned again by four to five months after a third dose

Vaccine effectiveness diminished less against severe disease than against moderate disease

A fourth dose improved vaccine effectiveness among most subgroups for whom it was recommended; overall, our findings support recommendations for broad use of booster doses

Introduction

Randomized trials of BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) vaccines showed 94-95% protection against covid-19 among adults and suggested efficacy against covid-19 requiring hospital admission.[1 2] Since the introduction of these vaccines in December 2020, evidence has accumulated that their effectiveness wanes over time since vaccination, especially against milder disease,[3-9] they are less effective against omicron than earlier SARS-CoV-2 variants,[10] and a third (booster) dose restores high effectiveness against severe disease.[10-13] Although protection against severe omicron related disease is

believed to be high for several months after a third dose, the durability of protection and how this effect can vary by age group, immunocompromised status, and vaccine product is uncertain. In March 2022, the US Centers for Disease Control and Prevention recommended a second booster dose only for specific subgroups at high risk (such as adults aged 50 and older).[14] A more complete understanding of the effectiveness and durability of third and fourth doses of the mRNA vaccines is important to inform policy about booster doses.

The CDC's VISION network previously examined the effectiveness of mRNA vaccines against admissions to hospital or emergency visits and urgent care visits associated with covid-19, with data from eight healthcare systems.[15] In this article, we update VISION's analyses of mRNA vaccine effectiveness, focusing on the durability of three and four dose protection against severe disease (ie, admission to hospital) during the omicron period. We assess the trajectory of vaccine effectiveness overall and in subgroups defined by age, immunocompromised status, and vaccine product.

Methods

Study design

The VISION network has been described previously.[15] We applied a test negative design to estimate vaccine effectiveness of mRNA vaccines using retrospectively collected data. We focused on mRNA vaccines because they comprise more than 95% of covid vaccines administered in the US.[16] Separate analyses were done of patients who were admitted to hospital (hospital sample) and patients who received care in an emergency department or urgent care clinic (emergency department or urgent care sample).

Study population and setting

The study population included adults (≥18 years) who received care for covid-like illness at a VISION network hospital or emergency department or urgent care center and had molecular testing for SARS-CoV-2 at least 14 days after vaccines became locally available for their age group (17 January to 3 May 2021). The last contact included in this study period occurred on 12 July 2022. We excluded individuals who received any vaccine other than the BNT162b2 or mRNA-1273 vaccine, individuals who received more than four doses of an mRNA vaccine before the index medical contact, individuals who received only one dose of an mRNA vaccine less than 14 days before the index contact or who had a third or fourth dose less than seven days before the index contact, individuals known to have a positive laboratory test result for a SARS-CoV-2 infection more than 14 days before the index contact, and individuals with a positive SARS-CoV-2 test result but no diagnoses or symptoms suggesting covid-19 illness.

Vaccination status

Vaccination status was categorized by the number of doses received and the number of months between the most recent vaccine dose and the index contact date (referred to as time since vaccination). Patients were considered partially vaccinated if they received only one dose at least 14 days prior to the index contact date or had received a second dose less than 14 days previously. Patients with no record of vaccination before the index contact date were considered unvaccinated. Patients with three doses were those who received a third dose in a primary vaccination series (eg, among immunocompromised individuals) or a booster dose after a primary series of two doses. Aligning with recommendations for receipt of a fourth dose, we examined the effectiveness of four doses among adults aged 50 years or older and among immunocompromised adults of any age. Vaccination status was ascertained from immunization registries, electronic health records, and insurance claims.

Outcomes

The primary outcome was a positive or negative molecular SARS-CoV-2 result for a test done within 14 days before a medical contact to less than 72 h after among patients presenting with covid-like illness, as identified from ICD-9 and ICD-10 (international classification of diseases, ninth and 10th revision, respectively) diagnostic codes (supplemental methods; supplemental table S1). The index date for each contact was the earlier of either the contact date or the date of the closest SARS-CoV-2 molecular assay. An individual could be included once in the emergency department or urgent care sample and once in the hospital sample. Individuals could be included as a control multiple times.

Statistical analysis

We used a test negative case-control design in which cases were patients with covid-like illness with laboratory confirmed covid-19 and controls were patients with covid-like illness and negative SARS-CoV-2 test results (controls could have had positive test results for other respiratory viruses such as influenza). We compared cases with controls in the hospital sample, and separately compared cases with controls in the emergency or urgent care sample. Cases were not individually matched to controls.

Conditional logistic regression was used to examine case-control status in relation to vaccination status categorized as vaccinated with four, three, or two doses, or partially vaccinated; unvaccinated individuals were used as the reference group. To examine waning of vaccine effectiveness, we categorized people who were vaccinated using time specific indicators defined by two month intervals of time since vaccination; unvaccinated individuals were used as the reference group. We exponentiated the regression coefficient of each vaccination status indicator to yield an odds ratio, subtracted the odds ratio from 1 to estimate vaccine effectiveness, and multiplied by 100 to scale vaccine effectiveness as a percentage. In several analyses, a sparse bimonthly interval for which the vaccine effectiveness

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Table 1 | Characteristics of adults with covid-19-like illness who were admitted to hospital or to an emergency department or urgent care, and percentage with laboratory confirmed SARS-CoV-2 infection. Data are number of patients (percentage of column or row) unless stated otherwise

Characteristics	Total hospital admissions (n=259 006)	SARS-CoV-2 negative (n=213 103)	SARS-CoV-2 positive (n=45 903)	SMD	Total ED/ UC contacts (n=634 455)	SARS-CoV-2 negative (n=531 168)	SARS-CoV-2 positive (n=103 287)	SMD
Month of contact index date								
January 2021	945 (0.4)	737 (78.0)	208 (22.0)	0.72	397 (0.1)	344 (86.6)	53 (13.4)	0.71
February 2021	4004 (1.5)	3450 (86.2)	554 (13.8)	—	2792 (0.4)	2507 (89.8)	285 (10.2)	—
March 2021	8418 (3.3)	7768 (92.3)	650 (7.7)	—	8750 (1.4)	8102 (92.6)	648 (7.4)	—
April 2021	12 580 (4.9)	11 064 (87.9)	1516 (12.1)	—	19 672 (3.1)	17 531 (89.1)	2141 (10.9)	—
May 2021	14 212 (5.5)	12 635 (88.9)	1577 (11.1)	—	26 092 (4.1)	23 756 (91.0)	2336 (9.0)	—
June 2021	13 407 (5.2)	12 437 (92.8)	970 (7.2)	—	24 920 (3.9)	23 197 (93.1)	1723 (6.9)	—
July 2021	14 233 (5.5)	12 214 (85.8)	2019 (14.2)	—	33 607 (5.3)	29 913 (89.0)	3694 (11.0)	—
August 2021	17 090 (6.6)	12 343 (72.2)	4747 (27.8)	—	46 421 (7.3)	38 795 (83.6)	7626 (16.4)	—
September 2021	20 350 (7.9)	15 215 (74.8)	5135 (25.2)	—	50 530 (8.0)	42 045 (83.2)	8485 (16.8)	—
October 2021	20 761 (8.0)	17 151 (82.6)	3610 (17.4)	—	50 261 (7.9)	44 240 (88.0)	6021 (12.0)	—
November 2021	20 088 (7.8)	16 248 (80.9)	3840 (19.1)	—	53 743 (8.5)	46 834 (87.1)	6909 (12.9)	—
December 2021	22 155 (8.6)	16 528 (74.6)	5627 (25.4)	—	69 509 (11.0)	54 866 (78.9)	14 643 (21.1)	—
January 2022	23 384 (9.0)	14 091 (60.3)	9293 (39.7)	—	71 345 (11.2)	42 131 (59.1)	29 214 (40.9)	—
February 2022	16 080 (6.2)	13 526 (84.1)	2554 (15.9)	—	32 998 (5.2)	28 130 (85.2)	4868 (14.8)	—
March 2022	15 206 (5.9)	14 635 (96.2)	571 (3.8)	—	35 625 (5.6)	34 419 (96.6)	1206 (3.4)	—
April 2022	13 025 (5.0)	12 555 (96.4)	470 (3.6)	—	33 983 (5.4)	32 119 (94.5)	1864 (5.5)	—
May 2022	13 844 (5.3)	12 564 (90.8)	1280 (9.2)	—	40 000 (6.3)	34 818 (87.0)	5182 (13.0)	—
June 2022	9224 (3.6)	7942 (86.1)	1282 (13.9)	—	33 810 (5.3)	27 421 (81.1)	6389 (18.9)	—
Variant lineage period								
Pre-delta	49 760 (19.2)	44 682 (89.8)	5078 (10.2)	0.29	73 885 (11.6)	67 681 (91.6)	6204 (8.4)	0.33
Delta	110 815 (42.8)	87 436 (78.9)	23 379 (21.1)	—	285 416 (45.0)	245 507 (86.0)	39 909 (14.0)	—
Omicron	98 431 (38.0)	80 985 (82.3)	17 446 (17.7)	—	275 154 (43.4)	217 980 (79.2)	57 174 (20.8)	—
Study sites								
Baylor Scott & White Health	37 069 (14.3)	30 382 (82.0)	6687 (18.0)	0.18	87 431 (13.8)	66 761 (76.4)	20 670 (23.6)	0.31
Columbia University	13 629 (5.3)	11 604 (85.1)	2025 (14.9)	—	18 611 (2.9)	16 606 (89.2)	2005 (10.8)	—
HealthPartners	15 670 (6.1)	13 246 (84.5)	2424 (15.5)	—	93 204 (14.7)	78 617 (84.3)	14 587 (15.7)	—
Intermountain Healthcare	20 925 (8.1)	16 866 (80.6)	4059 (19.4)	—	134 894 (21.3)	116 850 (86.6)	18 044 (13.4)	—
Kaiser Permanente Northern California	59 163 (22.8)	49 826 (84.2)	9337 (15.8)	—	121 392 (19.1)	107 498 (88.6)	13 894 (11.4)	—
Kaiser Permanente Northwest	13 392 (5.2)	11 433 (85.4)	1959 (14.6)	—	50 445 (8.0)	42 479 (84.2)	7966 (15.8)	—
Regenstrief Institute	69 561 (26.9)	54 612 (78.5)	14 949 (21.5)	—	84 162 (13.3)	66 442 (78.9)	17 720 (21.1)	—
University of Colorado	29 597 (11.4)	25 134 (84.9)	4463 (15.1)	—	44 316 (7.0)	35 915 (81.0)	8401 (19.0)	—
Age groups (years)								
18-34	18 296 (7.1)	14 806 (80.9)	3490 (19.1)	0.27	177 337 (28.0)	148 148 (83.5)	29 189 (16.5)	0.22
35-44	17 478 (6.7)	13 148 (75.2)	4330 (24.8)	—	90 770 (14.3)	72 914 (80.3)	17 856 (19.7)	—
45-64	68 816 (26.6)	53 370 (77.6)	15 446 (22.4)	—	164 746 (26.0)	133 607 (81.1)	31 139 (18.9)	—
65-74	62 819 (24.3)	52 813 (84.1)	10 006 (15.9)	—	90 912 (14.3)	78 326 (86.2)	12 586 (13.8)	—
75-84	56 813 (21.9)	48 698 (85.7)	8115 (14.3)	—	71 797 (11.3)	63 177 (88.0)	8620 (12.0)	—
≥85	34 784 (13.4)	30 268 (87.0)	4516 (13.0)	—	38 893 (6.1)	34 996 (90.0)	3897 (10.0)	—
Sex								
Women	135 393 (52.3)	113 095 (83.5)	22 298 (16.5)	0.09	376 054 (59.3)	318 038 (84.6)	58 016 (15.4)	0.08
Men	123 613 (47.7)	100 008 (80.9)	23 605 (19.1)	—	258 401 (40.7)	213 130 (82.5)	45 271 (17.5)	—
Race								
White	180 894 (69.8)	150 258 (83.1)	30 636 (16.9)	0.11	438 923 (69.2)	371 950 (84.7)	66 973 (15.3)	0.13
Black	29 126 (11.2)	23 572 (80.9)	5554 (19.1)	—	69 483 (11.0)	55 448 (79.8)	14 035 (20.2)	—
Other*	18 200 (7.0)	15 194 (83.5)	3006 (16.5)	—	52 524 (8.3)	44 289 (84.3)	8235 (15.7)	—
Unknown	30 786 (11.9)	24 079 (78.2)	6707 (21.8)	—	73 525 (11.6)	59 481 (80.9)	14 044 (19.1)	—
Ethnicity								
Hispanic	25 285 (9.8)	19 470 (77.0)	5815 (23.0)	0.12	84 543 (13.3)	69 454 (82.2)	15 089 (17.8)	0.10
Non-Hispanic	163 480 (63.1)	136 277 (83.4)	27 203 (16.6)	—	426 575 (67.2)	361 016 (84.6)	65 559 (15.4)	—
Unknown	70 241 (27.1)	57 356 (81.7)	12 885 (18.3)	—	123 337 (19.4)	100 698 (81.6)	22 639 (18.4)	—
Underlying condition at discharge								
Any chronic condition	239 536 (92.5)	197 457 (82.4)	42 079 (17.6)	0.04	224 787 (35.4)	194 556 (86.6)	30 231 (13.4)	0.16
Chronic respiratory condition†	153 013 (59.1)	120 551 (78.8)	32 462 (21.2)	0.30	108 850 (17.2)	91 633 (84.2)	17 217 (15.8)	0.02
Chronic non-respiratory condition‡	229 079 (88.4)	190 894 (83.3)	38 185 (16.7)	0.19	179 741 (28.3)	155 726 (86.6)	24 015 (13.4)	0.14
Immunosuppressive condition	60 405 (23.3)	53 301 (88.2)	7104 (11.8)	0.24	28 382 (4.5)	25 049 (88.3)	3333 (11.7)	0.08
CLI diagnosis as primary or first listed diagnosis code								
Yes	59 539 (23.0)	51 340 (86.2)	8199 (13.8)	0.15	284 919 (44.9)	251 847 (88.4)	33 072 (11.6)	0.32
No	199 467 (77.0)	161 763 (81.1)	37 704 (18.9)	—	349 536 (55.1)	279 321 (79.9)	70 215 (20.1)	—
ICU admissions								
Admitted to ICU	51 966 (20.1)	42 694 (82.2)	9272 (17.8)	0.00	—	—	—	—
Not in ICU during hospital stay	207 040 (79.9)	170 409 (82.3)	36 631 (17.7)	—	—	—	—	—

Table 1 | Continued

Characteristics	Total hospital admissions (n=259 006)	SARS-CoV-2 negative (n=213 103)	SARS-CoV-2 positive (n=45 903)	SMD	Total ED/ UC contacts (n=634 455)	SARS-CoV-2 negative (n=531 168)	SARS-CoV-2 positive (n=103 287)	SMD
Hospital length of stay								
Mean (SD) days	8.1 (11.28)	7.8 (11.2)	9.4 (11.53)	0.14	—	—	—	—
Covid-19 vaccination product§								
Unvaccinated	103 969 (40.1)	71 545 (68.8)	32 424 (31.2)	0.80	250 835 (39.5)	186 756 (74.5)	64 079 (25.5)	0.57
BNT162b2 (Pfizer-BioNTech)	88 882 (34.3)	80 311 (90.4)	8571 (9.6)	—	228 477 (36.0)	202 958 (88.8)	25 519 (11.2)	—
mRNA-1273 (Moderna)	62 913 (24.3)	58 223 (92.5)	4690 (7.5)	—	145 428 (22.9)	132 606 (91.2)	12 822 (8.8)	—
Combination of mRNA products	3242 (1.3)	3024 (93.3)	218 (6.7)	—	9715 (1.5)	8848 (91.1)	867 (8.9)	—
Covid-19 vaccination status								
Unvaccinated	103 969 (40.1)	71 545 (68.8)	32 424 (31.2)	0.89	250 835 (39.5)	186 756 (74.5)	64 079 (25.5)	0.67
Partially vaccinated¶	13 151 (5.1)	11 930 (90.7)	1221 (9.3)	—	30 373 (4.8)	27 240 (89.7)	3133 (10.3)	—
Time since two doses:								
14 days to <2 months	12 547 (4.8)	12 316 (98.2)	231 (1.8)	—	24 156 (3.8)	23 603 (97.7)	553 (2.3)	—
2 to <4 months	17 558 (6.8)	16 888 (96.2)	670 (3.8)	—	42 264 (6.7)	39 986 (94.6)	2278 (5.4)	—
4 to <6 months	18 917 (7.3)	17 395 (92.0)	1522 (8.0)	—	52 274 (8.2)	47 995 (91.8)	4279 (8.2)	—
6 to <8 months	19 091 (7.4)	16 930 (88.7)	2161 (11.3)	—	53 287 (8.4)	46 867 (88.0)	6420 (12.0)	—
8 to <10 months	12 618 (4.9)	10 292 (81.6)	2326 (18.4)	—	32 897 (5.2)	26 177 (79.6)	6720 (20.4)	—
10 to <12 months	6845 (2.6)	5545 (81.0)	1300 (19.0)	—	16 720 (2.6)	13 518 (80.8)	3202 (19.2)	—
12 to <14 months	4094 (1.6)	3750 (91.6)	344 (8.4)	—	9950 (1.6)	8587 (86.3)	1363 (13.7)	—
14 to <16 months	1919 (0.7)	1668 (86.9)	251 (13.1)	—	4323 (0.7)	3603 (83.3)	720 (16.7)	—
16 to <18 months	195 (0.1)	165 (84.6)	30 (15.4)	—	675 (0.1)	543 (80.4)	132 (19.6)	—
Time since three doses:				—				—
7 days to <2 months	12 134 (4.7)	11 499 (94.8)	635 (5.2)	—	32 126 (5.1)	30 135 (93.8)	1991 (6.2)	—
2 to <4 months	14 069 (5.4)	13 090 (93.0)	979 (7.0)	—	33 078 (5.2)	30 297 (91.6)	2781 (8.4)	—
4 to <6 months	12 173 (4.7)	11 308 (92.9)	865 (7.1)	—	27 981 (4.4)	25 350 (90.6)	2631 (9.4)	—
6 to <8 months	6067 (2.3)	5481 (90.3)	586 (9.7)	—	14 627 (2.3)	12 653 (86.5)	1974 (13.5)	—
8 to <10 months	1070 (0.4)	918 (85.8)	152 (14.2)	—	2397 (0.4)	1972 (82.3)	425 (17.7)	—
10 to <12 months	15 (0.0)	12 (80.0)	3 (20.0)	—	56 (0.0)	41 (73.2)	15 (26.8)	—
Time since four doses:								
7 days to <2 months	2213 (0.9)	2053 (92.8)	160 (7.2)	—	5382 (0.8)	4928 (91.6)	454 (8.4)	—
2 to <4 months	361 (0.1)	318 (88.1)	43 (11.9)	—	1054 (0.2)	917 (87.0)	137 (13.0)	—

CI=confidence interval; CLI=covid-like illness; ED=emergency department; ICD=International Classification of Disease; SMD=standardized mean difference; NA=not applicable; UC=urgent care. Patients with indeterminate immunization status (receipt of dose 1 of mRNA vaccine 1-13 days before index test date) were excluded.
*Includes Asian, Hawaiian, or other Pacific islander, American Indian, or Alaskan Native, other not listed, and multi-race.
†Includes asthma, chronic obstructive pulmonary disease, and other lung disease.
‡Includes heart failure, ischemic heart disease, hypertension, other heart disease, stroke, other cerebrovascular disease, diabetes (type 1, 2, and other specified conditions), other metabolic disease, clinical obesity, clinically underweight, renal disease, liver disease, blood disorder, other immunosuppressive conditions, organ transplant recipient, cancer, dementia, neurological disorder, musculoskeletal disorder, or Down's syndrome.
§Combination if more than one type of mRNA vaccine (BNT162b or mRNA-1273) was received.
¶Partially vaccinated was defined as receipt of one dose of mRNA vaccine ≥14 days before index date or receipt of two doses <14 days before index date.

estimate had a confidence interval wider than 50 percentage points was combined with the previous bimonthly interval to provide a more precise estimate of vaccine effectiveness (see supplemental methods). Vaccine effectiveness estimates (and confidence limits) were scaled to a range of −100% to 100%.[17]

Logistic regression models were conditioned by calendar week and geographical area such that we compared cases with controls tested during the same week in the same region (supplemental table S2). Covariates included in the models were those determined through bivariate analyses to be statistically significantly associated with both the outcome and vaccination status, as well as those specified a priori as established confounders, including age, race, ethnicity, presence of respiratory and non-respiratory comorbidities, immunocompromised status, and local viral circulation. Cubic splines were used for age, seven day average positivity of SARS-CoV-2 test in the area of the contact, and the propensity to be vaccinated; others were indicator variables. Propensity scores (supplemental methods) predicted vaccination (any versus none) based on demographics, comorbidities (supplemental table S3), and characteristics of the facility (supplemental table S4), and were derived independently for each period of variant dominance (supplemental table S5). Patients who were immunocompromised were identified by ICD-9 and ICD-10 diagnostic codes (supplemental methods).[18] We conducted separate analyses for three periods based on when a variant accounted for 50% or more of sequenced isolates in each site: before delta was predominant, when delta was predominant, and when omicron was predominant (supplemental table S6). We assessed the magnitude of waning as the difference in vaccine effectiveness between patients who had recently been vaccinated (defined as less than two months) and patients at a specified level of time since vaccination (eg, four to five months from dose 3), and we examined waning by age (18-44 years, 45-64 years, ≥65 years), vaccine product, and immunocompromised status. Bootstrapping was used to estimate a 95% confidence interval around the difference between vaccine effectiveness at less than two months and vaccine effectiveness at four to five months.

Vaccination status	No	Covid-like illness controls (col %)	Covid-19 cases (col %)	Row %	Vaccine effectiveness (95% CI)
Pre-delta predominance					
Unvaccinated	25 077	20 573 (46.0)	4504 (88.7)	18.0	
Partially vaccinated	6123	5792 (13.0)	331 (6.5)	5.4	73 (69 to 76)
2-dose vaccinated <2 months	9656	9538 (21.3)	118 (2.3)	1.2	94 (93 to 95)
2-dose vaccinated 2 to <4 months	8124	8011 (17.9)	113 (2.2)	1.4	92 (90 to 93)
2-dose vaccinated 4 to <6 months	780	768 (1.7)	12 (0.2)	1.5	87 (77 to 93)
Delta predominance					
Unvaccinated	47 847	29 140 (33.3)	18 707 (80)	39.1	
Partially vaccinated	3633	3248 (3.7)	385 (1.6)	10.6	81 (78 to 83)
2-dose vaccinated <2 months	2486	2428 (2.8)	58 (0.2)	2.3	96 (95 to 97)
2-dose vaccinated 2 to <4 months	8269	7925 (9.1)	344 (1.5)	4.2	93 (92 to 94)
2-dose vaccinated 4 to <6 months	16 369	15 193 (17.4)	1176 (5.0)	7.2	89 (88 to 90)
2-dose vaccinated 6 to <8 months	16 400	14 821 (17.0)	1579 (6.8)	9.6	83 (82 to 84)
2-dose vaccinated 8 to <10 months	6803	6015 (6.9)	788 (3.4)	11.6	77 (75 to 79)
2-dose vaccinated 10 to <12 months	444	357 (0.4)	87 (0.4)	19.6	68 (59 to 75)
3-dose vaccinated <2 months	6618	6450 (7.4)	168 (0.7)	2.5	96 (95 to 96)
3-dose vaccinated ≥2 months	1946	1859 (2.1)	87 (0.4)	4.5	92 (90 to 93)
Omicron predominance*					
Unvaccinated	31 045	21 832 (27.8)	9213 (53.4)	29.7	
Partially vaccinated	3395	2890 (3.7)	505 (2.9)	14.9	58 (53 to 62)
2-dose vaccinated <2 months	405	350 (0.4)	55 (0.3)	13.6	73 (63 to 80)
2-dose vaccinated 2 to <4 months	1165	952 (1.2)	213 (1.2)	18.3	61 (54 to 67)
2-dose vaccinated 4 to <6 months	1768	1434 (1.8)	334 (1.9)	18.9	57 (51 to 62)
2-dose vaccinated 6 to <8 months	2691	2109 (2.7)	582 (3.4)	21.6	48 (42 to 53)
2-dose vaccinated 8 to <10 months	5815	4277 (5.4)	1538 (8.9)	26.4	51 (47 to 54)
2-dose vaccinated 10 to <12 months	6401	5188 (6.6)	1213 (7.0)	19.0	55 (51 to 58)
2-dose vaccinated 12 to <14 months	4094	3750 (4.8)	344 (2.0)	8.4	40 (32 to 47)
2-dose vaccinated ≥14 months	2114	1833 (2.3)	281 (1.6)	13.3	19 (6 to 30)
3-dose vaccinated <2 months	5516	5049 (6.4)	467 (2.7)	8.5	89 (88 to 90)
3-dose vaccinated 2 to <4 months	12 144	11 250 (14.3)	894 (5.2)	7.4	86 (85 to 87)
3-dose vaccinated 4 to <6 months	12 152	11 289 (14.4)	863 (5.0)	7.1	66 (63 to 68)
3-dose vaccinated 6 to <8 months	6067	5481 (7.0)	586 (3.4)	9.7	41 (35 to 47)
3-dose vaccinated ≥8 months	1085	930 (1.2)	155 (0.9)	14.3	31 (17 to 43)

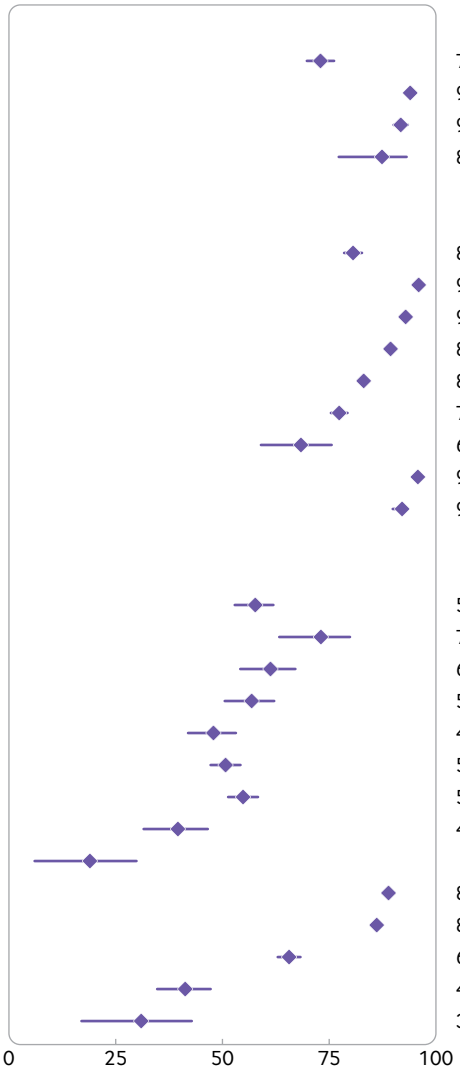

Fig 1 | Vaccine effectiveness (%) against covid-19-associated hospital admissions by time since vaccination and period of variant predominance. Vaccine effectiveness estimates are adjusted for geographic area, calendar week, age, race, ethnicity, presence of respiratory and non-respiratory comorbidities, immunocompromise status, local viral circulation, and propensity to be vaccinated score. CI=confidence interval; col=column. *Figure 3 presents findings for 4-dose recipients in the subgroups recommended for a fourth dose

We conducted several sensitivity analyses. First, we added to the study population patients with a known prior infection to assess the sensitivity of results to whether previously infected patients are included or excluded. Second, we wanted to distinguish results between patients who had been admitted to hospital and patients who had been admitted to an emergency department or to urgent care. Therefore, we examined vaccine effectiveness in the emergency department or urgent care sample and omitted patients admitted to hospital within 30 days. Third, we investigated a negative control exposure[19] by examining vaccine effectiveness in patients who received their first dose less than 14 days before the index date of contact. These patients were not expected to have substantial vaccine induced protection, and a vaccine effectiveness estimate substantially more than zero would be evidence of residual confounding.[20]

Analyses were conducted with SAS version 9.4 and R version 4.1.2. All confidence limits are 95% intervals. Confidence intervals excluding the null value were considered statistically significant.

Patient and public involvement

Study participants contributed in important ways to this research by supplying the underlying data on which the study is based. It was not, however, feasible to involve them in the design, conduct, reporting, or dissemination of this study because the study was conducted under the CDC's covid-19 incident response

Vaccination status	No	Covid-like illness controls (col %)	Covid-19 cases (col %)	Row %	Vaccine effectiveness (95% CI)
Pre-delta predominance					
Unvaccinated	39 039	33 356 (49.3)	5683 (91.6)	14.6	
Partially vaccinated	8677	8399 (12.4)	278 (4.5)	3.2	81 (78 to 83)
2-dose vaccinated <2 months	13 916	13 812 (20.4)	104 (1.7)	0.7	95 (94 to 96)
2-dose vaccinated 2 to <4 months	11 032	10 911 (16.1)	121 (2.0)	1.1	92 (90 to 93)
2-dose vaccinated 4 to <6 months	1221	1203 (1.8)	18 (0.3)	1.5	86 (78 to 91)
Delta predominance					
Unvaccinated	118 648	88 083 (35.9)	30 565 (76.6)	25.8	
Partially vaccinated	11 116	10 274 (4.2)	842 (2.1)	7.6	76 (74 to 78)
2-dose vaccinated <2 months	8537	8367 (3.4)	170 (0.4)	2.0	93 (92 to 94)
2-dose vaccinated 2 to <4 months	26 371	25 443 (10.4)	928 (2.3)	3.5	90 (89 to 90)
2-dose vaccinated 4 to <6 months	43 650	41 253 (16.8)	2397 (6.0)	5.5	86 (85 to 86)
2-dose vaccinated 6 to <8 months	41 640	38 472 (15.7)	3168 (7.9)	7.6	79 (78 to 79)
2-dose vaccinated 8 to <10 months	14 278	13 009 (5.3)	1269 (3.2)	8.9	73 (71 to 75)
2-dose vaccinated 10 to <12 months	1377	1219 (0.5)	158 (0.4)	11.5	66 (60 to 72)
3-dose vaccinated <2 months	15 653	15 377 (6.3)	276 (0.7)	1.8	96 (95 to 96)
3-dose vaccinated 2 to <4 months	4090	3957 (1.6)	133 (0.3)	3.3	91 (90 to 93)
3-dose vaccinated 4 to <6 months	56	53 (0)	3 (0)	5.4	88 (62 to 96)
Omicron predominance*					
Unvaccinated	93 148	65 317 (30.8)	27 831 (49.2)	29.9	
Partially vaccinated	10 580	8567 (4.0)	2013 (3.6)	19.0	43 (39 to 46)
2-dose vaccinated <2 months	1703	1424 (0.7)	279 (0.5)	16.4	63 (57 to 68)
2-dose vaccinated 2 to <4 months	4861	3632 (1.7)	1229 (2.2)	25.3	44 (40 to 48)
2-dose vaccinated 4 to <6 months	7403	5539 (2.6)	1864 (3.3)	25.2	37 (33 to 41)
2-dose vaccinated 6 to <8 months	11 647	8395 (4.0)	3252 (5.7)	27.9	30 (27 to 34)
2-dose vaccinated 8 to <10 months	18 619	13 168 (6.2)	5451 (9.6)	29.3	35 (32 to 37)
2-dose vaccinated 10 to <12 months	15 343	12 299 (5.8)	3044 (5.4)	19.8	35 (31 to 38)
2-dose vaccinated 12 to <14 months	9950	8587 (4.0)	1363 (2.4)	13.7	16 (10 to 21)
2-dose vaccinated 14 to <16 months	4323	3603 (1.7)	720 (1.3)	16.7	12 (4 to 19)
2-dose vaccinated 16 to <18 months	675	543 (0.3)	132 (0.2)	19.6	22 (5 to 36)
3-dose vaccinated <2 months	16 473	14 758 (7.0)	1715 (3.0)	10.4	83 (82 to 84)
3-dose vaccinated 2 to <4 months	28 988	26 340 (12.4)	2648 (4.7)	9.1	76 (75 to 77)
3-dose vaccinated 4 to <6 months	27 925	25 297 (11.9)	2628 (4.6)	9.4	46 (44 to 49)
3-dose vaccinated 6 to <8 months	14 627	12 653 (6.0)	1974 (3.5)	13.5	26 (22 to 30)
3-dose vaccinated ≥8 months	2453	2013 (0.9)	440 (0.8)	17.9	17 (7 to 26)

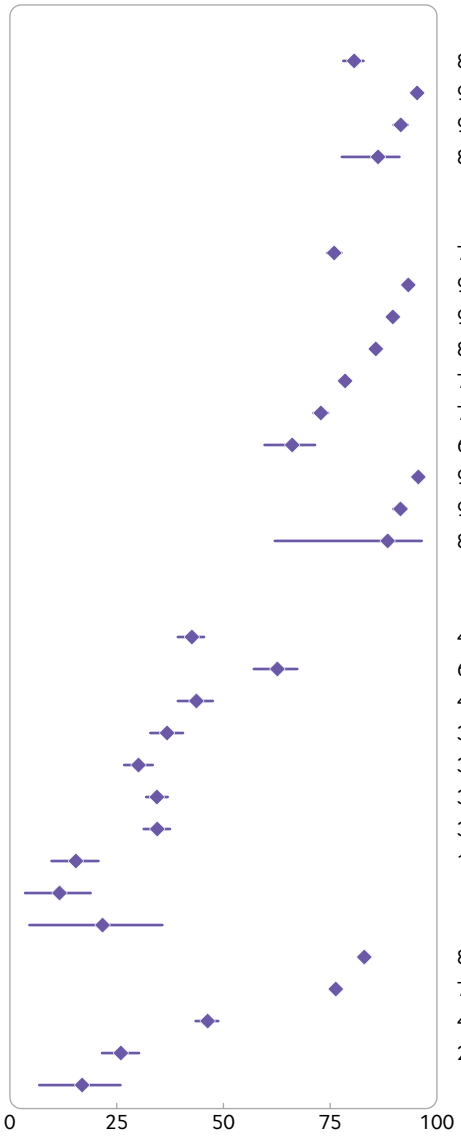

Fig 2 | Vaccine effectiveness (%) against covid-19-associated emergency department and urgent care visits by time since vaccination and period of variant predominance. Vaccine effectiveness estimates are adjusted for geographic area, calendar week, age, race, ethnicity, presence of respiratory and non-respiratory comorbidities, immunocompromise status, local viral circulation, and propensity to be vaccinated score. CI=confidence interval; col=column. *Supplemental Table 14 presents findings for 4-dose recipients in the subgroups recommended for a fourth dose

structure and limited to analysis of retrospectively collected electronic data only, with no patient interaction.

Results

Study population

From 17 January 2021 to 12 July 2022, 259 006 patients were admitted to 261 hospitals and 634 455 were admitted to 272 emergency departments or to 119 urgent care centers. The hospital sample included 17 446 people with covid-19 during the omicron period, 23 379 during the delta period, and 5078 before delta was dominant. The emergency department or urgent care sample included 57 174 people with covid-19 during the omicron period, 39 909 during the delta period, and 6204 before delta was dominant (table 1; supplementary figs S1-S18).

In the hospital sample, the median age was 69 years (interquartile range 56-79, 11.2% were black participants, 9.8% were Hispanic, and 23.3% had an immunocompromising condition. In the emergency department or urgent care sample, the median age was 51 years (interquartile range 33-69), 11.0% were black participants, 13.3% were Hispanic, and 4.5% had an immunocompromising condition (table 1). Characteristics by vaccination status are given in

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Vaccination status	No	Covid-like illness controls (col %)	Covid-19 cases (col %)	Row %	Vaccine effectiveness (95% CI)
Age 18 to 44 years					
Unvaccinated	6798	5298 (49.6)	1500 (68.8)	22.1	
Partially vaccinated	654	586 (5.5)	68 (3.1)	10.4	58 (43 to 68)
2-dose vaccinated <2 months	100	86 (0.8)	14 (0.6)	14.0	64 (31 to 81)
2-dose vaccinated 2 to <4 months	287	246 (2.3)	41 (1.9)	14.3	56 (36 to 70)
2-dose vaccinated 4 to <6 months	385	326 (3.1)	59 (2.7)	15.3	46 (25 to 61)
2-dose vaccinated 6 to <8 months	541	438 (4.1)	103 (4.7)	19.0	38 (20 to 53)
2-dose vaccinated 8 to <10 months	762	628 (5.9)	134 (6.1)	17.6	49 (35 to 59)
2-dose vaccinated ≥10 months	1074	973 (9.1)	101 (9.4)	27.2	29 (8 to 45)
3-dose vaccinated <2 months	516	478 (4.5)	38 (1.7)	7.4	85 (79 to 90)
3-dose vaccinated 2 to <4 months	817	774 (7.2)	43 (2.0)	5.3	77 (68 to 84)
3-dose vaccinated ≥4 months	926	846 (7.9)	80 (3.7)	8.6	33 (9 to 50)
Age 45 to 64 years					
Unvaccinated	9987	7014 (34.3)	2973 (59.8)	29.8	
Partially vaccinated	1049	877 (4.3)	172 (3.5)	16.4	50 (39 to 59)
2-dose vaccinated <2 months	133	114 (0.6)	19 (0.4)	14.3	75 (59 to 85)
2-dose vaccinated 2 to <4 months	388	302 (1.5)	86 (1.7)	22.2	54 (40 to 65)
2-dose vaccinated 4 to <6 months	655	547 (2.7)	108 (2.2)	16.5	65 (56 to 73)
2-dose vaccinated 6 to <8 months	1018	805 (3.9)	213 (4.3)	20.9	57 (48 to 64)
2-dose vaccinated 8 to <10 months	2059	1564 (7.6)	495 (10.0)	24.0	58 (52 to 63)
2-dose vaccinated 10 to <12 months	1494	1268 (6.2)	226 (4.5)	15.1	36 (24 to 46)
2-dose vaccinated ≥12 months	1294	1187 (5.8)	107 (2.2)	8.3	32 (14 to 46)
3-dose vaccinated <2 months	1486	1346 (6.6)	140 (2.8)	9.4	89 (86 to 91)
3-dose vaccinated 2 to <4 months	2327	2172 (10.6)	155 (3.1)	6.7	83 (80 to 86)
3-dose vaccinated 4 to <6 months	2201	2022 (9.9)	179 (3.6)	8.1	58 (49 to 65)
3-dose vaccinated ≥6 months	1037	958 (4.7)	79 (1.6)	7.6	48 (32 to 60)
4-dose vaccinated ≥7 days*	309	292 (1.7)	17 (0.4)	5.5	72 (51 to 83)
Age ≥65 years					
Unvaccinated	14 260	9520 (19.1)	4740 (46)	33.2	
Partially vaccinated	1692	1427 (2.9)	265 (2.6)	15.7	61 (55 to 67)
2-dose vaccinated <2 months	172	150 (0.3)	22 (0.2)	12.8	77 (63 to 86)
2-dose vaccinated 2 to <4 months	490	404 (0.8)	86 (0.8)	17.6	68 (59 to 75)
2-dose vaccinated 4 to <6 months	728	561 (1.1)	167 (1.6)	22.9	53 (43 to 61)
2-dose vaccinated 6 to <8 months	1132	866 (1.7)	266 (2.6)	23.5	47 (38 to 55)
2-dose vaccinated 8 to <10 months	2994	2085 (4.2)	909 (8.8)	30.4	46 (40 to 51)
2-dose vaccinated 10 to <12 months	4330	3404 (6.8)	926 (9.0)	21.4	59 (55 to 62)
2-dose vaccinated 12 to <14 months	2777	2538 (5.1)	239 (2.3)	8.6	45 (36 to 53)
2-dose vaccinated ≥14 months	1640	1401 (2.8)	239 (2.3)	14.6	31 (19 to 41)
3-dose vaccinated <2 months	3514	3225 (6.5)	289 (2.8)	8.2	89 (88 to 91)
3-dose vaccinated 2 to <4 months	9000	8304 (16.7)	696 (6.8)	7.7	87 (86 to 88)
3-dose vaccinated 4 to <6 months	9290	8652 (17.4)	638 (6.2)	6.9	70 (67 to 73)
3-dose vaccinated 6 to <8 months	4969	4473 (9.0)	496 (4.8)	10.0	52 (45 to 57)
3-dose vaccinated ≥8 months	881	749 (1.5)	132 (1.3)	15.0	45 (32 to 55)
4-dose vaccinated <2 months	1927	1780 (3.6)	147 (1.4)	7.6	76 (71 to 80)
4-dose vaccinated 2 to <4 months	323	286 (0.6)	37 (0.4)	11.5	70 (56 to 79)

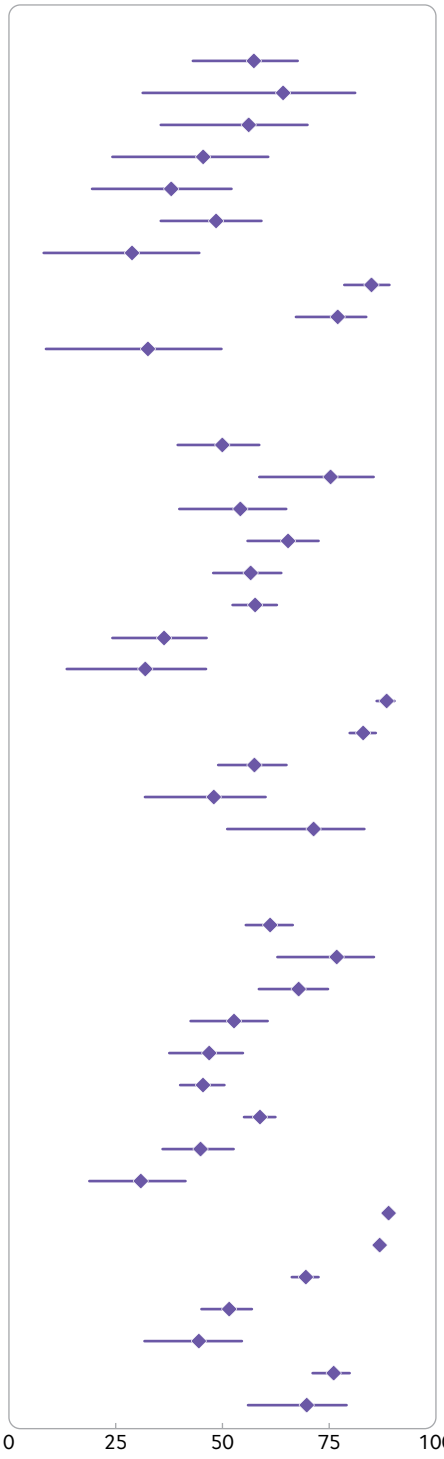

Fig 3 | Vaccine effectiveness (%) against covid-19-associated hospital admissions by time since vaccination and age group, restricted to omicron period. Vaccine effectiveness estimates are adjusted for geographic area, calendar week, age, race, ethnicity, presence of respiratory and non-respiratory comorbidities, immunocompromise status, local viral circulation, and propensity to be vaccinated score. CI=confidence interval; col=column. *Patients aged <50 years were excluded from the estimate of fourth dose effectiveness for the subgroup aged 45-64 years.

supplemental tables S7 and S8. Median times between the last vaccination date and index contact date in the hospital sample were 173 (interquartile range 97-248) days for two doses, 105 (56-156) days for three doses, and 33 (19-50) days for four doses, and in the emergency department or urgent care sample were 179

Vaccination status	No	Covid-like illness controls (Col %)	Covid-19 cases (Col %)	Row %	Vaccine effectiveness (95% CI)
No likely immunocompromising condition					
Unvaccinated	25215	17 350 (29.3)	7865 (57.3)	31.2	
Partially vaccinated	2583	2202 (3.7)	381 (2.8)	14.8	61 (56 to 65)
2-dose vaccinated <2 months	324	280 (0.5)	44 (0.3)	13.6	73 (63 to 81)
2-dose vaccinated 2 to <4 months	869	724 (1.2)	145 (1.1)	16.7	69 (62 to 74)
2-dose vaccinated 4 to <6 months	1315	1063 (1.8)	252 (1.8)	19.2	60 (54 to 66)
2-dose vaccinated 6 to <8 months	2012	1555 (2.6)	457 (3.3)	22.7	51 (45 to 56)
2-dose vaccinated 8 to <10 months	4378	3179 (5.4)	1199 (8.7)	27.4	53 (50 to 57)
2-dose vaccinated 10 to <12 months	4771	3849 (6.5)	922 (6.7)	19.3	60 (56 to 63)
2-dose vaccinated 12 to <14 months	3076	2812 (4.8)	264 (1.9)	8.6	43 (35 to 51)
2-dose vaccinated ≥14 months	1654	1430 (2.4)	224 (1.6)	13.5	24 (10 to 35)
3-dose vaccinated <2 months	4164	3837 (6.5)	327 (2.4)	7.9	91 (90 to 92)
3-dose vaccinated 2 to <4 months	9089	8499 (14.4)	590 (4.3)	6.5	89 (88 to 90)
3-dose vaccinated 4 to <6 months	8644	8130 (13.7)	514 (3.7)	5.9	71 (68 to 74)
3-dose vaccinated 6 to <8 months	4187	3742 (6.3)	445 (3.2)	10.6	44 (37 to 51)
3-dose vaccinated ≥8 months	624	530 (0.9)	94 (0.7)	15.1	36 (18 to 50)
Any likely immunocompromising condition					
Unvaccinated	5830	4482 (22.3)	1348 (37.6)	23.1	
Partially vaccinated	812	688 (3.4)	124 (3.5)	15.3	44 (30 to 55)
2-dose vaccinated <4 months	377	298 (1.5)	79 (2.2)	21.0	34 (13 to 51)
2-dose vaccinated 4 to <6 months	453	371 (1.8)	82 (2.3)	18.1	42 (24 to 56)
2-dose vaccinated 6 to <8 months	679	554 (2.8)	125 (3.5)	18.4	38 (22 to 50)
2-dose vaccinated 8 to <10 months	1437	1098 (5.5)	339 (9.5)	23.6	37 (27 to 46)
2-dose vaccinated 10 to <12 months	1630	1339 (6.7)	291 (8.1)	17.9	35 (24 to 45)
2-dose vaccinated ≥12 months	1478	1341 (6.7)	137 (3.8)	9.3	20 (1 to 36)
3-dose vaccinated <2 months	1352	1212 (6.0)	140 (3.9)	10.4	78 (73 to 82)
3-dose vaccinated 2 to <4 months	3055	2751 (13.7)	304 (8.5)	10.0	70 (65 to 75)
3-dose vaccinated 4 to <6 months	3508	3159 (15.7)	349 (9.7)	9.9	48 (40 to 55)
3-dose vaccinated ≥6 months	2341	2139 (10.7)	202 (5.6)	8.6	29 (13 to 42)
4-dose vaccinated ≥7 days	700	638 (3.2)	62 (1.7)	8.9	48 (29 to 62)

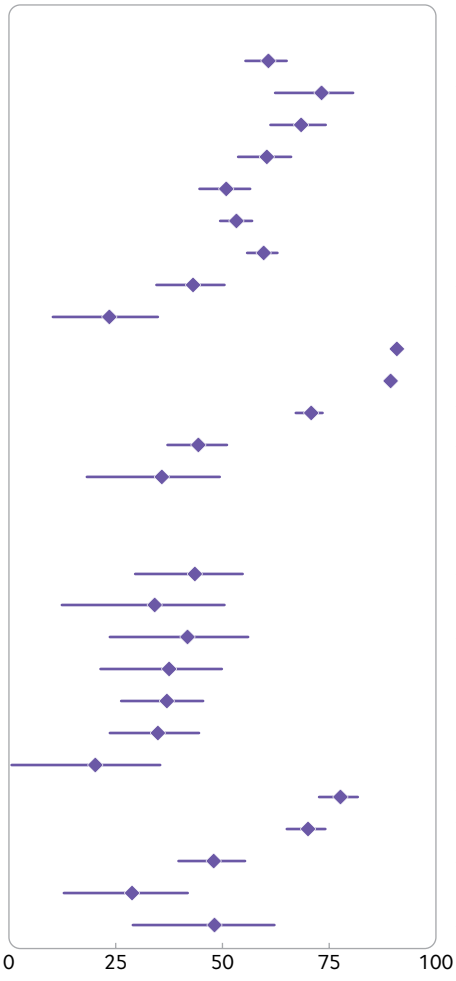

Fig 4 | Vaccine effectiveness (%) against covid-19-associated hospital admissions by time since vaccination and immunocompromise status, restricted to omicron period. Vaccine effectiveness estimates are adjusted for geographic area, calendar week, age, race, ethnicity, presence of respiratory and non-respiratory comorbidities, local viral circulation, and propensity to be vaccinated score. CI=confidence interval; col=column

(110-247) days for two doses, 100 (52-155) days for three doses, and 34 (20-52) days for four doses.

Vaccine effectiveness

Vaccine effectiveness estimates from the hospital and emergency department or urgent care samples are shown in figures 1 and figure 2 and detailed in supplemental tables S9-S14.

Vaccine effectiveness against covid-19 requiring hospital admission was 94% (95% confidence interval 93% to 95%) in the pre-delta period and 96% (95% to 97%) in the delta period, during the initial two months after the second dose. By months four to five after the second dose, vaccine effectiveness against hospital admission decreased to 87% (77% to 93%) in the pre-delta period and 89% (88% to 90%) in the delta period. In the omicron period, two dose vaccine effectiveness against hospital admission was lower than in the earlier periods, both before and when delta was dominant, and waned more, decreasing from 73% (63% to 80%) initially to 57% (51% to 62%) by months 4-5, and to 40% (32% to 47%) by 12 months after the second dose.

The patterns of vaccine effectiveness estimates from the emergency department or urgent care sample were similar. Vaccine effectiveness of two doses against emergency department or urgent care visits was initially high in the pre-delta period (95%; 94% to 96%) and delta period (93%; 92% to 94%) and then waned. During the omicron period, vaccine effectiveness of two doses against emergency department or urgent care visits was lower initially (63%; 57% to 68%) than in the earlier pre-delta and delta periods and then waned more. From up to 1 month after the second dose to months four to five, the vaccine effectiveness of a second dose decreased by 9 percentage points (95% confidence interval 4 to 16) during the pre-delta period, by 7 percentage points (7 to 9) during the delta

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Table 2 | Estimates of mRNA vaccine effectiveness against covid-19 related hospital admissions during omicron period by age group. Data are number of patients (percentage of column or row) unless stated otherwise.

Age group and vaccine dose	Total	SARS-CoV-2 negative	SARS-CoV-2 positive (% column) (% row)	Unadjusted vaccine effectiveness (% (95% CI))	Adjusted vaccine effectiveness* (% (95% CI))
All ages					
Unvaccinated	31 045	21 832 (27.8)	9213 (53.4) (29.7)	—	—
Partially vaccinated	3395	2890 (3.7)	505 (2.9) (14.9)	59 (54 to 62)	58 (53 to 62)
Time since two doses:					
<2 months	405	350 (0.4)	55 (0.3) (13.6)	63 (50 to 72)	73 (63 to 80)
2 to <4 months	1165	952 (1.2)	213 (1.2) (18.3)	47 (38 to 54)	61 (54 to 67)
4 to <6 months	1768	1434 (1.8)	334 (1.9) (18.9)	45 (38 to 51)	57 (51 to 62)
6 to <8 months	2691	2109 (2.7)	582 (3.4) (21.6)	35 (28 to 41)	48 (42 to 53)
8 to <10 months	5815	4277 (5.4)	1538 (8.9) (26.4)	15 (9 to 20)	51 (47 to 54)
10 to <12 months	6401	5188 (6.6)	1213 (7.0) (19.0)	45 (41 to 48)	55 (51 to 58)
12 to <14 months	4094	3750 (4.8)	344 (2.0) (8.4)	78 (76 to 81)	40 (32 to 47)
≥14 months	2114	1833 (2.3)	281 (1.6) (13.3)	63 (59 to 68)	19 (6 to 30)
14 to <16 months	1919	1668 (2.1)	251 (1.5) (13.1)	64 (59 to 69)	18 (5 to 30)
16 to <18 months	195	165 (0.2)	30 (0.2) (15.4)	57 (36 to 71)	23 (−15 to 49)
Time since three doses:					
<2 months	5516	5049 (6.4)	467 (2.7) (8.5)	78 (76 to 80)	89 (88 to 90)
2 to <4 months	12 144	11 250 (14.3)	894 (5.2) (7.4)	81 (80 to 82)	86 (85 to 87)
4 to <6 months	12 152	11 289 (14.4)	863 (5.0) (7.1)	82 (81 to 83)	66 (63 to 68)
6 to <8 months	6067	5481 (7.0)	586 (3.4) (9.7)	75 (72 to 77)	41 (35 to 47)
≥8 months	1085	930 (1.2)	155 (0.9) (14.3)	61 (53 to 67)	31 (17 to 43)
8 to <10 months	1070	918 (1.2)	152 (0.9) (3.0)	61 (53 to 67)	32 (17 to 44)
10 to <12 months	15	12 (0.0)	3 (0.0) (20.0)	41 (−52 to 83)	16 (−69 to 78)
18-44 years					
Unvaccinated	6798	5298 (49.6)	1500 (68.8) (22.1)	—	—
Partially vaccinated	654	586 (5.5)	68 (3.1) (10.4)	59 (47 to 68)	58 (43 to 68)
Time since two doses:					
2 to <4 months	287	246 (2.3)	41 (1.9) (14.3)	41 (18 to 58)	56 (36 to 70)
4 to <6 months	385	326 (3.1)	59 (2.7) (15.3)	36 (15 to 52)	46 (25 to 61)
6 to <8 months	541	438 (4.1)	103 (4.7) (19.0)	17 (−4 to 33)	38 (20 to 53)
8 to <10 months	762	628 (5.9)	134 (6.1) (17.6)	25 (8 to 38)	49 (35 to 59)
≥10 months	1074	973 (9.1)	101 (9.4) (27.2)	63 (55 to 70)	29 (8 to 45)
10 to <12 months	577	516 (4.8)	61 (2.8) (10.6)	58 (45 to 68)	30 (4 to 50)
12 to <14 months	375	344 (3.2)	31 (1.4) (8.3)	68 (54 to 78)	20 (−23 to 48)
14 to <16 months	107	98 (0.9)	9 (0.4) (8.4)	68 (36 to 84)	17 (−80 to 62)
16 to <18 months	15	15 (0.1)	0 (0.0) (0.0)	100 (1 to 100)	NC (NC to NC)
Time since three doses:					
<2 months	516	478 (4.5)	38 (1.7) (7.4)	72 (61 to 80)	85 (79 to 90)
2 to <4 months	817	774 (7.2)	43 (2.0) (5.3)	80 (73 to 86)	77 (68 to 84)
≥4 months	926	846 (7.9)	80 (3.7) (8.6)	67 (58 to 74)	33 (9 to 50)
4 to <6 months	661	615 (5.8)	46 (2.1) (7.0)	74 (64 to 81)	52 (30 to 66)
6 to <8 months	224	198 (1.9)	26 (1.2) (11.6)	54 (30 to 69)	−24 (−51 to 25)
8 to <10 months	41	33 (0.3)	8 (0.4) (19.5)	14 (−86 to 61)	−68 (−88 to −22)
45-64 years					
Unvaccinated	9987	7014 (34.3)	2973 (59.8) (29.8)	—	—
Partially vaccinated	1049	877 (4.3)	172 (3.5) (16.4)	54 (45 to 61)	50 (39 to 59)
Time since two doses:					
<2 months	133	114 (0.6)	19 (0.4) (14.3)	61 (36 to 76)	75 (59 to 85)
2 to <4 months	388	302 (1.5)	86 (1.7) (22.2)	33 (14 to 47)	54 (40 to 65)
4 to <6 months	655	547 (2.7)	108 (2.2) (16.5)	53 (42 to 62)	65 (56 to 73)
6 to <8 months	1018	805 (3.9)	213 (4.3) (20.9)	38 (27 to 47)	57 (48 to 64)
8 to <10 months	2059	1564 (7.6)	495 (10.0) (24.0)	25 (17 to 33)	58 (52 to 63)
10 to <12 months	1494	1268 (6.2)	226 (4.5) (15.1)	58 (51 to 64)	36 (24 to 46)
≥12 months	1294	1187 (5.8)	107 (2.2) (8.3)	79 (74 to 83)	32 (14 to 46)
12 to <14 months	942	868 (4.2)	74 (1.5) (7.9)	80 (74 to 84)	33 (12 to 49)
14 to <16 months	321	293 (1.4)	28 (0.6) (8.7)	77 (67 to 85)	33 (−4 to 57)
16 to <18 months	31	26 (0.1)	5 (0.1) (16.1)	55 (−18 to 83)	−22 (−70 to 56)
Time since three doses:					
<2 months	1486	1346 (6.6)	140 (2.8) (9.4)	75 (71 to 79)	89 (86 to 91)
2 to <4 months	2327	2172 (10.6)	155 (3.1) (6.7)	83 (80 to 86)	83 (80 to 86)
4 to <6 months	2201	2022 (9.9)	179 (3.6) (8.1)	79 (76 to 82)	58 (49 to 65)
≥6 months	1037	958 (4.7)	79 (1.6) (7.6)	81 (75 to 85)	48 (32 to 60)
6 to <8 months	874	810 (4.0)	64 (1.3) (7.3)	81 (76 to 86)	47 (28 to 60)
8 to <10 months	160	145 (0.7)	15 (0.3) (9.4)	76 (58 to 86)	52 (15 to 73)
10 to <12 months	3	3 (0.0)	0 (0.0) (0.0)	100 (−82 to 100)	NC (NC to NC)
Time since four doses:					
≥7 days†	309	292 (1.7)	17 (0.4) (5.5)	87 (78 to 92)	72 (51 to 83)

Table 2 | Continued

Age group and vaccine dose	Total	SARS-CoV-2 negative	SARS-CoV-2 positive (% column) (% row)	Unadjusted vaccine effectiveness (% (95% CI))	Adjusted vaccine effectiveness* (% (95% CI))
<2 months†	273	261 (1.5)	12 (0.3) (4.4)	89 (81 to 94)	75 (54 to 87)
2 to <4 months†	36	31 (0.2)	5 (0.1) (13.9)	63 (4 to 86)	54 (−28 to 83)
≥65 years					
Unvaccinated	14 260	9520 (19.1)	4740 (46.0) (33.2)	—	—
Partially vaccinated	1692	1427 (2.9)	265 (2.6) (15.7)	63 (57 to 67)	61 (55 to 67)
Time since two doses:					
<2 months	172	150 (0.3)	22 (0.2) (12.8)	71 (54 to 81)	77 (63 to 86)
2 to <4 months	490	404 (0.8)	86 (0.8) (17.6)	57 (46 to 66)	68 (59 to 75)
4 to <6 months	728	561 (1.1)	167 (1.6) (22.9)	40 (29 to 50)	53 (43 to 61)
6 to <8 months	1132	866 (1.7)	266 (2.6) (23.5)	38 (29 to 46)	47 (38 to 55)
8 to <10 months	2994	2085 (4.2)	909 (8.8) (30.4)	12 (5 to 20)	46 (40 to 51)
10 to <12 months	4330	3404 (6.8)	926 (9.0) (21.4)	45 (41 to 50)	59 (55 to 62)
12 to <14 months	2777	2538 (5.1)	239 (2.3) (8.6)	81 (78 to 84)	45 (36 to 53)
≥14 months	1640	1401 (2.8)	239 (2.3) (14.6)	66 (61 to 70)	31 (19 to 41)
14 to <16 months	1491	1277 (2.6)	214 (2.1) (14.4)	66 (61 to 71)	31 (18 to 41)
16 to <18 months	149	124 (0.2)	25 (0.2) (16.8)	60 (38 to 74)	35 (−3 to 58)
Time since three doses:					
<2 months	3514	3225 (6.5)	289 (2.8) (8.2)	82 (80 to 84)	89 (88 to 91)
2 to <4 months	9000	8304 (16.7)	696 (6.8) (7.7)	83 (82 to 85)	87 (86 to 88)
4 to <6 months	9290	8652 (17.4)	638 (6.2) (6.9)	85 (84 to 86)	70 (67 to 73)
6 to <8 months	4969	4473 (9.0)	496 (4.8) (10.0)	78 (75 to 80)	52 (45 to 57)
≥8 months	881	749 (1.5)	132 (1.3) (15.0)	65 (57 to 71)	45 (32 to 55)
8 to <10 months	869	740 (1.5)	129 (1.3) (14.8)	65 (58 to 71)	45 (32 to 56)
10 to <12 months	12	9 (0.0)	3 (0.0) (25.0)	33 (−60 to 82)	27 (−66 to 82)
Time since four doses:					
<2 months	1927	1780 (3.6)	147 (1.4) (7.6)	83 (80 to 86)	76 (71 to 80)
2 to <4 months	323	286 (0.6)	37 (0.4) (11.5)	74 (63 to 82)	70 (56 to 79)

CI=confidence interval.
*Regression models conditioned on calendar week and geographical area and adjusted for age, sex, race, ethnicity, immunocompromised status, respiratory or non-respiratory medical conditions, seven day average percentage of SARS-CoV-2 positive test results, and propensity to be vaccinated score.
†Patients aged <50 years were excluded from estimates of fourth dose effectiveness; thus, column sum might not equal 100% of encounters.

period, and by 26 percentage points (19 to 32) during the omicron period.

A third dose initially restored high levels of protection against both hospital admissions and emergency department or urgent care visits, then began to wane. In the hospital sample, vaccine effectiveness of three doses was initially 96% (95% to 96%) during the delta period and 89% (88% to 90%) during the omicron period. Similarly, in the emergency department or urgent care sample, the vaccine effectiveness of a third dose was initially 96% (95% to 96%) during the delta period and 83% (82% to 84%) during the omicron period. Waning was evident in both samples by four to five months after the third dose during the omicron period, when vaccine effectiveness decreased to 66% (63% to 68%) against hospital admission and to 46% (44% to 49%) against emergency department or urgent care visits.

Vaccine effectiveness against hospital admission after a fourth dose increased to 72% (51% to 83%) in the 50-64 year group and to 76% (71% to 80%) in the 65 years and older age group (fig 3). Similarly, vaccine effectiveness against emergency department or urgent care visits after a fourth dose increased to 57% (47% to 65%) and 73% (69% to 76%) among the 50-64 year and 65 years and older age groups, respectively (supplemental table S14). Vaccine effectiveness of a fourth dose among immunocompromised individuals in the hospital sample was 48% (29% to 62%; fig 4), but we were unable to measure this precisely enough in the emergency department or urgent care sample.

Vaccine effectiveness in subgroups

In all subgroups examined, vaccine effectiveness waned as time elapsed after the second dose, increased markedly with a third dose, and waned as time elapsed (supplemental tables S9-14). Vaccine effectiveness also substantially improved after a fourth dose among most subgroups for whom this booster dose was recommended. Comparing the initial two months after the third dose with months four to five, vaccine effectiveness against hospital admission during the omicron period decreased by 33 percentage points (95% confidence interval 16 to 56) in the 18-44 years group, 31 (21 to 40) in the 45-64 years group, and 19 (16 to 22) in the 65 years or older group (fig 3,table 2). Results were similar in post hoc analyses that were restricted to individuals without immunocompromising conditions (supplemental table S15).

Vaccine effectiveness was higher in recipients of the mRNA-1273 than BNT162b2 vaccine in all three variant periods in both the hospital sample and the emergency department or urgent care sample. Vaccine effectiveness waned in recipients of both vaccine products. In the hospital sample during the omicron period, vaccine effectiveness of mRNA-1273 waned from 91% (89% to 92%) to 65% (60% to 70%) by four to five months after three doses whereas vaccine

Table 3 | Estimates of vaccine effectiveness against covid-19 related hospital admissions during omicron period by mRNA vaccine product. Data are number of patients (percentage of column or row) unless stated otherwise

mRNA product and dose	Total	SARS-CoV-2 negative	SARS-CoV-2 positive (% column) (% row)	Unadjusted vaccine effectiveness (% (95% CI))	Adjusted vaccine effectiveness* (% (95% CI))
BNT162b2 (Pfizer-BioNTech)					
Unvaccinated	31 045	21 832 (40.6)	9213 (64.9) (29.7)	—	—
Partially vaccinated	1900	1580 (2.9)	320 (2.3) (16.8)	52 (46 to 58)	49 (42 to 56)
Time since two doses:					
<2 months	246	205 (0.4)	41 (0.3) (16.7)	53 (34 to 66)	63 (46 to 74)
2 to <4 months	787	621 (1.2)	166 (1.2) (21.1)	37 (25 to 47)	55 (46 to 63)
4 to <6 months	1163	936 (1.7)	227 (1.6) (19.5)	43 (33 to 50)	54 (45 to 61)
6 to <8 months	1678	1308 (2.4)	370 (2.6) (22.1)	33 (25 to 40)	42 (34 to 50)
8 to <10 months	3361	2407 (4.5)	954 (6.7) (28.4)	6 (−2 to 13)	44 (39 to 49)
10 to <12 months	3599	2900 (5.4)	699 (4.9) (19.4)	43 (38 to 48)	51 (46 to 56)
12 to <14 months	2257	2043 (3.8)	214 (1.5) (9.5)	75 (71 to 78)	32 (20 to 42)
≥14 months	1167	996 (1.9)	171 (1.2) (14.7)	59 (52 to 65)	2 (−18 to 18)
14 to <16 months	1043	892 (1.7)	151 (1.1) (14.5)	60 (52 to 66)	0 (−21 to 18)
16 to <18 months	124	104 (0.2)	20 (0.1) (16.1)	54 (26 to 72)	11 (−48 to 46)
Time since three doses:					
<2 months	2553	2330 (4.3)	223 (1.6) (8.7)	77 (74 to 80)	88 (86 to 90)
2 to <4 months	6578	5961 (11.1)	617 (4.3) (9.4)	75 (73 to 78)	85 (83 to 86)
4 to <6 months	6975	6469 (12.0)	506 (3.6) (7.3)	81 (80 to 83)	66 (63 to 70)
6 to <8 months	3870	3504 (6.5)	366 (2.6) (9.5)	75 (72 to 78)	33 (24 to 42)
≥8 months	801	688 (1.3)	113 (0.8) (14.1)	61 (52 to 68)	32 (15 to 46)
8 to <10 months	789	679 (1.3)	110 (0.8) (13.9)	62 (53 to 69)	32 (15 to 46)
10 to <12 months	12	9 (0.0)	3 (0.0) (25.0)	21 (−66 to 79)	17 (−71 to 80)
mRNA-1273 (Moderna)					
Unvaccinated	31 045	21 832 (49.3)	9213 (76.3) (29.7)	—	—
Partially vaccinated	1493	1308 (3.0)	185 (1.5) (12.4)	66 (61 to 71)	67 (61 to 72)
Time since two doses:					
<2 months	150	137 (0.3)	13 (0.1) (8.7)	78 (60 to 87)	87 (75 to 93)
2 to <4 months	355	309 (0.7)	46 (0.4) (13.0)	65 (52 to 74)	74 (64 to 82)
4 to <6 months	586	481 (1.1)	105 (0.9) (17.9)	48 (36 to 58)	64 (55 to 72)
6 to <8 months	1003	792 (1.8)	211 (1.7) (21.0)	37 (26 to 46)	57 (49 to 64)
8 to <10 months	2443	1864 (4.2)	579 (4.8) (23.7)	26 (19 to 33)	62 (57 to 66)
10 to <12 months	2791	2280 (5.1)	511 (4.2) (18.3)	47 (41 to 52)	61 (56 to 65)
12 to <14 months	1830	1701 (3.8)	129 (1.1) (7.0)	82 (78 to 85)	43 (30 to 53)
≥14 months	943	833 (1.9)	110 (0.9) (11.7)	69 (62 to 74)	25 (6 to 40)
14 to <16 months	872	772 (1.7)	100 (0.8) (11.5)	69 (62 to 75)	25 (6 to 41)
16 to <18 months	71	61 (0.1)	10 (0.1) (14.1)	61 (24 to 80)	20 (−62 to 60)
Time since three doses:					
<2 months	2380	2185 (4.9)	195 (1.6) (8.2)	79 (75 to 82)	91 (89 to 92)
2 to <4 months	4676	4438 (10.0)	238 (2.0) (5.1)	87 (85 to 89)	90 (88 to 91)
4 to <6 months	4455	4149 (9.4)	306 (2.5) (6.9)	83 (80 to 84)	65 (60 to 70)
≥6 months	2219	1979 (4.5)	240 (2.0) (10.8)	71 (67 to 75)	40 (30 to 49)
6 to <8 months	1960	1759 (4.0)	201 (1.7) (10.3)	73 (69 to 77)	44 (33 to 52)
8 to <10 months	256	217 (0.5)	39 (0.3) (15.2)	57 (40 to 70)	10 (−32 to 38)
10 to <12 months	3	3 (0.0)	0 (0.0) (0.0)	100 (−83 to 100)	NC (NC to NC)

CI=confidence interval; NC=not calculable.
*Regression models conditioned on calendar week and geographical area and adjusted for age, sex, race, ethnicity, immunocompromised status, respiratory or non-respiratory medical conditions, seven day average percentage of SARS-CoV-2 positive test results, and propensity to be vaccinated score.

effectiveness of BNT162b2 waned from 88% (86% to 90%) to 66% (63% to 70%) after three doses (table 3).

Vaccine effectiveness after two and three doses was generally lower among individuals who were immunocompromised, in both the hospital and the emergency department or urgent care samples, in each period and at all times since vaccination (fig 4, table 4, supplemental tables S9-S14). In the omicron period, vaccine effectiveness of three doses against hospital admission waned from 78% (73% to 82%) to 48% (40% to 55%) by months four to five in the immunocompromised subgroup compared with 91% (90% to 92%) to 71% (68% to 74%) in the subgroup without immunocompromise (table 4).

Sensitivity analyses

In the first sensitivity analysis, vaccine effectiveness estimates in both samples were similar but slightly lower if patients with previous SARS-CoV-2 infection were included (supplemental tables S16 and S17). In the second sensitivity analysis, vaccine effectiveness estimates were similar but lower if the emergency department or urgent care sample excluded patients who were later admitted to hospital. In the third sensitivity analysis, vaccine effectiveness ranged from −5% to 24% among patients whose index date for medical contact was less than 14 days after the first dose, consistent with the little protection induced by the vaccine during this two week period.

Table 4 | Estimates of mRNA vaccine effectiveness against covid-19 related hospital admissions during omicron period by immunocompromised status. Data are number of patients (percentage of column or row) unless stated otherwise.

Immunocompromising condition and vaccine dose	Total	SARS-CoV-2 negative (n=213 103)	SARS-CoV-2 positive (n=45 903); (% column) (% row)	Unadjusted vaccine effectiveness (% (95% CI))	Adjusted vaccine effectiveness* (% (95% CI))
No likely immunocompromising condition					
Unvaccinated	25 215	17 350 (29.3)	7865 (57.3) (31.2)	—	
Partially vaccinated	2583	2202 (3.7)	381 (2.8) (14.8)	62 (57 to 66)	61 (56 to 65)
Time since two doses:					
<2 months	324	280 (0.5)	44 (0.3) (13.6)	65 (52 to 75)	73 (63 to 81)
2 to <4 months	869	724 (1.2)	145 (1.1) (16.7)	56 (47 to 63)	69 (62 to 74)
4 to <6 months	1315	1063 (1.8)	252 (1.8) (19.2)	48 (40 to 55)	60 (54 to 66)
6 to <8 months	2012	1555 (2.6)	457 (3.3) (22.7)	35 (28 to 42)	51 (45 to 56)
8 to <10 months	4378	3179 (5.4)	1199 (8.7) (27.4)	17 (11 to 23)	53 (50 to 57)
10 to <12 months	4771	3849 (6.5)	922 (6.7) (19.3)	47 (43 to 51)	60 (56 to 63)
12 to <14 months	3076	2812 (4.8)	264 (1.9) (8.6)	79 (76 to 82)	43 (35 to 51)
≥14 months	1654	1430 (2.4)	224 (1.6) (13.5)	65 (60 to 70)	24 (10 to 35)
14 to <16 months	1499	1298 (2.2)	201 (1.5) (13.4)	66 (60 to 71)	23 (8 to 35)
16 to <18 months	155	132 (0.2)	23 (0.2) (14.8)	62 (40 to 75)	33 (−7 to 58)
Time since three doses:					
<2 months	4164	3837 (6.5)	327 (2.4) (7.9)	81 (79 to 83)	91 (90 to 92)
2 to <4 months	9089	8499 (14.4)	590 (4.3) (6.5)	85 (83 to 86)	89 (88 to 90)
4 to <6 months	8644	8130 (13.7)	514 (3.7) (5.9)	86 (85 to 87)	71 (68 to 74)
6 to <8 months	4187	3742 (6.3)	445 (3.2) (10.6)	74 (71 to 76)	44 (37 to 51)
≥8 months	624	530 (0.9)	94 (0.7) (15.1)	61 (51 to 69)	36 (18 to 50)
8 to <10 months	616	523 (0.9)	93 (0.7) (15.1)	61 (51 to 69)	36 (18 to 50)
10 to <12 months	8	7 (0.0)	1 (0.0) (12.5)	68 (−61 to 96)	55 (−76 to 95)
Any likely immunocompromising condition					
Unvaccinated	5830	4482 (22.3)	1348 (37.6) (23.1)	—	—
Partially vaccinated	812	688 (3.4)	124 (3.5) (15.3)	40 (27 to 51)	44 (30 to 55)
Time since two doses:					
<4 months	377	298 (1.5)	79 (2.2) (21.0)	12 (−14 to 32)	34 (13 to 51)
<2 months	81	70 (0.3)	11 (0.3) (13.6)	48 (1 to 72)	66 (31 to 83)
2 to <4 months	296	228 (1.1)	68 (1.9) (23.0)	1 (−31 to25)	24 (−3 to 44)
4 to <6 months	453	371 (1.8)	82 (2.3) (18.1)	27 (6 to 43)	42 (24 to 56)
6 to <8 months	679	554 (2.8)	125 (3.5) (18.4)	25 (8 to 39)	38 (22 to 50)
8 to <10 months	1437	1098 (5.5)	339 (9.5) (23.6)	−3 (−18 to 10)	37 (27 to 46)
10 to <12 months	1630	1339 (6.7)	291 (8.1) (17.9)	28 (17 to 37)	35 (24 to 45)
≥12 months	1478	1341 (6.7)	137 (3.8) (9.3)	66 (59 to 72)	20 (1 to 36)
12 to <14 months	1018	938 (4.7)	80 (2.2) (7.9)	72 (64 to 78)	26 (4 to 43)
14 to <16 months	420	370 (1.8)	50 (1.4) (11.9)	55 (39 to 67)	11 (−26 to 37)
16 to <18 months	40	33 (0.2)	7 (0.2) (17.5)	29 (−60 to 69)	−20 (−66 to 51)
Time since three doses:					
<2 months	1352	1212 (6.0)	140 (3.9) (10.4)	62 (54 to 68)	78 (73 to 82)
2 to <4 months	3055	2751 (13.7)	304 (8.5) (10.0)	63 (58 to 68)	70 (65 to 75)
4 to <6 months	3508	3159 (15.7)	349 (9.7) (9.9)	63 (58 to 68)	48 (40 to 55)
≥6 months	2341	2139 (10.7)	202 (5.6) (8.6)	69 (63 to 73)	29 (13 to 42)
6 to <8 months	1880	1739 (8.7)	141 (3.9) (7.5)	73 (68 to 78)	32 (16 to 46)
8 to <10 months	454	395 (2.0)	59 (1.6) (13.0)	50 (34 to 62)	16 (−16 to 39)
10 to <12 months	7	5 (0.0)	2 (0.1) (28.6)	−33 (−85 to 74)	−66 (−90 to 71)
Time since four doses:					
≥7 days	700	638 (3.2)	62 (1.7) (8.9)	68 (58 to 75)	48 (29 to 62)
<2 months	601	553 (2.8)	48 (1.3) (8.0)	71 (61 to 79)	51 (30 to 65)
2 to <4 months	99	85 (0.4)	14 (0.4) (14.1)	45 (3 to 69)	28 (−36 to 61)

CI=confidence interval.
*Regression models conditioned on calendar week and geographical area and adjusted for age, sex, race, ethnicity, respiratory or non-respiratory medical conditions, seven day average percentage of SARS-CoV-2 positive test results, and propensity to be vaccinated score.

Discussion

Principal findings

Protection against severe omicron related covid-19 was high after three doses of an mRNA vaccine but began to wane less than six months after the third dose. In the hospital sample, vaccine effectiveness after a third doses was 89% among individuals within two months but decreased to 66% among individuals at four to five months. In the emergency department or urgent care sample, vaccine effectiveness of a third dose was 83% within two months but decreased to 46% at four to five months. In all subgroups defined by age, immunocompromised status, and vaccine product, the third dose was initially associated with markedly increased protection, but vaccine effectiveness was lower by four to five months. Vaccine effectiveness increased after a fourth dose for most subgroups for whom this booster dose is recommended in the US. Although we have not yet observed events more than four months from a fourth dose, our results suggest

that protection after the fourth dose begins to wane after a few months.

Comparison with other studies

Our vaccine effectiveness estimates for mRNA vaccines are broadly consistent with those in other reports: vaccine effectiveness was lower against the omicron variant than earlier variants,[10 21 22] vaccine effectiveness waned after a second dose,[3-9] and a third dose restored high levels of protection against severe covid-19 during the omicron and delta periods.[10-13] Our results are also consistent with other reports of waning protection after three mRNA doses.[23-25] As with others, we noted less waning against more severe outcomes,[3 26] lower vaccine effectiveness among individuals who were immunocompromised,[17 27] and higher vaccine effectiveness among recipients of mRNA-1273 compared with recipients of BNT162b2.[10 23 24] We also observed improvement in vaccine effectiveness after a fourth dose.[28]

Strengths and limitations of this study

One strength of our study is the number and diversity of sites and inclusion of outcomes of varying severity. Additionally, our sample size was large enough to detect modest waning of vaccine protection and to allow stratification of vaccine effectiveness estimates by immunocompromise status. We rigorously controlled for calendar time and geography such that cases were compared with controls tested during the same week in the same geographical area. This comparison allowed us to distinguish differences in vaccine effectiveness attributable to the waning of vaccine induced immunity from those attributable to the change in dominance of SARS-CoV-2 variants.

Our study has limitations. First, there is residual confounding if the timing of primary vaccination or booster doses was related to covid-19 risk in unmeasured ways (eg, mask use or occupation). However, we did not observe substantial vaccine protection in the two weeks after a first dose, which provides reassurance that residual confounding is limited. Second, although our test negative design is intended to avoid selection bias from healthcare seeking behavior, the design could induce selection bias arising from factors associated with a covid-like illness but not with covid-19. For example, inclusion of individuals who had influenza as controls could underestimate vaccine effectiveness due to the correlation between covid-19 vaccination and influenza vaccination. Because fewer than 5% of people in the control group in our study were positive for influenza, we expect this bias to be minimal. Also, we cannot rule out selection bias arising from reliance on clinician directed testing, although we note that almost all the patients admitted to hospital with covid-like illness were tested for SARS-CoV-2. Third, immunocompromised status was ascertained only from diagnostic codes at the time of medical contact (without data on prescriptions or laboratory tests), and we could not distinguish whether a third dose was in a primary series for people who were immunocompromised or was a booster dose. Insufficient adjustment for immunocompromised status might have biased vaccine effectiveness estimates downward, especially for those who were vaccinated and received a booster dose relatively early. However, we found waning protection in stratified analyses among both individuals who were immunocompromised and individuals who were not immunocompromised. Fourth, we did not have viral genomic sequence data. Fifth, although we excluded individuals with documented previous SARS-CoV-2 infection, our data might have missed many past infections. Sensitivity analyses that included people with known previous infections suggest that our vaccine effectiveness estimates would be higher if we could have ascertained and excluded everyone with protection induced by infection. Sixth, although we interpret our analyses of the hospital sample as pertaining to severe covid-19, some patients admitted to hospital could have tested positive for other reasons while being in hospital, especially during the omicron period.[29] To address this, patients were not eligible for inclusion if they had a positive SARS-CoV-2 test result but no diagnoses suggesting a covid-19 infection. Seventh, although our sample includes enough outcome events to yield precise estimates of vaccine effectiveness for the overall adult population, estimates of vaccine effectiveness against admissions to hospital for covid-19 were less precise for younger adults and individuals who were immunocompromised owing to smaller sample sizes. Finally, pooled data from heterogeneous populations in 10 US states; however, our findings might not be generalizable to other populations.

Policy implications

To evaluate the clinical significance of waning vaccine effectiveness, consideration of the absolute number of people admitted to hospital that would have been prevented had no waning occurred is helpful. However, this number depends on the background rate of severe covid-19, which sometimes varied 10-fold or more over several weeks. In this context, hospital admissions that would be prevented during an anticipated surge are an appropriate alternative. For example, the rate of hospital admissions related to covid-19 reached about 1500 per million unvaccinated adults each week in January 2022 in the US[30]; if incidence surges that high again, then for every million adults who lose 20 percentage points of vaccine protection, about 300 additional people each week (1500×0.20) will be admitted to hospital owing to covid-19 compared with no waning effect. During the omicron period, vaccine effectiveness waned within six months of the third dose by about 20 percentage points among those without immunocompromising conditions and by more than 40 percentage points among those with immunocompromising conditions. This amount of waning is enough to be relevant for clinical and policy considerations about the need for boosters or other protective measures. Combined with evidence of the

safety and immunogenicity of an additional vaccine dose,[31-33] our findings lend support for consideration of additional doses beyond the primary series.

Conclusions

Protection conferred by mRNA vaccines against moderate (emergency department or urgent care) and severe (hospital admission) covid-19 waned during the months after primary vaccination, increased substantially after the third dose, and waned again by four to five months. A fourth dose improved vaccine effectiveness among those for whom this booster dose was recommended. Vaccine effectiveness waned less against severe disease than against moderate disease. Vaccine effectiveness of either mRNA vaccine waned among adults of all ages. Among immunocompromised individuals, vaccine effectiveness was lower and waning was more noticeable. These findings support recommendations for a third vaccine dose and consideration of additional booster doses.

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Data sharing: No additional data available.

The lead author (JMF) affirms that this manuscript is an accurate and transparent account of the study being reported and that no important aspects of the study have been omitted.

Dissemination to participants and related patient and public communities: The individual level dataset from this study is held securely in limited deidentified form at the US Centers for Disease Control and Prevention. Data sharing agreements between CDC and data providers prohibit CDC from making this dataset publicly available. CDC will share aggregate study data once study objectives are complete, consistent with data use agreements with partner institutions.

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Web appendix: Supplemental methods, figures S1-S18, and tables S1-S17
Web appendix: Supplemental tables