Circulation

ORIGINAL RESEARCH ARTICLE

Risk of Myocarditis After Sequential Doses of COVID-19 Vaccine and SARS-CoV-2 Infection by Age and Sex

Martina Patone, PhD; Xue W. Mei, PhD; Lahiru Handunnetthi, PhD; Sharon Dixon, MD; Francesco Zaccardi, PhD; Manu Shankar-Hari, PhD; Peter Watkinson, MD; Kamlesh Khunti, PhD; Anthony Harnden, PhD; Carol A.C. Coupland, PhD; Keith M. Channon, MD; Nicholas L. Mills, PhD; Aziz Sheikh, MD; Julia Hippisley-Cox, MD

BACKGROUND: Myocarditis is more common after severe acute respiratory syndrome coronavirus 2 infection than after COVID-19 vaccination, but the risks in younger people and after sequential vaccine doses are less certain.

METHODS: A self-controlled case series study of people ages 13 years or older vaccinated for COVID-19 in England between December 1, 2020, and December 15, 2021, evaluated the association between vaccination and myocarditis, stratified by age and sex. The incidence rate ratio and excess number of hospital admissions or deaths from myocarditis per million people were estimated for the 1 to 28 days after sequential doses of adenovirus (ChAdOx1) or mRNA-based (BNT162b2, mRNA-1273) vaccines, or after a positive SARS-CoV-2 test.

RESULTS: In 42 842 345 people receiving at least 1 dose of vaccine, 21 242 629 received 3 doses, and 5 934 153 had SARS-CoV-2 infection before or after vaccination. Myocarditis occurred in 2861 (0.007%) people, with 617 events 1 to 28 days after vaccination. Risk of myocarditis was increased in the 1 to 28 days after a first dose of ChAdOx1 (incidence rate ratio, 1.33 [95% CI, 1.09–1.62]) and a first, second, and booster dose of BNT162b2 (1.52 [95% CI, 1.24–1.85]; 1.57 [95% CI, 1.28–1.92], and 1.72 [95% CI, 1.33–2.22], respectively) but was lower than the risks after a positive SARS-CoV-2 test before or after vaccination (11.14 [95% CI, 8.64–14.36] and 5.97 [95% CI, 4.54–7.87], respectively). The risk of myocarditis was higher 1 to 28 days after a second dose of mRNA-1273 (11.76 [95% CI, 7.25–19.08]) and persisted after a booster dose (2.64 [95% CI, 1.25–5.58]). Associations were stronger in men younger than 40 years for all vaccines. In men younger than 40 years old, the number of excess myocarditis events per million people was higher after a second dose of mRNA-1273 than after a positive SARS-CoV-2 test (97 [95% CI, 91–99] versus 16 [95% CI, 12–18]). In women younger than 40 years, the number of excess events per million was similar after a second dose of mRNA-1273 and a positive test (7 [95% CI, 1–9] versus 8 [95% CI, 6–8]).

CONCLUSIONS: Overall, the risk of myocarditis is greater after SARS-CoV-2 infection than after COVID-19 vaccination and remains modest after sequential doses including a booster dose of BNT162b2 mRNA vaccine. However, the risk of myocarditis after vaccination is higher in younger men, particularly after a second dose of the mRNA-1273 vaccine.

Key Words: 2019-nCoV vaccine mRNA-1273 ■ BNT162 vaccine ■ ChAdOx1 nCoV-19 ■ COVID-19 ■ COVID-19 vaccines ■ myocarditis ■ SARS-CoV-2

Correspondence to: Julia Hippisley-Cox, MD, Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Woodstock Road, Oxford OX2 6GG. Email julia.hippisley-cox@phc.ox.ac.uk

This manuscript was sent to Stephane Heymans, MD, PhD, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material, the podcast, and transcript are available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.122.059970.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

For Sources of Funding and Disclosures, see page 753–754.

Circulation is available at www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- We performed an evaluation of the risk of myocarditis after COVID-19 vaccine in >42 million vaccinated people 13 years or older, including 21 million people receiving a booster dose, stratified by age and sex.
- We extend our previous findings demonstrating that the risk of hospitalization or death from myocarditis after SARS-CoV-2 infection is substantially higher than the risk associated with a first dose of ChAdOx1, and a first, second, or booster dose of BNT162b2 mRNA vaccine.
- Associations were stronger in younger men <40 years for all vaccines and after a second dose of mRNA-1273 vaccine, where the risk of myocarditis was higher after vaccination than SARS-CoV-2 infection.

What Are the Clinical Implications?

- Our findings will inform recommendations on the type of vaccine offered to younger people and will help to shape public health policy on booster programs enabling an informed discussion of the risk of vaccine associated myocarditis when considering the net benefit of vaccination.

We recently reported an association between the first and second dose of COVID-19 vaccination and myocarditis, which generated considerable scientific, policy, and public interest.[1] It added to evidence emerging from multiple countries that has linked exposure to BNT162b2 mRNA vaccine with acute myocarditis.[2–8] In the largest and most comprehensive analysis to date, we reported an increased risk of hospital admission or death from myocarditis after both adenoviral (ChAdOx1) vaccines and mRNA (BNT162b2 or mRNA-1273) vaccines. It is important that we also demonstrated across the entire vaccinated population in England that the risk of myocarditis after vaccination was small compared with the risk after a positive SARS-CoV-2 test.[1]

However, myocarditis is more common in younger people younger than the age of 40 years and in men in particular.[9,10] Additional analyses stratified by age and sex are important because vaccine campaigns are rapidly being extended to include children and young adults. Furthermore, given the consistent observation that the risk of myocarditis is higher after the second dose of vaccine compared with the first dose,[1,11] there is an urgent need to evaluate the risk associated with a booster dose because booster programs are accelerated internationally to combat the omicron variant.[12]

Because new data were available, we have extended our analysis to include people ages 13 years or older and those receiving a booster dose to further evaluate the association between COVID-19 vaccination or infection and risk of myocarditis, stratified by age and sex.

METHODS

Transparency and Openness Promotion

This analysis makes use of multiple routinely collected health care data sources that were linked, deidentified, and held in a trusted research environment that was accessible to approved individuals who had undertaken the necessary governance training. Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to National Health Service Digital and the United Kingdom Health Security Agency. Simulated data and the analysis code are available publicly at https://github.com/qresearchcode/COVID-19-vaccine-safety. National Health Service Research Ethics Committee approval was obtained from the East Midlands–Derby Research Ethics Committee (Reference 18/EM/0400]. Anonymized data are analyzed, so there is no requirement for written informed consent.

Data Sources

We used the National Immunisation Database of COVID-19 vaccination to identify vaccine exposure. This includes vaccine type, date, and doses for all people vaccinated in England. We linked National Immunisation Database vaccination data, at the individual level, to national data for mortality (Office for National Statistics), hospital admissions (Hospital Episode Statistics and Secondary User's service data), and SARS-CoV-2 infection data (Second Generation Surveillance System).

Study Design and Oversight

We undertook a self-controlled case series design, originally developed to examine vaccine safety.[12] The analyses are conditional on each case, so any fixed characteristics during the study period, such as sex, ethnicity, or chronic conditions, are inherently controlled for. Age was considered as a fixed variable because the study period was short. Any time-varying factors, such as seasonal variation, need to be adjusted for in the analyses. Hospital admissions were likely to be influenced by the pressure on the health systems because of COVID-19, which was not uniform during the pandemic study period. To allow for these underlying seasonal effects, we split the study observation period into weeks and adjusted for week as a factor variable in the statistical models.

Study Period and Population

We included all people ages 13 years or older who had received at least 1 dose of ChAdOx1 (AstraZeneca), BNT162b2 (Pfizer), and mRNA-1273 (Moderna) vaccine and were admitted to hospital or died from myocarditis between December 1, 2020, and December 15, 2021.

Outcome

The primary outcome of interest was the first hospital admission caused by the myocarditis, or death recorded on the death

certificate with the *International Classification of Diseases, Tenth Revision* code (Table S1) related to myocarditis within the study period (December 1, 2020, to December 15, 2022). We used the earliest date of hospitalization or date of death as the event date.

Exposures

The exposure variables were a first, second, or booster dose of the ChAdOx1, BNT162b2, or mRNA-1273 vaccines, and SARS-CoV-2 infection, defined as the first SARS-CoV-2–positive test in the study period. All exposures were included in the same model. We defined the exposure risk intervals as the following prespecified time periods: 0, 1 to 7, 8 to 14, 15 to 21, and 22 to 28 days after each exposure date, under the assumption that the adverse events under consideration are unlikely to be related to exposure later than 28 days after exposure. A pre-risk interval of 1 to 28 days before each exposure date was included to account for potential bias that might arise if the occurrence of the outcome temporarily influenced the likelihood of exposure. The baseline period for the vaccination exposures was the remaining time from December 1, 2020, until 29 days before the first dose date and from 29 days after the first or second dose until 29 days before the second or booster dose (if applicable), and from 29 days after the booster dose until December 15, 2021, or the censored date if earlier. We assumed that the risks might be different after each vaccine dose, and hence we allowed for a dose effect, by defining a separate risk interval after each dose: 0, 1 to 7, 8 to 14, 15 to 21, or 22 to 28 days after the first, second, or booster dose. To avoid overlapping risk periods, we assumed that later exposures take precedence over earlier ones, except for the 1- to 28-day pre-risk period for the second or booster dose. A positive SARS-CoV-2 test was considered as a separate exposure in the models, which allowed overlapping risk windows with vaccination exposure.

Statistical Analysis

We described the characteristics of the whole study population by vaccine dose and type, and in those with myocarditis stratified by age and sex.

In vaccinated people with myocarditis, the self-controlled case series models were fitted using a conditional Poisson regression model with an offset for the length of the exposure risk period. Incidence rate ratios (IRR), the relative rate of hospital admissions or deaths caused by myocarditis in exposure risk periods relative to baseline periods, and their 95% CIs were estimated by the self-controlled case series model adjusted for calendar time. We investigated if associations between vaccine exposure and the myocarditis outcome were sex- or age-dependent by performing subgroup analyses stratified by sex and age (men age <40 years, men age≥ 40 years, women age <40 years, and women age ≥40 years). We also conducted analyses stratified by vaccination history, restricted to those who had the same type of vaccine in the first and second dose and by lag in days between the first and second dose (≤65, 66 to 79, and ≥80 days).

We conducted sensitivity analyses to assess the robustness of results to assumptions, such as that the occurrence of an outcome event did not influence the probability of subsequent exposures by (1) excluding those who died from the outcome and (2) restricting analysis to the period after the first dose and (3) after the second dose, without censoring at death; and to assess potential reporting delays in the data by (4) restricting the study to the period up to December 1, 2021.

We also performed sensitivity analyses (5) removing patients who had outcomes in the 28 days after a first dose, but before a second dose, and (6) removing patients who had outcomes in the 28 days after a second dose, but before a booster dose, because they are less likely to have a second dose if they experienced an adverse event after the first. Last, we conducted a sensitivity analysis (7) restricted to those without a positive SARS-CoV-2 test during the observation period.

We used Stata (version 17) for these analyses.

RESULTS

Between December 1, 2020, and December 15, 2021, there were 42 842 345 people vaccinated with at least 1 dose of ChAdOx1 (n=20 650 685), BNT162b2 (n=20 979 704), or mRNA-1273 (n=1 211 956) (Table 1). Of these, 39 118 282 received a second dose of ChAdOx1 (n=20 080 976), BNT162b2 (n=17 950 086), or mRNA-1273 (n=1 087 220), and 21 242 629 people received a third vaccine dose: ChAdOx1 (n=53 606), BNT162b2 (n=17 517 692), and mRNA-1273 (n=3 671 331).

Among people receiving at least 1 vaccine dose, 5 934 153 (13.9%) tested positive for SARS-CoV-2, including 2 958 026 (49.8%) before their first vaccination.

Of the 42 842 345 people in the study population, 2861 (0.007%) were hospitalized or died from myocarditis during the study period; 345 (<0.001%) patients died within 28 days from a hospital admission with myocarditis or with myocarditis as cause of death recorded in the death certificate. A total of 617 (0.001%) of these events occurred 1 to 28 days after any dose of vaccine (Table 2). Of the 524 patients admitted to the hospital with myocarditis in the 1 to 28 days after any first or second vaccine dose, 151 (28.8%) had received a booster dose: 34.4% (79/230) of those who had ChAdOx1 in the first or second dose and 29.7% (72/243) of those who had BNT162b2 in the first or second dose (Table 2). Of the 5 934 153 patients with a SARS-CoV-2 infection, 195 (0.003%) were hospitalized or died with myocarditis in the 1 to 28 days after the positive test; 114 (58.5%) of these events occurred before vaccination (Table S2).

Vaccine-Associated Myocarditis

In the study period, we observed 140 and 90 patients who were admitted to the hospital or died of myocarditis after a first and second dose of ChAdOx1 vaccine, respectively. Of these, 40 (28.6%) and 11 (12.2%), respectively, died with myocarditis or within 28 days from hospital admission. Similarly, there were 124, 119, and 85 patients who were admitted to the hospital or died

Table 1. Baseline Demographic Characteristics of People Receiving ChAdOx1, BNT162b2, or mRNA-1273 Vaccines or Testing Positive for SARS-CoV-2 Virus (in Those Vaccinated) in England Between December 1, 2020, and December 15, 2021

	ChAdOx1	BNT162b2	mRNA-1273	ChAdOx1	BNT162b2	mRNA-1273	ChAdOx1	BNT162b2	mRNA-1273	SARS- CoV-2 positive*
	One dose (n=42 842 345)			Two doses (n=39 118 282)			Booster doses (n=21 242 629)			(n= 5 934 153)
	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Total no. of people	20 650 685	20 979 704	1 211 956	20 080 976	17 950 086	1 087 220	53 606	17 517 692	3 671 331	5 934 153
Sex										
Women	49.5 (10 215 079)	49.1 (10 295 561)	38.7 (469 114)	49.5 (9 945 533)	50.1 (9 000 748)	39.5 (429 705)	61.2 (32 792)	54.2 (9 489 364)	48.4 (1 778 317)	52.3 (3 103 168)
Men	43.3 (8 933 572)	40.4 (8 476 032)	42.0 (508 416)	43.3 (8 697 560)	39.8 (7 148 539)	42.1 (457 629)	34.8 (18 674)	41.4 (7 244 858)	44.2 (1 623 230)	40.5 (2 405 336)
Not recorded	7.3 (1 502 034)	10.5 (2 208 110)	19.3 (234 426)	7.2 (1 437 882)	10.0 (1 800 799)	18.4 (199 886)	4.0 (2140)	4.5 (783 471)	7.3 (269 784)	7.2 (425 649)
Age, y										
Mean age (SD)	54.9 (14.8)	43.0 (22.4)	32.3 (9.7)	55.0 (14.7)	46.5 (21.7)	32.7 (9.8)	63.1 (17.0)	61.8 (15.9)	53.7 (12.4)	41.4 (18.0)
13–17	<0.1 (10 214)	10.6 (2 219 006)	0.1 (838)	<0.1 (9105)	2.6 (468 569)	0.1 (623)	0.1 (31)	0.1 (23 826)	0.1 (2961)	8.3 (493 728)
18–29	5.2 (1 081 177)	24.4 (5 127 151)	43.1 (521 916)	5.1 (1 022 847)	24.9 (4 472 159)	41.3 (449 436)	3.7 (1964)	3.6 (624 465)	4.0 (146 688)	21.6 (1 279 933)
30–39	7.9 (1 634 841)	21.5 (4 517 781)	35.6 (431 515)	7.8 (1 556 785)	23.1 (4 146 117)	36.1 (392 581)	5.8 (3102)	6.1 (1 067 916)	8.6 (315 936)	18.3 (1 084 406)
40–49	22.1 (4 564 393)	8.5 (1 784 664)	18.4 (222 849)	22.0 (4 414 864)	9.3 (1 665 983)	19.5 (212 187)	11.5 (6171)	11.1 (1 949 092)	19.2 (706 004)	19.4 (1 152 196)
50–59	27.5 (5 673 878)	8.0 (1 684 013)	1.8 (22 320)	27.6 (5 549 187)	9.1 (1 636 430)	1.9 (20 463)	19.9 (10 644)	20.8 (3 635 337)	35.3 (1 295 168)	16.7 (989 499)
60–69	19.8 (4 083 887)	8.5 (1 777 370)	0.7 (8330)	20.0 (4 013 588)	9.8 (1 753 552)	0.7 (8145)	19.3 (10 371)	22.5 (3 938 515)	24.8 (910 586)	8.5 (505 389)
70–79	13.4 (2 763 041)	9.4 (1 979 901)	0.3 (3241)	13.5 (2 717 638)	10.9 (1 959 318)	0.3 (2789)	22.6 (12 090)	23.1 (4 049 042)	6.5 (237 287)	4.2 (248 415)
80–89	3.1 (630 457)	7.7 (1 621 129)	0.1 (842)	3.0 (604 788)	8.9 (1 591 216)	0.1 (837)	12.5 (6710)	10.8 (1 888 973)	1.3 (47 228)	2.2 (132 459)
90+	1.0 (208 753)	1.3 (268 563)	<0.1 (103)	1.0 (192 162)	1.4 (256 698)	<0.1 (158)	4.7 (2523)	1.9 (340 498)	0.3 (9473)	0.8 (48 117)
Not recorded	<0.1 (44)	<0.1 (125)	<0.1 (2)	<0.1 (11)	<0.1 (44)	<0.0 (1)	0	<0.1 (29)	0	<0.1 (11)
Women age groups, y										
<40	14.8 (1 510 119)	51.7 (5 325 910)	77.9 (365 443)	14.4 (1 437 517)	45.9 (4 131 123)	76.4 (328 311)	9.2 (3020)	10.9 (1 032 366)	14.2 (252 054)	47.6 (1 477 776)
≥40	85.2 (8 704 960)	48.3 (4 969 651)	22.1 (103 671)	85.5 (8 508 009)	54.1 (4 869 604)	23.6 (101 394)	90.8 (29 772)	89.1 (8 456 981)	85.8 (1 526 263)	52.4 (1 625 385)
Not recorded	<0.1 (16)	<0.1 (59)	0	<0.1 (7)	<0.1 (21)	0	0	0	0	<0.1 (7)
Men age groups, y										
<40	11.2 (998 025)	56.2 (4 762 038)	78.2 (397 521)	10.9 (949 865)	49.4 (3 533 806)	76.7 (35 074)	8.8 (1650)	7.5 (541 432)	10.5 (171 132)	46.2 (1 110 723)
≥40	88.8 (7 935 546)	43.8 (3 712 994)	21.8 (110 895)	89.1 (7 747 692)	50.8 (3 614 721)	23.3 (106 834)	91.2 (17 024)	92.5 (6 703 416)	89.5 (1 452 098)	53.8 (1 294 609)
Not recorded	<0.1 (21)	<0.1 (42)	<0.1 (2)	<0.1 (3)	<0.1 (12)	<0.1 (1)	0	0	0	<0.1 (4)
Ethnicity/race										
White	67.9 (14 012 353)	63.6 (13 344 722)	53.0 (642 168)	68.0 (13 656 716)	64.2 (11 530 182)	54.0 (587 123)	74.3 (39 827)	73.6 (12 891 303)	69.6 (2 553 453)	66.9 (3 971 366)
Indian	2.0 (406 066)	2.2 (469 302)	1.1 (13 385)	2.0 (395 171)	2.2 (394 274)	1.1 (11 902)	2.1 (1141)	2.0 (354 433)	1.4 (51 193)	2.6 (153 403)
Pakistani	1.2 (253 523)	1.6 (335 100)	1.0 (12 213)	1.2 (239 511)	1.4 (249 446)	0.9 (9732)	0.9 (477)	0.6 (109 038)	0.5 (19 186)	2.0 (118 522)
Bangladeshi	0.5 (96 392)	0.5 (111 314)	0.5 (5966)	0.5 (92 835)	0.5 (83 524)	0.5 (4902)	0.4 (217)	0.2 (43 360)	0.3 (10 775)	0.7 (40 093)
Other Asian	0.9 (177 629)	1.1 (238 245)	1.0 (11 859)	0.9 (171 863)	1.1 (191 996)	1.0 (10 365)	0.8 (436)	0.7 (128 434)	0.6 (23 284)	1.1 (67 392)
Caribbean	0.6 (117 507)	0.5 (96 994)	0.4 (4265)	0.6 (110 470)	0.4 (80 146)	0.3 (3296)	1.3 (706)	0.4 (77 095)	0.3 (11 820)	0.5 (28 327)

(*Continued*)

Table 1. Continued

	ChAdOx1	BNT162b2	mRNA-1273	ChAdOx1	BNT162b2	mRNA-1273	ChAdOx1	BNT162b2	mRNA-1273	SARS- CoV-2 positive*
	One dose (n=42 842 345)			Two doses (n=39 118 282)			Booster doses (n=21 242 629)			(n= 5 934 153)
	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Black African	0.9 (185 852)	1.0 (218 158)	1.0 (12 121)	0.9 (176 094)	0.9 (164 260)	0.9 (9258)	1.1 (588)	0.6 (98 216)	0.5 (16 997)	1.0 (57 157)
Chinese	0.3 (63 180)	0.3 (70 206)	0.4 (5176)	0.3 (61 902)	0.3 (58 438)	0.5 (4902)	0.3 (149)	0.3 (47 390)	0.3 (11 899)	0.2 (11 732)
Other‡	1.8 (378 719)	2.4 (502 815)	2.6 (31 811)	1.8 (363 257)	2.2 (388 674)	2.5 (27 107)	1.7 (902)	1.4 (245 301)	1.4 (50 501)	2.3 (138 024)
Not recorded	24.0 (4 959 464)	26.7 (5 592 847)	39.0 (472 992)	24.0 (4 813 156)	26.8 (4 809 146)	38.5 (418 633)	17.1 (9163)	20.1 (3 523 123)	25.1 (922 223)	22.7 (1 348 137)
History of myocarditis										
Previous myocarditis	<0.1 (1837)	<0.1 (1632)	<0.1 (69)	<0.1 (1778)	<0.1 (1511)	<0.1 (56)	<0.1 (18)	<0.1 (1885)	<0.1 (272)	<0.1 (687)
COVID-19 status†										
No COVID-19	86.3 (17 815 732)	86.0 (18 052 842)	85.8 (1 039 833)	86.3 (17 334 448)	87.3 (15 674 125)	86.2 (937 147)	88.4 (47 367)	90.5 (15 846 583)	88.0 (3 230 055)	…
COVID-19 previous vaccination	5.9 (1 227 131)	7.8 (1 629 334)	8.4 (101 484)	5.9 (1 183 882)	6.5 (1 170 434)	7.8 (85 166)	6.3 (3398)	4.7 (815 805)	5.3 (194 056)	49.8 (2 958 026)
COVID-19 after first dose	0.7 (143 526)	2.8 (594 914)	3.2 (38 200)	0.5 (99 981)	2.2 (401 516)	3.0 (32 222)	0.9 (456)	0.6 (108 097)	0.4 (15 316)	13.1 (776 725)
COVID-19 after second dose	6.7 (1 383 490)	3.0 (638 578)	2.7 (32 215)	6.9 (1 381 868)	3.6 (639 976)	3.0 (32 452)	1.8 (969)	3.5 (621 836)	5.8 (213 627)	34.6 (2 054 331)
COVID-19 after booster dose	0.4 (80 807)	0.3 (64 035)	<0.1 (224)	0.4 (80 796)	0.4 (64 035)	<0.1 (233)	2.6 (1416)	0.7 (125 372)	0.5 (18 277)	2.4 (145 071)
No. of doses										
One dose only	2.3 (467 328)	14.8 (3 114 034)	11.9 (144 026)	…	…	…	…	…	…	12.8 (761 515)
Two doses only	36.0 (7 430 747)	45.1 (9 464 269)	80.8 (979 495)	36.5 (7 328 422)	53.2 (9 550 989)	91.7 (996 599)	…	…	…	51.5 (3 054 000)
Two doses + booster	61.8 (12 752 610)	40.0 (8 401 400)	7.3 (88 435)	63.5 (12 752 553)	46.8 (8 399 097)	8.3 (90 621)	100.0 (53 606)	100.0 (17 517 692)	100.0 (3 671 331)	35.7 (2 118 638)
Type of vaccines										
Two doses of ChAdOx1	97.0 (20 040 458)	…	…	99.8 (20 040 458)	…	…	83.0 (44 472)	55.8 (9 780 549)	79.1 (2 903 545)	46.2 (2 741 419)
Two doses of BNT162b2	…	84.9 (17 815 058)	…	…	99.2 (17 815 058)	…	5.1 (2760)	43.7 (7 653 274)	19.6 (720 535)	38.0 (2 256 069)
Two doses of mRNA-1273	…	…	87.5 (1 060 277)	…	…	97.5 (1 060 277)	<0.1 (8)	0.3 (45 269)	1.2 (42 783)	2.5 (146 385)

*Among vaccinated individuals.
†Determined by a SARS-CoV-2 test.
‡Other indicates any other ethnic group not covered by the categories listed in the Table.

of myocarditis after a first, second, and third dose of BNT162b2 vaccine, respectively. Of these, 22 (17.7%), 14 (11.8%), and 13 (15.3%) patients died with myocarditis or within 28 days from hospital admission. Last, there were 11, 40, and 8 patients who were admitted to the hospital for myocarditis after, respectively, a first, second, and third dose of mRNA-1273 vaccine. None of these patients died with myocarditis or within 28 days from hospital admission with myocarditis (Table 2).

In the overall population, we confirmed our previous findings that the risk of hospitalization or death from myocarditis was higher after SARS-CoV-2 infection than vaccination and was greater after the first 2 doses of mRNA vaccine than after adenovirus vaccine (Table 3; Table S3; Figure). There was an increased risk of myocarditis at 1 to 28 days after the first dose of ChAdOx1 (IRR, 1.33 [95% CI, 1.09–1.62]) and BNT162b2 (IRR, 1.52 [95% CI, 1.24–1.85]).

There was an increased risk of myocarditis at 1 to 28 days after a second dose of BNT162b2 (IRR, 1.57 [95% CI, 1.28–1.92]) and mRNA-1273 (IRR, 11.76 [95% CI, 7.25–19.08]); and after a booster dose of BNT162b2 (IRR, 1.72 [95% CI, 1.33–2.22]) and mRNA-1273 (IRR, 2.64 [95% CI, 1.25–5.58]).

Vaccine-Associated Myocarditis in Men

Of the 17 918 020 men vaccinated in England in the study period, 6 158 584 (34.4%) were younger than 40 years, and 11 759 436 (65.6%) were 40 years or older (Table 1). Analysis restricted to younger men age younger than 40 years showed an increased risk of myocarditis

Table 2. Demographic and Clinical Characteristics of Patients Who Were Admitted to the Hospital for Myocarditis in the 1 to 28 Days After a COVID-19 Vaccine First Dose, Second Dose, and Booster Dose or SARS-CoV-2 Infection Among the Vaccinated Population in England from December 1, 2020, Until December 15, 2021

Variable	Baseline	Risk set (1–28 days after exposure)								
		ChAdOx1			BNT162b2			mRNA-1273		
		First dose	Second dose	Booster dose	First dose	Second dose	Booster dose	First dose	Second dose	Booster dose
Total no. of people	2244	140	90	0	124	119	85	11	40	8
Sex										
Women	40.4 (907)	40.7 (57)	26.7 (24)	…	41.1 (51)	28.6 (34)	45.9 (39)	*	*	*
Men	59.4 (1333)	59.3 (83)	73.3 (66)	…	58.1 (72)	70.6 (84)	54.1 (46)	>5	>5	>5
Not recorded	0.2 (4)	0	0	…	0.8 (1)	0.8 (1)	0	0	0	0
Age										
Mean age (SD)	53.8 (19.7)	57.5 (17.5)	54.2 (18.0)	…	48.7 (24.3)	45.0 (24.8)	67.2 (15.8)	27.0 (9.5)	24.9 (6.3)	61.8 (14.8)
<40 y	26.3 (590)	14.3 (20)	25.6 (23)	…	46.8 (58)	58.8 (70)	7.1 (6)	>5	>5	*
≥40 y	73.7 (1654)	85.7 (120)	74.4 (67)	…	53.2 (66)	41.2 (49)	92.9 (79)	*	*	>5
Deaths with myocarditis or within 28 days of hospital admission with myocarditis										
No. of deaths	10.9 (245)	28.6 (40)	12.2 (11)	…	17.7 (22)	11.8 (14)	15.3 (13)	…	…	…
Mean age of death (SD), y	68.7 (14.3)	62.1 (17.4)	65.2 (10.4)	…	67.8 (20.4)	69.2 (21.6)	78 (8.7)	…	…	…
No. of deaths										
Women	38.2 (92)	35.0 (14)	*	…	57.1 (12)	46.1 (6)	*	…	…	…
Men	61.8 (149)	65.0 (26)	>5	…	42.9 (9)	53.9 (7)	> 5	…	…	…
Not recorded	0.2 (4)	0	0		0.8 (1)	0.8 (1)	0			
COVID-19 status (positive SARS-CoV-2 test)										
No COVID-19	…	72.9 (102)	82.2 (74)	…	71.8 (89)	88.2 (105)	81.2 (69)	54.5 (6)	90.0 (36)	100.0 (8)
COVID-19 previous vaccination	…	12.9 (18)	11.1 (10)	…	10.5 (13)	*	8.2 (7)	*	*	…
COVID-19 after first dose	…	11.4 (16)	*	…	15.3 (19)	*	*	*	*	…
COVID-19 after second dose	…	*	5.6 (5)	…	*	5.0 (6)	*	*	*	…
COVID-19 after booster dose	…	*	*	…	*	*	7.1 (6)	*	*	…
No. of doses										
One	…	45.7 (64)	*	…	53.2 (66)	*	*	90.9 (10)	*	*
Two	…	23.6 (33)	60.0 (54)	…	16.9 (21)	70.6 (84)	*	*	97.5 (39)	*
Two + booster	…	30.7 (43)	40.0 (36)	…	29.8 (37)	29.4 (35)	100.0 (85)	*	*	100.0 (8)
Type of first 2 doses received										
ChAdOx1	…	50.7 (71)	98.9 (89)	…	…	…	49.4 (42)	…	…	62.5 (5)
BNT162b2	…	…	…	…	43.5 (54)	99.2 (118)	50.6 (43)	…	…	*
mRNA-1273	…	…	…	…	…	…	*	*	100.0 (40)	*
Lag between first and second doses (days)										
≤65		5.7 (8)	16.7 (15)	…	8.1 (10)	47.9 (57)	24.7 (21)	*	55.0 (22)	*
66–79		31.4 (44)	55.6 (50)	…	25.8 (32)	32.8 (39)	54.1 (46)	…	22.5 (9)	*
≥80		17.1 (24)	27.8 (25)	…	12.9 (16)	19.3 (23)	21.2 (18)	…	22.5 (9)	*

*Cells with counts <5 are suppressed.

after a first dose of BNT162b2 (IRR, 1.85 [95% CI, 1.30–2.62]) and mRNA-1273 (IRR, 3.06 [95% CI, 1.33–7.03]); and a second dose of ChAdOx1 (IRR, 2.73 [95% CI, 1.62–4.60]), BNT162b2 (IRR, 3.08 [95% CI, 2.24–4.24]), and mRNA-1273 (IRR, 16.83 [95% CI, 9.11–31.11]). The risk of myocarditis for older men 40 years or more was associated with a booster dose of both mRNA vaccines, BNT162b2 (IRR, 2.15 [95% CI, 1.46–3.17]) and mRNA-1273 (IRR, 3.76 [95% CI, 1.41–10.02]) (Table 3).

Vaccine-Associated Myocarditis in Women

Of the 20 979 754 women vaccinated in England in the study period, 7 201 472 (34.3%) were younger than 40

Table 3. Incidence Rate Ratios (IRR [95% CI]) for Main Analysis and by Age Group (Age 40 Years or Older, Younger Than 40 Years) and Sex (Female and Male) for Myocarditis in Predefined Risk Periods Immediately Before and After Exposure to Vaccination and Before and After a Positive SARS-CoV-2 Test Result, Adjusted for Calendar Time From December 1, 2020, to December 15, 2021 (if 1 or no events, IRR has not been estimated and reported as n/a).

	ChAdOx1 nCoV-19 vaccine		BNT162b2 mRNA vaccine		mRNA-1273 vaccine		Positive SARS-CoV-2 test (before vaccine)		Positive SARS-CoV-2 test (vaccinated)	
Time period	Events	IRR (95% CI)	Events	IRR (95% CI)	Events	IRR (95% CI)	Events	IRR (95% CI)	Events	IRR (95% CI)
Main analysis										
1–28 days: first dose/positive test before any vaccination	140	1.33 (1.09–1.62)	124	1.52 (1.24–1.85)	11	1.85 (0.93–3.66)	114	11.14 (8.64–14.36)	81	5.97 (4.54–7.87)
1–28 days: second dose	90	0.93 (0.74–1.17)	119	1.57 (1.28–1.92)	40	11.76 (7.25–19.08)				
1–28 days: booster dose	*	n/a	85	1.72 (1.33–2.22)	8	2.64 (1.25–5.58)				
Women										
1–28 days: first dose/positive test before any vaccination	57	1.32 (0.97–1.81)	51	1.59 (1.16–2.20)	*	1.07 (0.23–4.90)	47	14.23 (9.34–21.68)	32	6.87 (4.38–10.78)
1–28 days: second dose	24	0.54 (0.35–0.83)	34	1.04 (0.72–1.50)	*	3.95 (1.20–13.04)				
1–28 days: booster dose	*	n/a	39	1.55 (1.06–2.27)	*	1.51 (0.35–6.47)				
Men										
1–28 days: first dose/positive test before any vaccination	83	1.33 (1.03–1.72)	72	1.47 (1.14–1.90)	9	2.35 (1.09–5.08)	67	9.71 (7.03–13.40)	49	5.55 (3.91–7.88)
1–28 days: second dose	66	1.26 (0.96–1.65)	84	1.93 (1.51–2.45)	36	14.98 (8.61–26.07)				
1–28 days: booster dose	*	n/a	46	1.89 (1.34–2.67)	6	3.57 (1.48–8.64)				
Age <40 y										
1–28 days: first dose/positive test before any vaccination	20	1.31 (0.79–2.16)	58	1.79 (1.33–2.41)	10	2.76 (1.32–5.75)	20	5.25 (3.11–8.86)	8	1.18 (0.56–2.48)
1–28 days: second dose	23	1.69 (1.06–2.71)	70	2.59 (1.96–3.44)	39	13.97 (8.07–24.19)				
1–28 days: booster dose	*	n/a	6	1.53 (0.64–3.64)	*	n/a				
Age ≥40 y										
1–28 days: first dose/positive test before any vaccination	120	1.21 (0.97–1.51)	66	1.28 (0.97–1.71)	*	n/a	94	14.87 (10.98–20.14)	73	10.52 (7.61–14.54)
1–28 days: second dose	67	0.72 (0.55–0.93)	49	0.85 (0.62–1.16)	*	n/a				
1–28 days: booster dose	*	n/a	79	1.96 (1.48–2.59)	7	2.97 (1.32–6.69)				
Women age <40 y										
1–28 days: first dose/positive test before any vaccination	7	1.20 (0.51–2.84)	14	1.65 (0.91–2.97)	*	2.68 (0.54–13.25)	7	9.80 (3.70–25.97)	6	3.98 (1.52–10.42)
1–28 days: second dose/positive test after any vaccination	*	0.32 (0.08–1.37)	9	1.16 (0.57–2.34)	*	4.75 (1.11–20.40)				
1–28 days: booster dose	*	n/a	*	0.83 (0.19–3.64)	*	n/a				
Men age <40 y										
1–28 days: first dose/positive test before any vaccination	13	1.34 (0.72–2.48)	43	1.85 (1.30–2.62)	8	3.06 (1.33–7.03)	13	4.35 (2.31–8.21)	*	0.39 (0.09–1.60)
1–28 days: second dose	21	2.73 (1.62–4.60)	60	3.08 (2.24–4.24)	36	16.83 (9.11–31.11)				
1–28 days: booster dose	*	n/a	*	2.28 (0.77–6.80)	*	n/a				

(*Continued*)

Table 3. Continued

Time period	ChAdOx1 nCoV-19 vaccine		BNT162b2 mRNA vaccine		mRNA-1273 vaccine		Positive SARS-CoV-2 test (before vaccine)		Positive SARS-CoV-2 test (vaccinated)	
	Events	IRR (95% CI)	Events	IRR (95% CI)	Events	IRR (95% CI)	Events	IRR (95% CI)	Events	IRR (95% CI)
Women age ≥40 y										
1–28 days: first dose/positive test before any vaccination	50	1.30 (0.92–1.84)	37	1.57 (1.05–2.33)	*	n/a	40	17.29 (10.70–27.96)	26	8.65 (5.13–14.59)
1–28 days: second dose	22	0.55 (0.35–0.86)	25	0.98 (0.63–1.52)	*	n/a				
1–28 days: booster dose	*	n/a	37	1.76 (1.17–2.65)	*	2.00 (0.46–8.72)				
Men age ≥40 y										
1–28 days: 1st dose/positive test before any vaccination	70	1.16 (0.87–1.54)	29	1.05 (0.69–1.59)	*	n/a	54	13.40 (9.04–19.88)	47	11.77 (7.77–17.85)
1–28 days: second dose	45	0.85 (0.61–1.19)	24	0.77 (0.49–1.18)	*	n/a				
1–28 days: booster dose	*	n/a	42	2.15 (1.46–3.17)	5	3.76 (1.41–10.02)				

Day 0 of each exposure has been removed because of small numbers.
*Cells with counts <5 are suppressed.

years, and 13 778 282 (65.7%) were 40 years or older (Table 1). Analysis restricted to women younger than 40 years showed an increased risk of myocarditis after a second dose of mRNA-1273 (IRR, 4.75 [95% CI, 1.11–20.40]). For women 40 years or older, there was an increased risk of myocarditis associated with a first (IRR, 1.57 [95% CI, 1.05–2.33]) and third (IRR, 1.76 [95% CI, 1.17–2.65]) dose of BNT162b2 vaccine.

It is important that for all subgroups, the higher risk of myocarditis was found in the 1 to 7 days or 8 to 14 days after vaccination (Table S4).

Vaccine-Associated Myocarditis by Vaccination History

Analyses restricted to people who had the same type of vaccine for the first and second doses (Table S5) showed that for patients having a first and second dose of ChAdOx1, there was an increased risk of myocarditis associated with a booster dose of BNT162b2 (IRR, 1.78 [95% CI, 1.22–2.60]) and mRNA-1273 (IRR, 2.97 [95% CI, 1.13–7.82]). For patients who had a first and second dose of BNT162b2 vaccine, there was an increased risk of myocarditis after the second dose of BNT162b2 (IRR, 1.53 [95% CI, 1.24–1.88]). Last, for patients who had a first and second dose of mRNA-1273 vaccine, there was an increased risk of myocarditis after a second dose of mRNA-1273 (IRR, 8.63 [95% CI, 3.98–18.75]).

The risk after a second dose of BNT162b2 was higher for people who received the first 2 doses within 65 days of each other (IRR, 2.16 [95% CI, 1.60–2.91]) compared with people who received the first 2 doses with a longer lag: between 66 and 79 days (IRR, 1.01 [95% CI, 0.71–1.44]) and 80 days or more (IRR, 1.40 [95% CI, 0.88–2.21]). The risk after a second dose of mRNA-1273 was higher when the lag was of 80 or more days (IRR, 22.80 [95% CI, 7.48–69.48]) compared with when the lag was 65 days or less (IRR, 7.41 [95% CI, 3.98–13.77) (Table S6).

SARS-CoV-2 Infection–Associated Myocarditis

There was an increased risk of myocarditis in the 1 to 28 days after a SARS-CoV-2–positive test, which was higher if infection occurred before vaccination (IRR, 11.14 [95% CI, 8.64–14.36]) than in vaccinated individuals (IRR, 5.97 [95% CI, 4.54–7.87]). The risk of myocarditis associated with a SARS-CoV-2–positive test before vaccination was higher in people 40 years or older (IRR, 14.87 [95% CI, 10.98–20.14]) than individuals younger than 40 years (IRR, 5.25 [95% CI, 3.11–8.86]), but no significant difference was observed between risks in women (IRR, 14.23 [95% CI, 9.34–21.68]) and men (IRR, 9.71 [95% CI, 7.03–13.40), although the point estimate for women was higher than the equivalent for men. A similar pattern of risk of myocarditis was associated with a SARS-CoV-2–positive test occurring in vaccinated individuals; however, in this case, the increased risk was substantially lower and in particular was not observed for individuals younger than 40 years (IRR, 1.18 [95% CI, 0.56–2.48]) (Table 3).

Absolute and Excess Risks

After the first dose of the ChAdOx1 and BNT162b2 vaccines, an additional 2 (95% CI, 1–3) and 2 (95% CI, 1–3) myocarditis events per million people vaccinated would be anticipated, respectively. After the second dose of BNT162b2 and mRNA-1273, an additional 2 (95% CI, 2–3) and 34 (95% CI, 32–35) myocarditis events per million people would be anticipated,

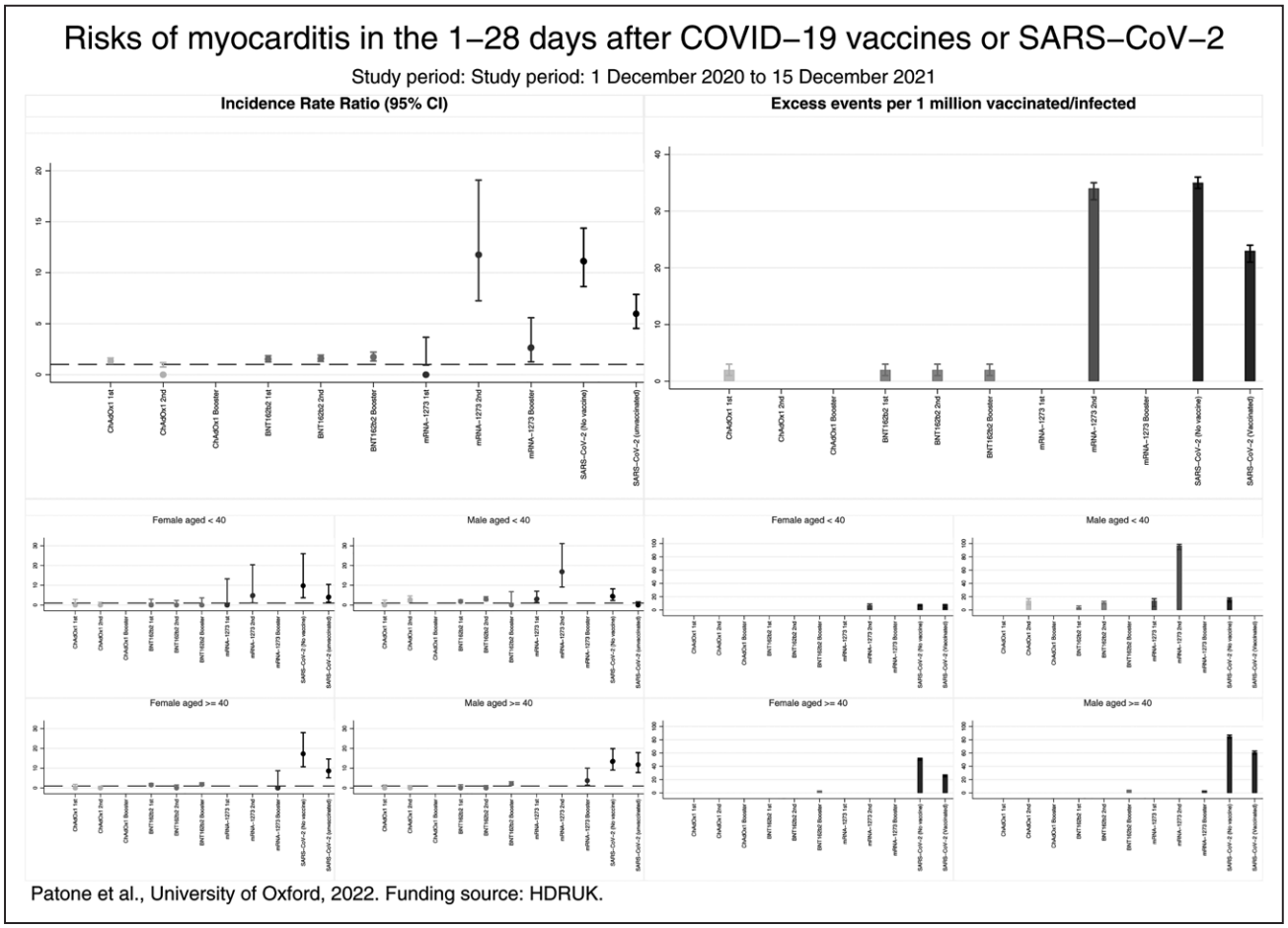

Figure. Risk of myocarditis in the 1 to 28 days after COVID-19 vaccines or SARS-CoV-2.
(**Left**) Incidence rate ratios with 95% CIs and (**right**) number of excess myocarditis events for million people with 95% CIs in the 1 to 28 day risk periods after the first, second, and booster doses of ChAdOx1, BNT162b2,and mRNA-1273 vaccine or a positive SARS-CoV-2 test in (**top**) a population of 42 842 345 vaccinated individuals and (**bottom**) younger men (age <40 years), older men (age ≥40 years), younger women (age <40 years), and older women (aged ≥40 years).

respectively. After a booster dose of BNT162b2 and mRNA-1273, an additional 2 (95% CI, 1–3) and 1 (95% CI, 0–2) myocarditis events per million people would be anticipated, respectively. These estimates compare with an additional 35 (95% CI, 34–36) and 23 (95% CI, 21–24) myocarditis events per million people in the 1 to 28 days after a SARS-CoV-2–positive test before vaccination and in vaccinated individuals, respectively (Table 4; Figure).

In men younger than 40 years, we estimate an additional 4 (95% CI, 2–6) and 14 (95% CI, 5–17) myocarditis events per million in the 1 to 28 days after a first dose of BNT162b2 and mRNA-1273, respectively; and an additional 14 (95% CI, 8–17), 11 (95% CI, 9–13) and 97 (95% CI, 91–99) myocarditis events after a second dose of ChAdOx1, BNT162b2, and mRNA-1273, respectively. These estimates compare with an additional 16 (95% CI, 12–18) myocarditis events per million men younger than 40 years in the 1 to 28 days after a SARS-CoV-2–positive test before vaccination (Table 4; Figure).

Robustness of the Results

Overall, our main findings were not sensitive to censoring because of death (Table S7, sensitivity analyses 1 through 3), and IRRs for the second dose of vaccination agreed with main results when we removed those who had the outcome after the first dose of any vaccine, but before the second dose (Table S7, sensitivity analysis 5). Similarly, IRRs for the booster dose of vaccination agreed with main results when we removed those who had the outcome after the second dose of any vaccine, but before the booster dose (Table S7, sensitivity analysis 6). There was no bias caused by possibly not complete data near the end of the study period (Table S7, sensitivity analysis 4). Estimates for vaccines exposures agreed with the main analysis when restricted to patients who never tested positive to SARS-CoV-2 (Table S8, sensitivity analysis 7).

DISCUSSION

In a population of >42 million vaccinated individuals, we report several new findings that could influence public health

Table 4. Measures of the Effect of Vaccinations and SARS-CoV-2 Infections Presented as Excess Events Per 1 Million Exposed

	Excess myocarditis events per 1 000 000 exposed (95% CI)								
						Age <40 y		Age ≥40 y	
	Main analysis	Age <40 y	Age ≥40 y	Women	Men	Women	Men	Women	Men
ChAdOx1									
First dose	2 (1–3)	…	…	…	2 (0–4)	…	…	…	…
Second dose	…	4 (0–6)	…	…	…	…	14 (8–17)	…	…
Booster dose	…	…	…	…	…	…	…	…	…
BNT162b2									
First dose	2 (1–3)	2 (1–3)	…	2 (1–3)	3 (1–4)	…	4 (2–6)	3 (0–4)	…
Second dose	2 (1–3)	5 (4–5)	…	…	6 (4–7)	…	11 (9–13)	…	…
Booster dose	2 (1–3)	…	2 (2–3)	1 (0–2)	3 (2–4)	…	…	2 (1–3)	3 (2–4)
mRNA-1273									
First dose	…	7 (3–9)	…	…	10 (1–14)	…	14 (5–17)	…	…
Second dose	34 (32–35)	43 (41–44)	…	7 (2–9)	73 (70–76)	7 (1–9)	97 (91–99)	…	…
Booster dose	1 (0–2)	…	1 (1–2)	…	3 (1–3)	…	…	…	3 (1–3)
SARS-CoV-2									
Positive test (before vaccine)	35 (34–36)	10 (9–11)	63 (62–64)	28 (27–29)	50 (48–51)	8 (6–8)	16 (12–18)	51 (49–52)	85 (82–87)
Positive test (vaccinated)	23 (21–24)	…	39 (38–40)	17 (16–19)	34 (30–36)	7 (3–8)	…	26 (24–27)	61 (58–63)

Only significant increased risks were reported during the 1 to 28 days after exposure. When incidence rate ratios were not significant during the 1 to 28 days after vaccine, absolute measures are not given.

policy on COVID-19 vaccination. First, the risk of myocarditis is substantially higher after SARS-CoV-2 infection in unvaccinated individuals than the increase in risk observed after a first dose of ChAdOx1nCoV-19 vaccine, and a first, second, or booster dose of BNT162b2 vaccine. Second, although the risk of myocarditis with SARS-CoV-2 infection remains after vaccination, it was substantially reduced, suggesting vaccination provides some protection from the cardiovascular consequences of SARS-CoV-2. Third, in contrast with other vaccines, the risk of myocarditis observed 1 to 28 days after a second dose of mRNA-1273 vaccine was higher and similar to the risk after infection. Last, vaccine-associated myocarditis was largely restricted to men younger than 40 years with 1 exception; both younger men and women were at increased risk of myocarditis after a second dose of mRNA-1273.

Vaccination against COVID-19 has both major public health and economic benefits. Although the net benefit of vaccination for the individual or on a population level should not be framed exclusively around the risks of myocarditis, quantifying this risk is important, particularly in young people who are less likely to have a severe illness with SARS-CoV-2 infection. Multiple studies have identified an increase in myocarditis after exposure to the BNT162b2 mRNA vaccine.[1–8,13] Some of our findings are confirmatory, but we also demonstrate that the risk of myocarditis is not restricted to this vaccine but is observed after vaccination with adenovirus and other mRNA vaccines and after a booster dose.

It is important to place our findings into context. One of the strengths of our analysis is that we quantify the risk of myocarditis associated with both vaccination and SARS-CoV-2 infection in the same population. Myocarditis is an uncommon condition. The risk of vaccine-associated myocarditis is small, with up to an additional 2 events per million people in the 28-day period after exposure to all vaccine doses other than mRNA-1273. This is substantially lower than the 35 additional myocarditis events observed with SARS-CoV-2 infection before vaccination. Furthermore, vaccination reduced the risk of infection associated myocarditis by approximately half, suggesting that the prevention of infection associated myocarditis may be an additional longer-term benefit of vaccination.

The risk of vaccine-associated myocarditis is consistently higher in younger men, particularly after a second dose of mRNA-1273, where the number of additional events during 28 days was estimated to be 97 per million people exposed. An important consideration for this group is that the risk of myocarditis after a second dose of mRNA-1273 was higher than the risk after infection. Indeed, in younger women, although the relative risks of myocarditis were lower than in younger men, the number of additional events per million after a second dose of mRNA-1273 was similar to the number after infection. These findings may justify some reconsideration of the selection of vaccine type, the timing of vaccine doses, and the net benefit of booster doses in young people, particularly in young men. However, there are some important caveats that need to be considered. First, the number of people vaccinated with mRNA-1273 was small compared with those receiving other types of vaccine,

which reduces the precision of our estimates. Second, the average age of those receiving this vaccine was younger at 32 years compared with other vaccines where recipients were in their mid-40s and 50s. The observed excess risk related to mRNA-1273 may in part be a result of the higher probability of myocarditis in this younger age group.

Our findings are consistent with 2 recent studies from the United States and Denmark in which the risks of myocarditis after mRNA-1273 and BNT162b2 were compared.[7,14] In the Vaccine Adverse Event Reporting System, 1991 cases of myocarditis were reported to August 31, 2021, with a median age of 21 years and 82% male.[14] Although our findings are not directly comparable because the Vaccine Adverse Event Reporting System dataset relies on clinician reporting, the risks of myocarditis were higher after a second dose of both BNT162b2 and mRNA-1273 and were greater for mRNA-1273 in most younger age groups. In Denmark, a population-based study that applied both case-control and self-controlled case series study methods observed a greater increase in the risk of myocarditis or myopericarditis 1 to 28 days after mRNA-1273 (adjusted hazard ratio, 3.92 [95% CI, 2.30–6.68]) than after BNT162b2 (adjusted hazard ratio, 1.34 [95% CI, 0.90–2.00]).[7] They also observed the risk was largely confined to those younger than 40 years and was present for both younger men and women for mRNA-1273. The reasons for male predominance in myocarditis is not known but may relate to sex hormone differences in both the immune response and myocarditis, or to the underdiagnosis of cardiac disease in women.[15,16]

This study has several strengths. First, the United Kingdom offered an ideal place to carry out this study given that 3 types of COVID-19 vaccination have been rolled out at the same speed and scale as each other. Second, this was a population-based study of data recorded prospectively and avoided recall and selection biases linked to case reports. Third, the large sample size provided sufficient power to investigate these rare outcomes, which could not be assessed through clinical trials. Fourth, the self-controlled case series study design removes potential confounding from fixed characteristics, and the breakdown of our study period into weekly blocks accounted for temporal confounding. Of note, the estimated IRRs were consistently <1 in the pre-exposure period before vaccination and >1 in the pre-risk period before a SARS-CoV-2–positive test. This was expected because events are unlikely to happen shortly before vaccination (relatively healthy people are receiving the vaccine) and more likely to happen before a SARS-CoV-2–positive test (as a standard procedure, patients admitted to the hospital are tested for SARS-CoV-2). We also assessed the robustness of our results through several sensitivity analyses.

There are some limitations to consider. First, the number of people receiving a booster dose of ChAdOx1 or mRNA-1273 vaccine was too small to evaluate the risk of myocarditis. Second, we relied on hospital admission codes and death certification to define myocarditis, and it is possible that we might have over- or underestimated risk because of misclassification. Third, although we were able to include 2 230 058 children age 13 to 17 years in this analysis, the number of myocarditis events was small (56 events in all periods and 16 events in the 1 to 28 days after vaccination) in this subpopulation and precluded a separate evaluation of risk. It should also be noted that only the first occurrence of myocarditis in the study period is used in this analysis. Therefore, the results found for the risk of myocarditis after a third dose do not include repeated instances of myocarditis in the same individual. A comparison of rates of death with myocarditis between those infected with SARS-CoV-2 or vaccinated was not possible, given that for this analysis, we have included only people who had been vaccinated. Therefore, a patient with COVID-19 who died after myocarditis before receiving a vaccination will not be included, and rates of myocarditis death after SARS-CoV-2 will be underestimated.

In summary, the risk of hospital admission or death from myocarditis is greater after SARS- CoV2 infection than COVID-19 vaccination and remains modest after sequential doses including a booster dose of BNT162b2 mRNA vaccine. However, the risk of myocarditis after vaccination is higher in younger men, particularly after a second dose of the mRNA-1273 vaccine.

ARTICLE INFORMATION

Received March 10, 2022; accepted June 7, 2022.

Affiliations

Nuffield Department of Primary Health Care Sciences (M.P., X.W.M., S.D., A.H., C.A.C.C., J.H.-C.), Wellcome Centre for Human Genetics (L.H.), British Heart Foundation Centre of Research Excellence, National Institute for Health Research, Oxford Biomedical Research Centre, Radcliffe Department of Medicine, John Radcliffe Hospital (K.M.C.): National Institute for Health Research Biomedical Research Centre, Oxford University Hospitals National Health Service Trust (P.W.); University of Oxford. School of Immunology and Microbial Sciences, King's College London, Centre for Inflammation Research (M.S.-H.). Leicester Real World Evidence Unit, Diabetes Research Centre (F.Z., K.K.), University of Leicester. Usher Institute (M.S.-H., N.L.M., A.S.), British Heart Foundation University Centre for Cardiovascular Science (N.L.M.), University of Edinburgh. Centre for Academic Primary Care, School of Medicine, University of Nottingham (C.A.C.C.).

Sources of Funding

This research is part of the Data and Connectivity National Core Study, led by Health Data Research United Kingdom (UK) in partnership with the office of National Statistics and funded by UK Research and Innovation (grant ref. MC_PC_20029). This project involves data derived from patient-level information collected by the National Health Service (NHS), as part of the care and support of patients with cancer. The Hospital Episode Statistics, Secondary Users Service (SUS-PLUS) datasets and civil registration data are used by permission from NHS Digital, who retain the copyright in that data. NHS Digital and Public Health England bear no responsibility for the analysis or interpretation of the data. K.K. is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands and NIHR Lifestyle Biomedical Research Centre. M.S.-H. is supported by the NIHR Clinician Scientist Award (NIHR-CS-2016-16-011). J.H.C. and K.M.C. are supported by the NIHR Oxford Biomedical Research Centre. N.L.M. and K.M.C. are supported by the British Heart Foundation (Chair Awards CH/F/21/90010,

CH/16/1/32013), a Programme Grant (RG/20/10/34966), and Research Excellence Awards (RE/18/5/34216, RE18/3/34214). A.S. is supported by the Health Data Research UK BREATHE Hub, the Health Data Research Hub for Respiratory Health. The investigators acknowledge the philanthropic support of the donors to the University of Oxford's COVID-19 Research Response Fund. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the UK NIHR, or the Department of Health. The funders of this study had no role in the design and conduct of the study and did not review or approve the article. The views expressed are those of the authors and not necessarily the funders. M.P., J.H.C., and C.A.C.C. had full access to all the study data, and J.H.C. had final responsibility for submission. This project is supported by a patient and public involvement advisory panel, which the authors thank for its continued support and guidance. The input of the panel has helped the authors identify priority questions for consideration and also supported analysis. Patient and Public Involvement and Engagement advisers were supportive of the vital importance of reporting on cardiac risks associated with both vaccination against COVID-19 and COVID-19 itself.

Disclosures

A.S. is a member of the Scottish Government Chief Medical Officer's COVID-19 Advisory Group, the Scottish Government's Standing Committee on Pandemics, and AstraZeneca's Thrombotic Thrombocytopenic Advisory Group. All roles are unremunerated. J.H.C. reports grants from the National Institute for Health Research Biomedical Research Centre, Oxford, grants from John Fell Oxford University Press Research Fund, grants from Cancer Research UK grant No. C5255/A18085 through the Cancer Research UK Oxford Centre, and grants from the Oxford Wellcome Institutional Strategic Support Fund (204826/Z/16/Z) and other research councils during the conduct of the study. J.H.C. is an unpaid director of QResearch, a not-for-profit organization that is a partnership between the University of Oxford and Egton Medical Information Systems (EMIS) Health, who supply the QResearch database used for this work. J.H.C. is a founder and shareholder of ClinRisk Ltd and was its medical director until May 31, 2019. ClinRisk Ltd produces open and closed source software to implement clinical risk algorithms (outside this work) into clinical computer systems. J.H.C. is chair of the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) risk stratification subgroup and a member of Scientific Advisory Group for Emergencies (SAGE) COVID-19 groups and the NHS group advising on prioritization of use of monoclonal antibodies in SARS-CoV-2 infection. A.H. is a member of the Joint Committee on Vaccination and Immunisation. K.K. is a member of the SAGE. The other authors declare no conflicts.

Supplemental Material

Tables S1–S8

REFERENCES

1. Patone M, Mei XW, Handunnetthi L, Dixon S, Zaccardi F, Shankar-Hari M, Watkinson P, Khunti K, Harnden A, Coupland CAC. et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. *Nat Med.* 2021;28:410–422. doi: 10.1038/s41591-021-01630-0
2. Witberg G, Barda N, Hoss S, Richter I, Wiessman M, Aviv Y, Grinberg T, Auster O, Dagan N, Balicer RD. et al. Myocarditis after Covid-19 vaccination in a large health care organization. *N Engl J Med.* 2021;385:2132–2139. doi: 10.1056/NEJMoa2110737
3. Mevorach D, Anis E, Cedar N, Bromberg M, Haas EJ, Nadir E, Olsha-Castell S, Arad D, Hasin T, Levi N. et al. Myocarditis after BNT162b2 mRNA vaccine against Covid-19 in Israel. *N Engl J Med.* 2021;385:2140–2149. doi: 10.1056/NEJMoa2109730
4. Simone A, Herald J, Chen A, Gulati N, Shen AY-J, Lewin B, Lee M-S. Acute myocarditis following COVID-19 mRNA vaccination in adults aged 18 years or older. *JAMA Int Med.* 2021;181:1668–1670. doi: 10.1001/jamainternmed.2021.5511
5. Klein NP, Lewis N, Goddard K, Fireman B, Zerbo O, Hanson KE, Donahue JG, Kharbanda EO, Naleway A, Nelson JC. et al. Surveillance for adverse events after COVID-19 mRNA vaccination. *JAMA.* 2021;326:1390–1399. doi: 10.1001/jama.2021.15072
6. Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, Hernán MA, Lipsitch M, Kohane I, Netzer D. et al. Safety of the BNT162b2 mRNA Covid-19 vaccine in a nationwide setting. *N Engl J Med.* 2021;385:1078–1090. doi: 10.1056/NEJMoa2110475
7. Husby A, Hansen JV, Fosbøl E, Thiesson EM, Madsen M, Thomsen RW, Sørensen HT, Andersen M, Wohlfahrt J, Gislason G. et al. SARS-CoV-2 vaccination and myocarditis or myopericarditis: population based cohort study. *BMJ.* 2021;375:e068665. doi: 10.1136/bmj-2021-068665
8. Truong DT, Dionne A, Muniz JC, McHugh KE, Portman MA, Lambert LM, Thacker D, Elias MD, Li JS, Toro-Salazar OH. et al. Clinically suspected myocarditis temporally related to COVID-19 vaccination in adolescents and young adults. *Circulation.* 2021;145:345–356. doi: 10.1161/CIRCULATIONAHA.121.056583
9. Fairweather D, Cooper LT, Blauwet LA. Sex and gender differences in myocarditis and dilated cardiomyopathy. *Curr Probl Cardiol.* 2013;38:7–46. doi: 10.1016/j.cpcardiol.2012.07.003
10. Arola A, Pikkarainen E, Sipilä JO, Pykäri J, Rautava P, Kytö V. Occurrence and features of childhood myocarditis: a nationwide study in Finland. *J Am Heart Assoc.* 2017;6:e005306. doi: 10.1161/JAHA.116.005306
11. Heymans S, Cooper LT. Myocarditis after COVID-19 mRNA vaccination: clinical observations and potential mechanisms. *Nat Rev Cardiol.* 2021;19:75–77. doi: 10.1038/s41569-021-00662-w
12. Farrington CP, Nash J, Miller E. Case series analysis of adverse reactions to vaccines: a comparative evaluation. *Am J Epidemiol.* 1996;147:93. doi: 10.1093/oxfordjournals.aje.a008695
13. Lai FTT, Li X, Peng K, Huang L, Ip P, Tong X, Chui CSL, Wan EYF, Wong CKH, Chan EWY. et al. Carditis after COVID-19 vaccination with a messenger RNA vaccine and an inactivated virus vaccine: a case-control study. *Ann Intern Med.* 2022;175:362–370. doi: 10.7326/M21-3700
14. Oster ME, Shay DK, Su JR, Gee J, Creech CB, Broder KR, Edwards K, Soslow JH, Dendy JM, Schlaudecker E. et al. Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US from December 2020 to August 2021. *JAMA.* 2022;327:331–340. doi: 10.1001/jama.2021.24110
15. Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA vaccines. *Circulation.* 2021;144:471–484. doi: 10.1161/CIRCULATIONAHA.121.056135
16. Shah AS, Griffiths M, Lee KK, McAllister DA, Hunter AL, Ferry AV, Cruikshank A, Reid A, Stoddart M, Strachan F. et al. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. *BMJ.* 2015;350:g7873. doi: 10.1136/bmj.g7873