Supplemental Online Content

Abu-Raddad LJ, Chemaitelly H, Ayoub HH, et al. Association of prior SARS-CoV-2 infection with risk of breakthrough infection following mRNA vaccination in Qatar. *JAMA*. doi:10.1001/jama.2021.19623

eMethods

eTable 1. Demographic Characteristics of Cohorts That Received the BNT162b2 and mRNA-1273 Vaccines

eTable 2. Demographic Characteristics of Breakthrough-Infected and Breakthrough-Uninfected Vaccinated Individuals in the Matched Cohorts

eFigure 1. Time Trend of Cumulative Numbers of BNT162b2-Vaccinated and mRNA-1273–Vaccinated Persons Included in This Study and Numbers of Daily Diagnosed SARS-CoV-2 Infections During the Study Period

eFigure 2. Cumulative Infection Incidence Among Matched Cohorts of BNT162b2- and mRNA-1273–Vaccinated Individuals With and Without a Prior Infection

eFigure 3. Development of Cohorts With Prior Infections ≥6 Months Versus <6 Months Before the First Vaccine Dose in a Study of SARS-CoV-2 Infections After Vaccination

eFigure 4. Cumulative Infection Incidence Among Individuals With a Prior Infection by Time Interval Between Prior Infection and Vaccination

eReferences

This supplemental material has been provided by the authors to give readers additional information about their work.

© 2021 American Medical Association. All rights reserved.

eMethods.

Definitions of Severe, Critical, and Fatal COVID-19

Severe COVID-19 was defined per the World health Organization (WHO) classification as a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected person with "oxygen saturation of <90% on room air, and/or respiratory rate of >30 breaths/minute in adults and children >5 years old (or ≥60 breaths/minute in children <2 months old or ≥50 breaths/minute in children 2-11 months old or ≥40 breaths/minute in children 1–5 years old), and/or signs of severe respiratory distress (accessory muscle use and inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs)".[1] Detailed WHO criteria for classifying SARS-CoV-2 infection severity can be found in the WHO technical report.[1]

Critical COVID-19 was defined per WHO classification as a SARS-CoV-2-infected person with "acute respiratory distress syndrome, sepsis, septic shock, or other conditions that would normally require the provision of life sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy".[1] Detailed WHO criteria for classifying SARS-CoV-2 infection criticality can be found in the WHO technical report.[1]

COVID-19 death was defined per WHO classification as "a death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID-19 disease (e.g. trauma). There should be no period of complete recovery from COVID-19 between illness and death. A death due to COVID-19 may not be attributed to another disease (e.g. cancer) and should be counted independently of preexisting conditions that are suspected of triggering a severe course of COVID-19". Detailed WHO criteria for classifying COVID-19 death can be found in the WHO technical report.[2]

© 2021 American Medical Association. All rights reserved.

Laboratory methods

Nasopharyngeal and/or oropharyngeal swabs were collected for PCR testing and placed in Universal Transport Medium (UTM). Aliquots of UTM were: extracted on a QIAsymphony platform (QIAGEN, USA) and tested with real-time reverse-transcription PCR (RT-qPCR) using TaqPath™ COVID-19 Combo Kits (Thermo Fisher Scientific, USA) on an ABI 7500 FAST (Thermo Fisher, USA); tested directly on the Cepheid GeneXpert system using the Xpert Xpress SARS-CoV-2 (Cepheid, USA); or loaded directly into a Roche cobas® 6800 system and assayed with a cobas® SARS-CoV-2 Test (Roche, Switzerland). The first assay targets the viral S, N, and ORF1ab gene regions. The second targets the viral N and E-gene regions, and the third targets the ORF1ab and E-gene regions.

All PCR testing was conducted at the Hamad Medical Corporation Central Laboratory or Sidra Medicine Laboratory, following standardized protocols.

Classification of infections by variant type

Surveillance for SARS-CoV-2 variants in Qatar is based on viral genome sequencing and multiplex, real-time reverse-transcription PCR (RT-qPCR) variant screening[3] of random positive clinical samples,[4-8] and complemented by deep sequencing of wastewater samples.[6,9] The latter is used to compare the distribution of variants in wastewater with that in clinical samples collected from SARS-CoV-2 patients.

Between March 23, 2021 and September 7, 2021, RT-qPCR genotyping identified 6005 (35.5%) Beta (B.1.351)-like cases, 3658 (21.6%) Alpha (B.1.1.7)-like cases, 7218 (42.6%) “other” variant cases, and 51 (0.3%) B.1.375-like or B.1.258-like cases in 16 932 randomly collected

© 2021 American Medical Association. All rights reserved.

SARS-CoV-2-positive specimens.[6,8] Since RT-qPCR genotyping started on March 23, 2021, the proportion of all diagnosed infections in Qatar that have been RT-qPCR genotyped was 12.0%.

The accuracy of the RT-qPCR genotyping was verified against either Sanger sequencing of the receptor-binding domain (RBD) of SARS-CoV-2 surface glycoprotein (S) gene, or by viral whole-genome sequencing on a Nanopore GridION sequencing device. From 236 random samples (27 Alpha-like, 186 Beta-like, and 23 "other" variants), PCR genotyping results for Alpha-like, Beta-like, and 'other' variants were in 88.8% (23 out of 27), 99.5% (185 out of 186), and 100% (23 out of 23) agreement with the SARS-CoV-2 lineages assigned by sequencing.

Within the "other" variant category, Sanger sequencing and/or Illumina sequencing of the RBD of SARS-CoV-2 spike gene on 728 random samples confirmed that 701 (96.3%) were Delta cases and 17 (2.3%) were other variant cases, with 10 (1.4%) samples failing lineage assignment.[6,8] Accordingly, a Delta case was proxied as any "other" case identified through the RT-qPCR based variant screening.

All the variant RT-qPCR screening was conducted at the Sidra Medicine Laboratory following standardized protocols.

© 2021 American Medical Association. All rights reserved.

eTable 1. Demographic characteristics of cohorts that received the BNT162b2 and mRNA-1273 vaccines.

Characteristics	Individuals with a prior PCR-confirmed infection			Individuals with no prior PCR-confirmed infection		
	Full cohort vaccinated with BNT162b2	Full cohort vaccinated with mRNA-1273	SMD[a]	Full cohort vaccinated with BNT162b2	Full cohort vaccinated with mRNA-1273	SMD[a]
No	100 486	58 987		787 821	426 574	
Total follow-up time (person-weeks)	1 608 209	694 259		13 948 047	5 482 776	
Median age (IQR) — years	37 (29-44)	36 (31-44)	0.09[b]	37 (29-46)	36 (31-44)	0.004[b]
Age group — no. (%)			0.44			0.48
<20 years	10 257 (10.2)	545 (0.9)		83 043 (10.5)	4 975 (1.2)	
20-29 years	15 020 (15.0)	10 189 (17.3)		114 120 (14.5)	78 841 (18.5)	
30-39 years	35 567 (36.4)	24 973 (42.3)		262 939 (33.4)	172 736 (40.5)	
40-49 years	23 193 (23.1)	15 618 (26.5)		183 444 (23.3)	115 286 (27.0)	
50-59 years	10 802 (10.8)	6079 (10.3)		93 616 (11.9)	43 817 (10.3)	
60-69 years	3683 (3.7)	1328 (2.3)		38 760 (4.9)	9082 (2.1)	
70+ years	964 (1.0)	255 (0.4)		11 899 (1.5)	1837 (0.4)	
Sex			0.10			0.15
Male	68 186 (67.9)	42 653 (72.3)		505 040 (64.1)	302 456 (70.9)	
Female	32 300 (32.1)	16 334 (27.7)		282 781 (35.9)	124 118 (29.1)	
Nationality[c]			0.52			0.55
Bangladeshi	8009 (8.0)	6504 (11.0)		70 622 (9.0)	61 115 (14.3)	
Egyptian	6340 (6.3)	3432 (5.8)		51 232 (6.5)	25 629 (6.0)	
Filipino	10 484 (10.4)	7922 (13.4)		78 927 (10.0)	53 292 (12.5)	
Indian	24 560 (24.4)	18 432 (31.3)		171 630 (21.8)	120 516 (28.3)	
Nepalese	8180 (8.1)	5817 (9.9)		42 358 (5.4)	33 972 (8.0)	
Pakistani	4133 (4.1)	3184 (5.4)		28 897 (3.7)	21 009 (4.9)	
Qatari	16 943 (16.9)	1652 (2.8)		136 882 (17.4)	12 564 (3.0)	
Sri Lankan	2988 (3.0)	2565 (4.4)		21 653 (2.8)	18 631 (4.4)	
Sudanese	2545 (2.5)	1341 (2.3)		17 812 (2.3)	8729 (2.1)	
Other nationalities[d]	16 304 (16.2)	8138 (13.8)		167 808 (21.3)	71 117 (16.7)	
Calendar month of Dose 1			0.72			0.88
December	215 (0.2)	0 (0.0)		5304 (0.7)	2 (0.0005)	
January	3114 (3.1)	0 (0.0)		42 296 (5.4)	14 (0.003)	
February	9613 (9.6)	88 (0.2)		115 107 (14.6)	851 (0.2)	
March	17 727 (17.6)	8301 (14.1)		184 279 (23.4)	83 474 (19.6)	
April	19 988 (19.9)	16 539 (28.0)		148 557 (18.9)	142 424 (33.4)	
May	33 681 (33.5)	14 833 (25.2)		186 681 (23.7)	80 726 (18.9)	
June	10 256 (10.2)	7892 (13.4)		69 866 (8.9)	46 696 (11.0)	
July	4380 (4.4)	9154 (15.5)		26 589 (3.4)	57 672 (13.5)	
August	1512 (1.5)	2180 (3.7)		9142 (1.2)	14 715 (3.5)	

Abbreviations: IQR, interquartile range; SMD, standardized mean difference.

[a]SMD is the difference in the mean of a covariate between groups divided by the pooled standard deviation. An SMD less than 0.1 indicates adequate matching.

[b]SMD reported here is for the mean difference between groups divided by the pooled standard deviation.

[c]Nationalities were chosen to represent the most numerous groups in the population of Qatar.

© 2021 American Medical Association. All rights reserved.

[d]Individuals with a prior PCR-confirmed infection in Qatar comprised 133 other nationalities in the full cohort of individuals who received the BNT162b2 vaccine and 114 other nationalities in the full cohort of individuals who received the mRNA-1273 vaccine. Meanwhile, individuals with no prior PCR-confirmed infection in Qatar comprised 184 other nationalities in the full cohort of individuals who received the BNT162b2 vaccine and 163 other nationalities in the full cohort of individuals who received the mRNA-1273 vaccine.

© 2021 American Medical Association. All rights reserved.

eTable 2. Demographic characteristics of breakthrough-infected and breakthrough-uninfected vaccinated individuals in the matched cohorts.

Characteristics	Vaccinated with BNT162b2						Vaccinated with mRNA-1273					
	Individuals with a prior PCR-confirmed infection[a]			Individuals with no prior PCR-confirmed infection[a]			Individuals with a prior PCR-confirmed infection[a]			Individuals with no prior PCR-confirmed infection[a]		
	Reinfected	Not reinfected	SMD[b]	Infected	Not infected	SMD[b]	Reinfected	Not reinfected	SMD[b]	Infected	Not infected	SMD[b]
No	159	99 067		2509	287 923		43	58 053		368	169 146	
Median time ≥14 days from Dose 2 to infection (IQR) — days	55 (18-108)			60 (25-113)			46 (16-81)			77 (30-104)		
Median age (IQR) — years	35 (28-43)	37 (29-44)	0.08[c]	38 (31-48)	37 (29-44)	0.22[c]	39 (32-46)	36 (31-44)	0.15[c]	36 (31-44)	36 (31-44)	0.03[c]
Age group — no. (%)			0.34			0.28			0.25			0.08
<20 years	7 (4.4)	10 151 (10.3)		136 (5.4)	29 755 (10.3)		0 (0.0)	512 (0.9)		4 (1.1)	1357 (0.8)	
20-29 years	38 (23.9)	14 766 (14.9)		422 (16.8)	42 774 (14.9)		7 (16.3)	10 045 (17.3)		71 (19.3)	29 375 (17.4)	
30-39 years	59 (37.1)	36 256 (36.6)		833 (33.2)	106 625 (37.0)		16 (37.2)	24 755 (42.6)		147 (40.0)	72 866 (43.1)	
40-49 years	35 (22.0)	22 885 (23.1)		556 (22.2)	66 334 (23.0)		12 (27.9)	15 428 (26.6)		97 (26.4)	44 937 (26.6)	
50-59 years	14 (8.8)	10 565 (10.7)		334 (13.3)	30 099 (10.5)		7 (16.3)	5911 (10.2)		40 (10.9)	16 875 (10.0)	
60-69 years	6 (3.8)	3547 (3.6)		176 (7.0)	9895 (3.4)		1 (2.3)	1205 (2.1)		8 (2.2)	3251 (1.9)	
70+ years	0 (0.0)	897 (0.9)		52 (2.1)	2441 (0.9)		0 (0.0)	197 (0.3)		1 (0.3)	485 (0.3)	
Sex			0.02			0.14			0.15			0.22
Male	107 (67.3)	67 413 (68.1)		1547 (61.7)	196 809 (68.4)		34 (79.1)	42 146 (72.6)		232 (63.0)	123 640 (73.1)	
Female	52 (32.7)	31 654 (32.0)		962 (38.3)	91 114 (31.7)		9 (20.9)	15 907 (27.4)		136 (37.0)	45 506 (26.9)	
Nationality[d]			0.67			0.56			0.63			0.57
Bangladeshi	7 (4.4)	7982 (8.1)		101 (4.0)	23 618 (8.2)		4 (9.3)	6487 (11.2)		23 (6.3)	19 384 (11.5)	
Egyptian	11 (6.9)	6317 (6.4)		192 (7.7)	18 578 (6.5)		3 (7.0)	3417 (5.9)		40 (10.9)	10 087 (6.0)	
Filipino	6 (3.8)	10 453 (10.6)		120 (4.8)	30 135 (10.5)		3 (7.0)	7896 (13.6)		25 (6.8)	22 580 (13.4)	
Indian	31 (19.5)	24 518 (24.8)		473 (18.9)	72 953 (25.3)		17 (39.5)	18 409 (31.7)		114 (31.0)	55 041 (32.5)	
Nepalese	5 (3.1)	8136 (8.2)		79 (3.2)	23 938 (8.3)		2 (4.7)	5801 (10.0)		12 (3.3)	17 214 (10.2)	
Pakistani	5 (3.1)	4105 (4.1)		112 (4.5)	11 963 (4.2)		4 (9.3)	3160 (5.4)		21 (5.7)	9153 (5.4)	
Qatari	70 (44.0)	16 868 (17.0)		907 (36.2)	49 381 (17.2)		2 (4.7)	1637 (2.8)		36 (9.8)	4669 (2.8)	
Sri Lankan	3 (1.9)	2968 (3.0)		39 (1.6)	8780 (3.1)		5 (11.6)	2546 (4.4)		14 (3.8)	7579 (4.5)	
Sudanese	3 (1.9)	2519 (2.5)		49 (2.0)	7222 (2.5)		2 (4.7)	1327 (2.3)		10 (2.7)	3767 (2.2)	
Other nationalities[e]	18 (11.3)	15 201 (15.3)		437 (17.4)	41 355 (14.4)		1 (2.3)	7373 (12.7)		73 (19.8)	19 672 (11.6)	
Calendar month of Dose 1			0.78			1.01			0.87			1.00
December	1 (0.6)	202 (0.2)		18 (0.7)	549 (0.2)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
January	12 (7.6)	3015 (3.0)		331 (13.2)	8372 (2.9)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
February	44 (27.7)	9485 (9.6)		754 (30.1)	27 127 (9.4)		0 (0.0)	80 (0.1)		1 (0.3)	178 (0.1)	
March	43 (27.0)	17 564 (17.7)		717 (28.6)	51 798 (18.0)		12 (27.9)	8206 (14.1)		142 (38.6)	24 369 (14.4)	
April	19 (12.0)	19 792 (20.0)		287 (11.4)	58 506 (20.3)		22 (51.2)	16 357 (28.2)		161 (43.8)	48 265 (28.5)	
May	35 (22.0)	33 322 (33.6)		329 (13.1)	96 596 (33.6)		6 (14.0)	14 607 (25.2)		48 (13.0)	42 265 (25.0)	
June	5 (3.1)	10 062 (10.2)		62 (2.5)	29 340 (10.2)		2 (4.7)	7713 (13.3)		12 (3.3)	22 134 (13.1)	
July	0 (0.0)	4216 (4.3)		10 (0.4)	11 738 (4.1)		1 (2.3)	8964 (15.4)		4 (1.1)	25 569 (15.1)	
August	0 (0.0)	1409 (1.4)		1 (0.04)	3897 (1.4)		0 (0.0)	2126 (3.7)		0 (0.0)	6366 (3.8)	

Abbreviations: IQR, interquartile range; SMD, standardized mean difference.

[a]Cohorts of individuals with prior PCR-confirmed infection and with no prior PCR-confirmed infection were exact matched in a 1:3 ratio by sex, 5-year age group, nationality, and calendar week of first vaccine dose.

[b]SMD is the difference in the mean of a covariate between groups divided by the pooled standard deviation. An SMD less than 0.1 indicates adequate matching.

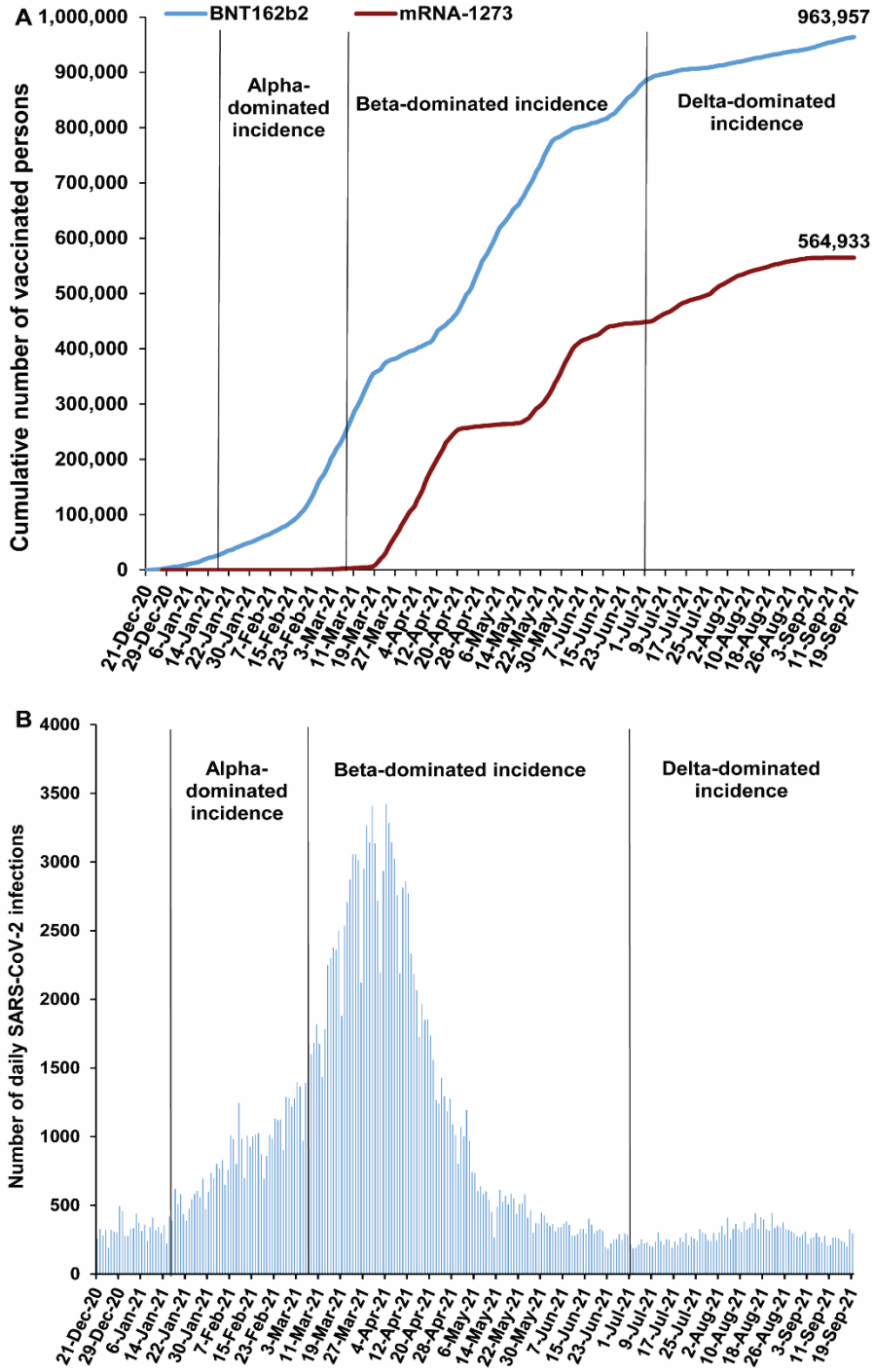
[c]SMD reported here is for the mean difference between groups divided by the pooled standard deviation.

[d]Nationalities were chosen to represent the most numerous groups in the population of Qatar.

[e]Individuals who received the BNT162b2 vaccine comprised 8 other nationalities in individuals with a prior PCR-confirmed infection who were reinfected, 102 other nationalities in individuals with a prior PCR-confirmed infection who were not infected, 34 other nationalities in individuals with no prior PCR-confirmed infection who were infected, and 103 other nationalities in individuals with no prior PCR-confirmed infection who were not infected. Meanwhile, individuals who received the mRNA-1273 vaccine comprised 1 other nationality in individuals with a prior PCR-confirmed infection who were reinfected, 85 other nationalities in individuals with a prior PCR-confirmed infection who were not infected, 23 other nationalities in individuals with no prior PCR-confirmed infection who were infected, and 87 other nationalities in individuals with no prior PCR-confirmed infection who were not infected.

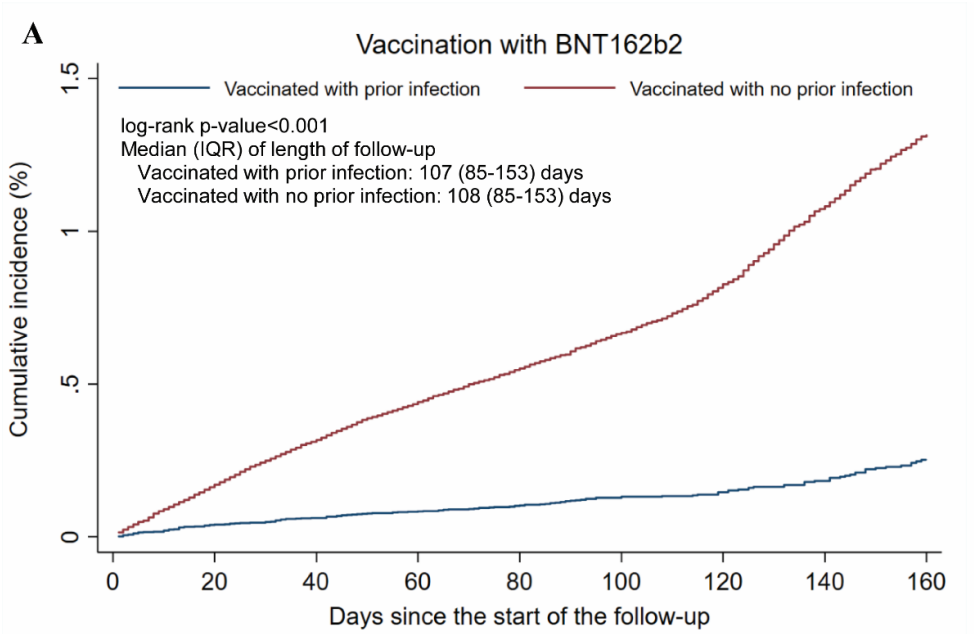
© 2021 American Medical Association. All rights reserved.

eFigure 1. Time trend of A) cumulative numbers of BNT162b2-vaccinated and mRNA-1273-vaccinated persons included in this study, B) numbers of daily diagnosed SARS-CoV-2 infections during the study period.

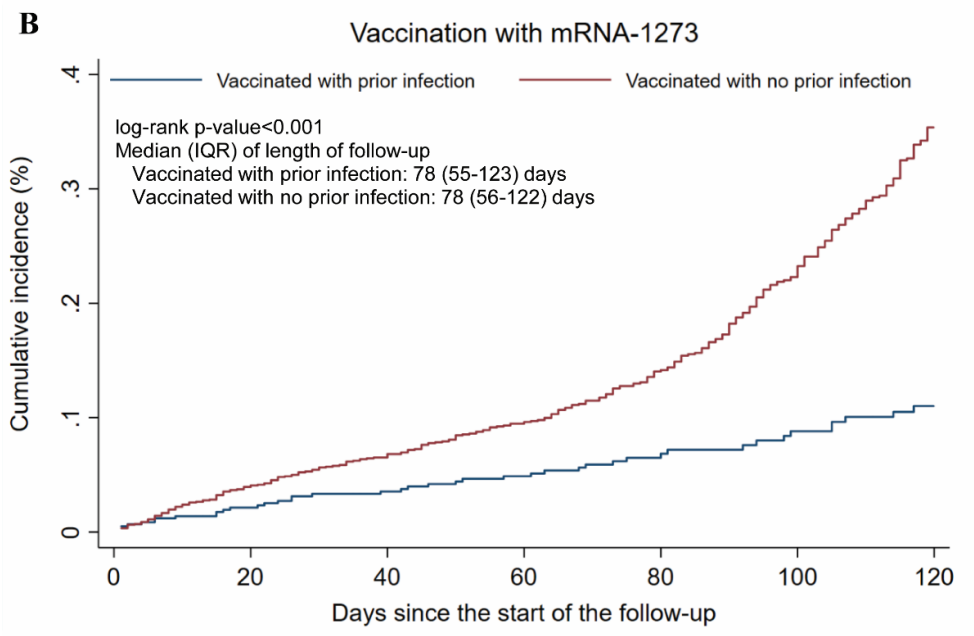


© 2021 American Medical Association. All rights reserved.

eFigure 2. Cumulative infection incidence among matched cohorts of BNT162b2- and mRNA-1273-vaccinated individuals with and without a prior infection.



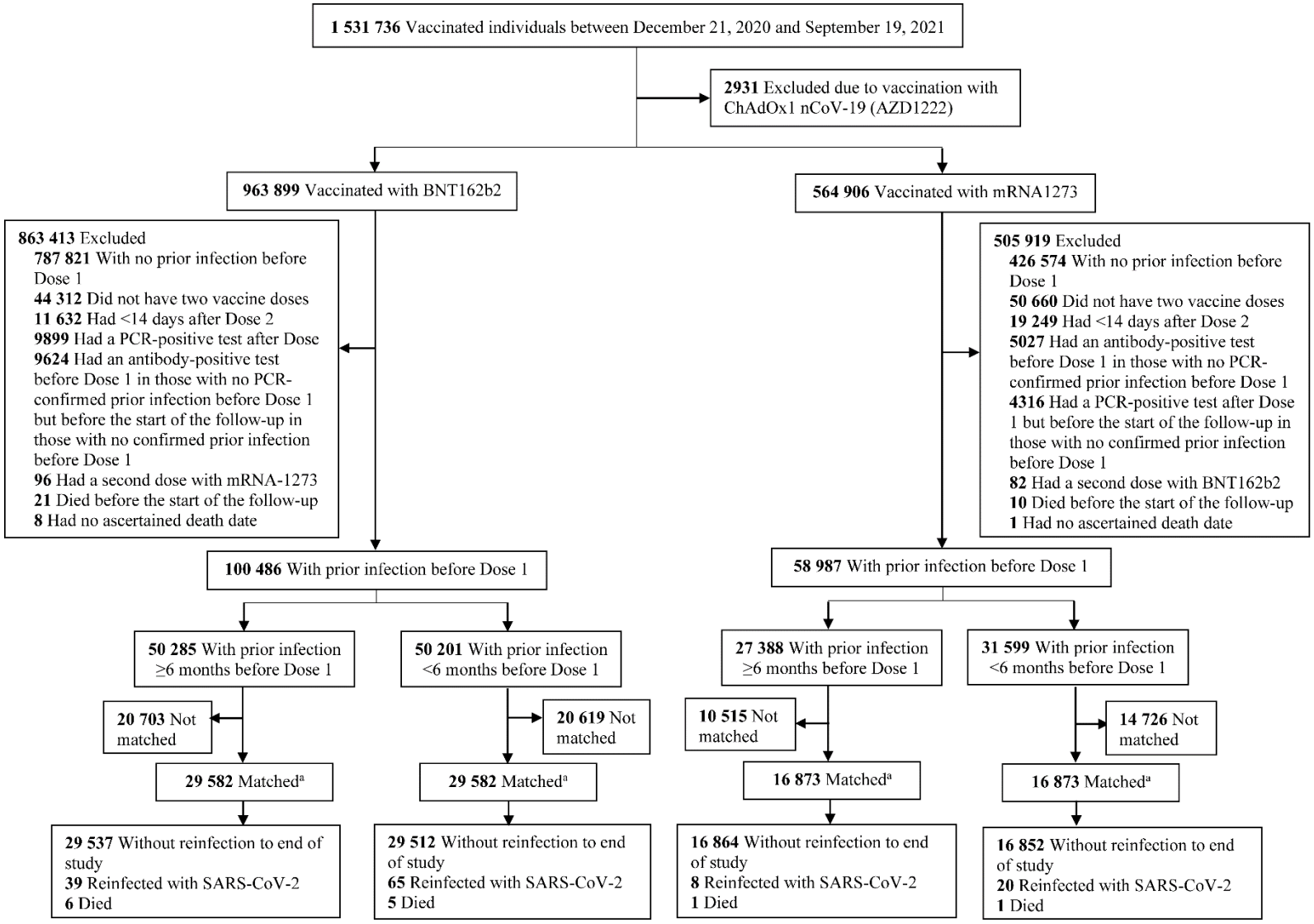
Time (days)	0	20	40	60	80	100	120	140	160
No. at risk									
Vaccinated with prior infection	99 226	96 960	93 683	85 593	80 822	58 258	36 385	29 650	19 138
Vaccinated with no prior infection	290 432	283 910	274 588	250 489	235 076	171 177	106 093	86 337	55 266



Time (days)	0	20	40	60	80	100	120
No. at risk							
Vaccinated with prior infection	58 096	52 179	46 579	41 902	28 551	24 541	16 492
Vaccinated with no prior infection	169 514	152 478	136 504	127 722	82 960	72 662	49 144

© 2021 American Medical Association. All rights reserved.

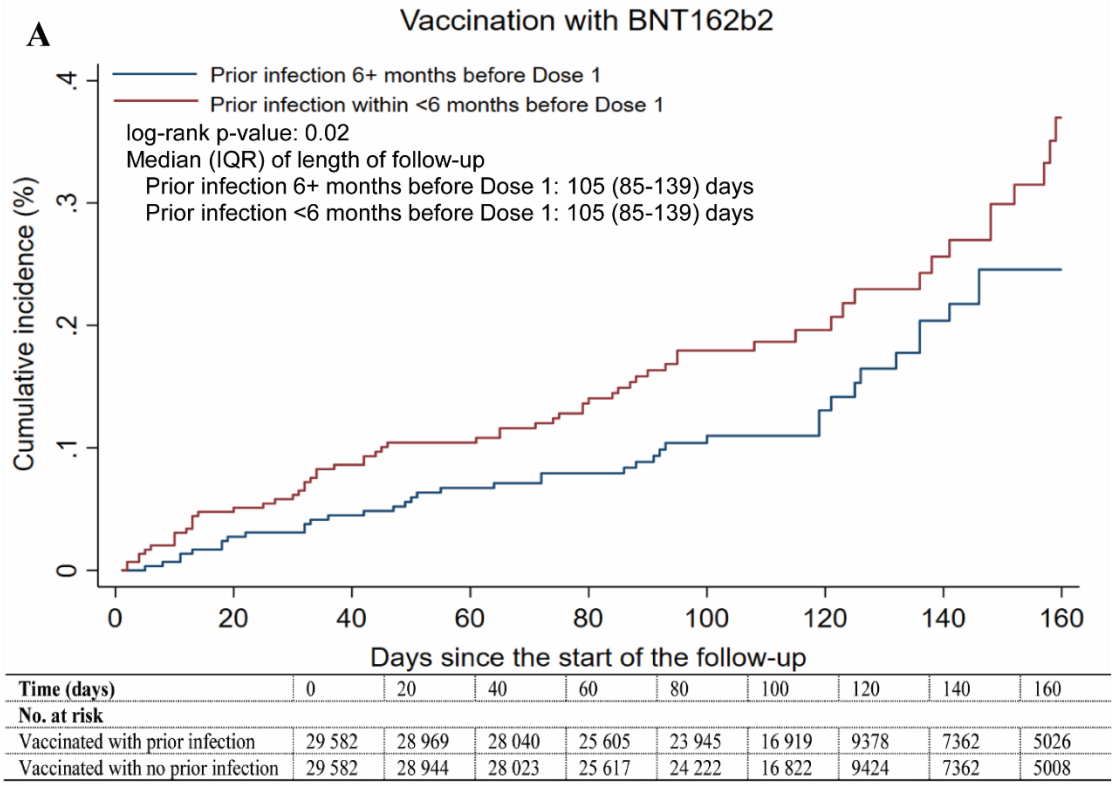
eFigure 3. Development of cohorts with prior infections ≥6 months versus <6 months before the first vaccine dose in a study of SARS-CoV-2 infections after vaccination.



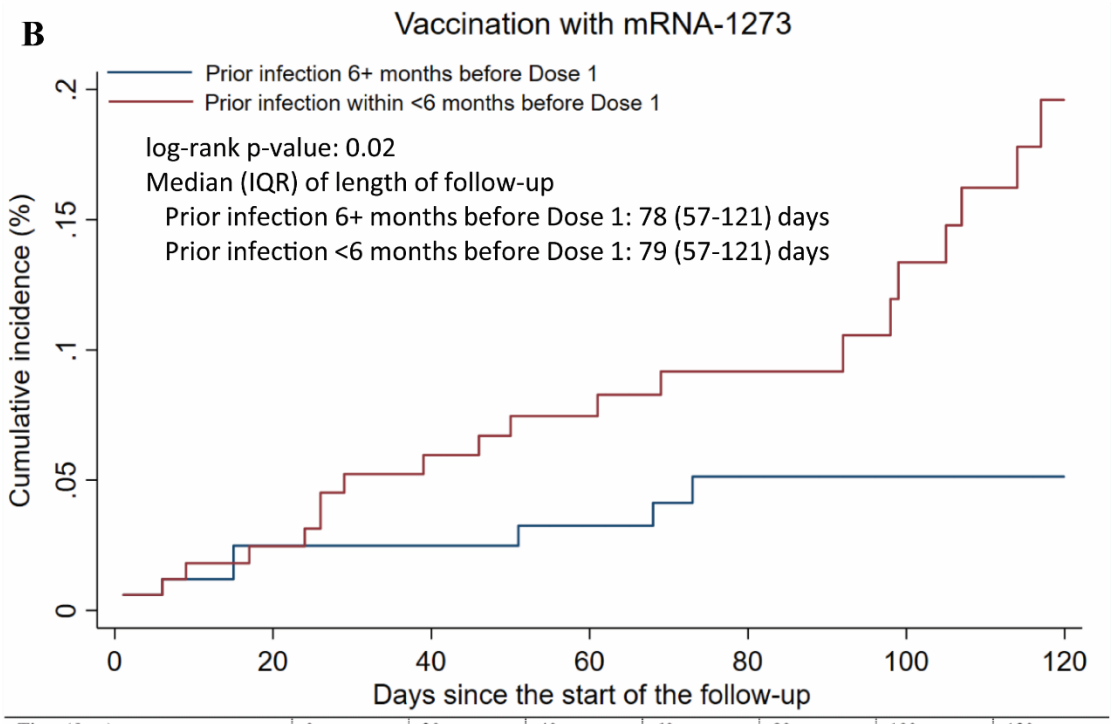
[a]Individuals were exact matched based on infection status on a 1:1 ratio by sex, 5-year age group, nationality, and calendar week of first vaccine dose.

© 2021 American Medical Association. All rights reserved.

eFigure 4. Cumulative infection incidence among individuals with a prior infection by time interval between prior infection and vaccination.



Time (days)	0	20	40	60	80	100	120	140	160
No. at risk									
Vaccinated with prior infection	29 582	28 969	28 040	25 605	23 945	16 919	9378	7362	5026
Vaccinated with no prior infection	29 582	28 944	28 023	25 617	24 222	16 822	9424	7362	5008



Time (days)	0	20	40	60	80	100	120
No. at risk							
Vaccinated with prior infection	16 873	15 263	13 695	12 401	8209	7127	4681
Vaccinated with no prior infection	16 873	15 242	13 668	12 375	8372	7108	4584

© 2021 American Medical Association. All rights reserved.

eReferences

1. World Health Organization. COVID-19 clinical management: living guidance. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1. Accessed on: May 15 2021. 2021.
2. World Health Organization. International guidelines for certification and classification (coding) of COVID-19 as cause of death. Available from: https://www.who.int/classifications/icd/Guidelines_Cause_of_Death_COVID-19-20200420-EN.pdf?ua=1. Document Number: WHO/HQ/DDI/DNA/CAT. Accessed on May 31, 2021. 2021.
3. Vogels C, Fauver J, Grubaugh N. Multiplexed RT-qPCR to screen for SARS-COV-2 B.1.1.7, B.1.351, and P.1 variants of concern V.3. dx.doi.org/10.17504/protocols.io.br9vm966. https://www.protocols.io/view/multiplexed-rt-qpcr-to-screen-for-sars-cov-2-b-1-1-br9vm966. Published 2021. Accessed June 6, 2021.
4. Abu-Raddad LJ, Chemaitelly H, Butt AA, National Study Group for Covid-19 Vaccination. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. *N Engl J Med.* 2021.
5. Chemaitelly H, Yassine HM, Benslimane FM, et al. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. *Nat Med.* 2021.
6. National Project of Surveillance for Variants of Concern and Viral Genome Sequencing. Qatar viral genome sequencing data. Data on randomly collected samples. https://www.gisaid.org/phylodynamics/global/nextstrain/. https://www.gisaid.org/phylodynamics/global/nextstrain/. Published 2021. Accessed.
7. Benslimane FM, Al Khatib HA, Al-Jamal O, et al. One year of SARS-CoV-2: Genomic characterization of COVID-19 outbreak in Qatar. *medRxiv.* 2021:2021.2005.2019.21257433.
8. Hasan MR, Kalikiri MKR, Mirza F, et al. Real-Time SARS-CoV-2 Genotyping by High-Throughput Multiplex PCR Reveals the Epidemiology of the Variants of Concern in Qatar. *Int J Infect Dis.* 2021.
9. Saththasivam J, El-Malah SS, Gomez TA, et al. COVID-19 (SARS-CoV-2) outbreak monitoring using wastewater-based epidemiology in Qatar. *Sci Total Environ.* 2021;774:145608.

© 2021 American Medical Association. All rights reserved.