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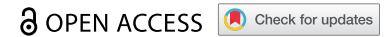


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ORIGINAL RESEARCH



## Risk of herpes zoster following mRNA COVID-19 vaccine administration

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### ABSTRACT

**Background:** Adverse events following mRNA COVID-19 vaccines, including herpes zoster (HZ), have been reported. We conducted a cohort study to evaluate the association between mRNA COVID-19 vaccination and subsequent HZ at Kaiser Permanente Southern California (KPSC).

**Research design and methods:** The vaccinated cohort consisted of KPSC members who received their first dose of mRNA COVID-19 vaccine (mRNA-1273 and BNT162b2) during 12/2020–05/2021 and were matched to unvaccinated individuals on age and sex. Incident HZ cases occurring within 90 days of follow-up were identified by diagnosis codes and antiviral medications. Cox proportional hazards models estimated adjusted hazard ratios (aHR), comparing HZ incidence between the vaccinated and unvaccinated cohorts.

**Results:** Cohort included 1,052,362 mRNA-1273 recipients, 1,055,461 BNT162b2 recipients, and 1,020,334 comparators. Compared to unvaccinated individuals, aHR for HZ up to 90 days after the second dose of mRNA-1273 and BNT162b2 was 1.14 (1.05–1.24) and 1.12 (1.03–1.22), respectively. In those aged  $\geq 50$  years not vaccinated with zoster vaccine, aHR was also increased after the second dose of mRNA-1273 (1.18 [1.06–1.33]) and BNT162b2 (1.15 [1.02–1.29]) vaccine vs. unvaccinated individuals.

**Conclusions:** Our findings suggest a potential increased risk of HZ after a second dose of mRNA vaccines, potentially driven by the increased risk in individuals aged  $\geq 50$  years without history of zoster vaccination.

### ARTICLE HISTORY

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Bnt162b2; COVID-19; herpes zoster; mRNA vaccines; Mrna-1273

## 1. Introduction

Herpes zoster (HZ), or shingles, is caused by the reactivation of the varicella zoster virus (VZV). People who had a primary infection of VZV (chickenpox) or received a varicella vaccine could develop HZ later during their lifetime. About 1 million people develop HZ annually in the United States [1]. The risks of developing HZ, as well as post-herpetic neuralgia and being hospitalized for complications, increase with age; those who are immunocompromised are particularly at increased risk. As such, the Centers for Disease Control and Prevention (CDC) recommends the recombinant zoster vaccine (RZV) in adults aged 50 years and older to prevent HZ and its complications; RZV is also recommended to adults aged 19 years and older who are immunocompromised [2,3].

As the coronavirus disease 2019 (COVID-19) quickly spread around the world, prevention options were highly sought after. Two mRNA COVID-19 vaccines (mRNA-1273, Spikevax, Moderna; and BNT162b2, Comirnaty, Pfizer-BioNTech) have been authorized for the prevention of COVID-19 since late 2020. Safety studies of mRNA COVID-19 vaccines administered under real-world conditions are needed. Early reports of adverse events following mRNA COVID-19 vaccination


included HZ, with most describing individual cases or case series [4–6]. Subsequent studies evaluated the risk of HZ after mRNA COVID-19 vaccination using a self-controlled risk interval design [7] or a cohort design with unvaccinated comparators [8,9]. Here, we expand upon this work by evaluating the association between mRNA-1273 or BNT162b2 vaccination and risk of HZ in an integrated health-care system serving a diverse population in Southern California.

## 2. Patients and methods

### 2.1. Study setting

This cohort study utilized the Kaiser Permanente Southern California (KPSC) member population data. KPSC is an integrated health-care system providing care to more than 4.6 million members [10] with an electronic health record (EHR) that captures detailed information about inpatient, outpatient, emergency, and virtual care visits; care received outside of KPSC is also captured via claims or Care Everywhere (Epic EHR feature that allows health-care systems to exchange medical information). The KPSC Institutional Review Board reviewed and approved the study with waivers of informed

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consent and written Health Insurance Portability and Accountability Act authorization.

## 2.2. Study population

For the study cohort, the index date was defined as the first mRNA COVID-19 vaccination dose date of the vaccinated individuals; their matched unvaccinated counterparts were assigned the same index date. Individuals were eligible for the study if they were aged  $\geq 16$  years at the index date and were KPSC members for  $\geq 1$  year prior to and on the index date (allowing for a 31-day membership gap). The vaccinated cohorts (1-dose and 2-dose) consisted of eligible KPSC members who received their first dose of mRNA-1273 or BNT162b2 from 14 December 2020 through 31 May 2021. Individuals who received any COVID-19 vaccine before 14 December 2020, a second dose within 14 days of their first dose, and different vaccine brands for the first and second doses were excluded. Individuals with a HZ diagnosis during the 6 months before or on the index date were also excluded. Individuals who developed HZ after the index date and prior to or on the second dose date were excluded from the 2-dose analysis.

Eligible unvaccinated individuals were randomly selected and matched to the vaccinated cohort by frequency distribution of age group (16–34 years, 35–49 years, 50–64 years, and  $\geq 65$  years) at index date and sex (female, male). Individuals with death before or on the index date, a HZ diagnosis during the 6 months before or on the index date, and no health-care utilization or vaccination within 2 years prior to the index date were excluded.

For the 1-dose analyses, vaccinated individuals were followed from the first mRNA COVID-19 vaccine dose date until occurrence of HZ, disenrollment from KPSC, receipt of any subsequent dose of COVID-19 vaccine, death, or 90 days after the first dose date. For the 2-dose analyses, vaccinated individuals were followed from the second dose date until occurrence of HZ, disenrollment from KPSC, death, or 90 days after the second dose date, or end of follow-up (31 August). Unvaccinated individuals for both analyses were followed from the index date until occurrence of HZ, disenrollment from KPSC, receipt of a first dose of COVID-19 vaccine, death, or 90 days after the index date.

## 2.3. Exposure, outcome, other variables

KPSC's EHR was used to collect information on mRNA-1273 and BNT162b2 exposures. The EHR captured COVID-19 vaccines administered through KPSC as well as COVID-19 vaccines administered outside of KPSC. These were imported daily from the California Immunization Registry (CAIR), Care Everywhere, claims (e.g. non-KPSC health plan pharmacies), mass vaccination sites (CalVax and MyTurn), and member self-report with documentation. All providers of COVID-19 vaccines were required by law to provide COVID-19 vaccine administration data to CAIR [11].

Our main outcome was incident HZ cases occurring within 90 days after the index date or after the second dose date. These were identified by *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)* diagnosis codes B02.xx

from hospital, outpatient, Emergency Department (ED), or virtual settings, as well as a non-topical antiviral (acyclovir, valacyclovir, or famciclovir) medication prescribed within 7 days before or after the date of HZ diagnosis, without a non-topical antiviral medication prescribed in the 183 days to 8 days prior to the date of HZ diagnosis.

Baseline characteristics extracted from the EHR included age at index date, sex, race/ethnicity, history of zoster vaccine live (ZVL) (prior to index date) and RZV (between 1 April 2018 and index date) vaccination, history of HZ (prior to 6 months before the index date), history of SARS-CoV-2 infection (between 1 March 2020 and index date), and immunocompromised status (HIV, leukemia, lymphoma, congenital immunodeficiencies, asplenia/hyposplenia, and transplant [including heart, kidney, liver, lung, pancreas, and bone marrow] prior to index date, or receipt of non-steroidal immunosuppressing medications overlapping with index date). Variables assessed in the year prior to the index date included chronic diseases (kidney, heart, lung, and liver disease, and diabetes), and health-care utilization (outpatient, emergency department, and virtual encounters, and hospitalizations). We also assessed follow-up 90 days from first mRNA COVID-19 vaccine dose and 90 days from second dose.

## 2.4. Statistical analyses

Incidence rates (IR) per 1,000 person-years were calculated by dividing the number of incident HZ cases by person-years for the mRNA-1273- and BNT162b2-vaccinated and unvaccinated groups. Cox proportional hazards models were used to estimate unadjusted hazard ratios (HR) and adjusted hazard ratios (aHR) with 95% confidence intervals (CIs) comparing HZ incidence between those vaccinated with a mRNA COVID-19 vaccine and the unvaccinated. aHRs were also estimated by age and history of zoster vaccine. aHRs were adjusted for age group at index date, sex, race/ethnicity, history of ZVL and RZV vaccination, history of HZ, immunocompromised status, history of SARS-CoV-2 infection, chronic disease, and health-care utilization.

## 3. Results

Our cohort included 1,052,362 individuals vaccinated with mRNA-1273, 1,055,461 individuals vaccinated with BNT162b2, and 1,020,334 unvaccinated matched individuals (Figure 1). Among those vaccinated with mRNA-1273, the majority were aged 50 years or older (57.1%) and female (53.7%), with 37.8% being Hispanic and 34.3% being Non-Hispanic White (Table 1). Over 90% did not have a history of RZV vaccination (90.6%) nor a history of HZ (93.2%); 87.0% did not have a history of ZVL vaccination. Of the comorbidities assessed, heart disease was the most prevalent (27.1%) followed by diabetes (13.0%), lung disease (5.8%), kidney disease (4.6%), and liver disease (2.1%). Three percent were immunocompromised and 9.5% had a history of SARS-CoV-2 infection. Among those vaccinated with BNT162b2, the majority were aged 16–49 (52.2%) and female (54.7%). The largest racial/ethnic group was Hispanic (38.7%) followed by non-Hispanic White (32.0%). A high proportion of individuals did not have a history of ZVL vaccination, RZV vaccination, and HZ (89.5%, 92.2%, and

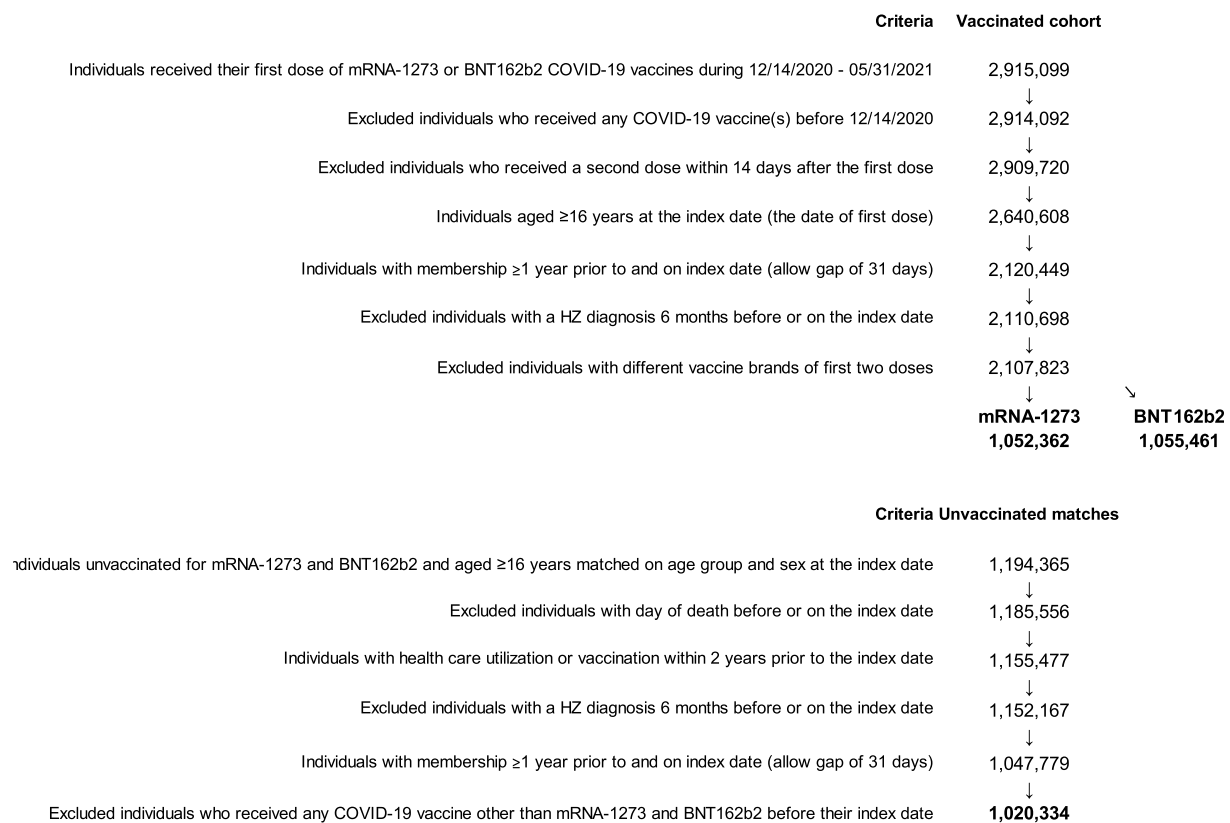


Figure 1. Flowchart for mRNA-1273- and BNT162b2-vaccinated cohorts, and for their unvaccinated matches.

94.2%, respectively). Of the comorbidities assessed, heart disease was the most prevalent (21.9%) followed by diabetes (9.9%), lung disease (5.0%), kidney disease (3.4%), and liver disease (1.7%). In addition, 2.5% were immunocompromised and 9.1% had a history of SARS-CoV-2 infection.

During the 90 days of follow-up after the first mRNA COVID-19 vaccine dose, there were 529 cases of HZ among mRNA-1273 recipients, 344 HZ cases among BNT162b2 recipients, and 942 HZ cases among the unvaccinated (Table 2). Compared to the unvaccinated individuals, the aHR of HZ was 1.08 (95% CI: 0.95–1.23) for mRNA-1273 recipients and 1.01 (95% CI: 0.87–1.17) for BNT162b2 recipients. During the 90 days of follow-up after the second mRNA COVID-19 vaccine dose, there were 1,484 cases of HZ in the mRNA-1273 group, 1,313 HZ cases in the BNT162b2 group, and 942 in the unvaccinated group (Table 3). The overall aHR of HZ comparing mRNA-1273 versus unvaccinated was 1.14 (95% CI: 1.05–1.24) and the aHR of HZ comparing BNT162b2 versus unvaccinated was 1.12 (95% CI: 1.03–1.22). In those aged  $\geq 50$  years with no history of RZV or ZVL vaccination, the aHRs for mRNA-1273 and BNT162b2 versus unvaccinated were 1.18 (95% CI: 1.06–1.33) and 1.15 (95% CI: 1.02–1.29), respectively, during the 90 days after the second dose (Table 4); during the 90 days after the second dose, in those aged  $\geq 50$  years with a history of RZV or ZVL vaccination, the aHRs for mRNA-1273 and BNT162b2 versus unvaccinated were 0.97 (95% CI: 0.72–1.30) and 1.03 (95% CI: 0.76–1.39), respectively. Additionally, during the 90 days after the second dose, in those aged 16–49 years with no history of RZV or ZVL vaccination (zoster vaccination not recommended in this age group during the study period),

the aHRs for mRNA-1273 and BNT162b2 versus unvaccinated were 1.14 (95% CI: 0.98–1.31) and 1.09 (95% CI: 0.94–1.25), respectively (Supplemental Table S1).

#### 4. Discussion

In this large cohort study, we focused our analyses on the primary mRNA COVID-19 vaccine series during a time when these vaccines were novel and recommended under emergency use authorization. Overall, we found no increased risk of HZ after the first dose of the primary series. However, in the overall study population, we observed a small increased risk of HZ of approximately 10% in the 90 days following the second dose of the primary series of the mRNA COVID-19 vaccines. This likely may have been driven by the increased risk seen in individuals aged  $\geq 50$  years with no history of RZV or ZVL vaccination.

As the COVID-19 vaccines were administered under real-world conditions, reports of HZ post-vaccination started to emerge, including from the Vaccine Adverse Event Reporting System (VAERS) [4–6,12,13]. These led to further systematic reviews and cohort studies which produced mixed results. One such review by Desai *et al.* identified 14 studies with 54 patients (50% male and 50% female) and found 86% of the HZ cases had received mRNA COVID-19 vaccine while the remainder received an inactivated or non-replicating viral vector COVID-19 vaccine [14]. However, no causality could be established. Another systematic review and meta-analysis identified four cohort studies and found no increased incidence of HZ following COVID-19 vaccination [15]. Conversely, other studies utilizing large study

databases with over a million patients in their cohort found a higher incidence of HZ following mRNA or adenovirus vector COVID-19 vaccination [16] and an elevated risk of HZ post BNT162b2 vaccination [9]. In our study conducted in a large, diverse population, we observed similar results. In addition, we evaluated risk of HZ following mRNA-1273 and BNT162b2 separately, while controlling for history of zoster vaccination and other possible confounders. As studies have suggested an increased risk of HZ following diagnosed COVID-19 [17,18], any

potential increased risk of HZ after COVID-19 vaccination must be weighed against the benefit of COVID-19 vaccination against COVID-19 disease-associated HZ.

The mechanism by which the latent VZV is reactivated post-mRNA COVID-19 vaccination has been debated [19–21]. One report evaluating five cases of VZV reactivation after BNT162b2 vaccination hypothesized that immunomodulation may kick VZV out of its latent phase [6]; the mRNA vaccines may activate toll-like receptor signaling which could lead to

**Table 1.** Baseline characteristics of Mrna-1273- and BNT162b2-vaccinated<sup>a</sup> and unvaccinated cohorts, 12/14/2020–05/31/2021 (N = 3,128,157).

Characteristic	mRNA-1273-vaccinated	BNT162b2-vaccinated	Unvaccinated
	N = 1,052,362	N = 1,055,461	N = 1,020,334
	n (%)		
<b>Age at index date<sup>b</sup>, years</b>			
16–34	211912 (20.1)	290712 (27.5)	420933 (41.3)
35–49	239360 (22.7)	260945 (24.7)	275041 (27)
50–64	292754 (27.8)	258921 (24.5)	217591 (21.3)
65+	308336 (29.3)	244883 (23.2)	106769 (10.5)
<b>Sex</b>			
Female	564802 (53.7)	577102 (54.7)	534339 (52.4)
Male	487560 (46.3)	478359 (45.3)	485995 (47.6)
<b>Race/Ethnicity</b>			
Non-Hispanic White	360986 (34.3)	337798 (32.0)	329680 (32.3)
Non-Hispanic Black	75326 (7.2)	66280 (6.3)	109125 (10.7)
Hispanic	397787 (37.8)	408455 (38.7)	449844 (44.1)
Non-Hispanic Asian	142960 (13.6)	156631 (14.8)	55721 (5.5)
Other <sup>c</sup>	75303 (7.2)	86297 (8.2)	75964 (7.4)
<b>Index date</b>			
December 2020	19818 (1.9)	52193 (4.9)	42005 (4.1)
January 2021	191666 (18.2)	130333 (12.3)	124429 (12.2)
February 2021	186885 (17.8)	221212 (21.0)	136094 (13.3)
March 2021	354037 (33.6)	300047 (28.4)	375722 (36.8)
April 2021	238021 (22.6)	254615 (24.1)	251903 (24.7)
May 2021	61935 (5.9)	97061 (9.2)	90181 (8.8)
<b>History of ZVL vaccination<sup>d</sup></b>			
No	915772 (87.0)	945147 (89.5)	990437 (97.1)
Yes, ≤5 years	22437 (2.1)	18069 (1.7)	5923 (0.6)
Yes, >5 years	114153 (10.8)	92245 (8.7)	23974 (2.3)
<b>History of RZV vaccination<sup>e</sup></b>			
No	953604 (90.6)	972815 (92.2)	999903 (98.0)
Yes	98758 (9.4)	82646 (7.8)	20431 (2.0)
<b>History of HZ<sup>f</sup></b>			
No	980702 (93.2)	993724 (94.2)	979646 (96.0)
Yes	71660 (6.8)	61737 (5.8)	40688 (4.0)
<b>Immunocompromised status<sup>g</sup></b>			
No	1020783 (97.0)	1028977 (97.5)	1001977 (98.2)
Yes	31579 (3.0)	26484 (2.5)	18357 (1.8)
<b>History of SARS-CoV-2 infection<sup>h</sup></b>			
No	952560 (90.5)	959361 (90.9)	887040 (86.9)
Yes	99802 (9.5)	96100 (9.1)	133294 (13.1)
<b>Chronic diseases<sup>i</sup></b>			
Kidney disease	48757 (4.6)	35967 (3.4)	16996 (1.7)
Heart disease	285372 (27.1)	230662 (21.9)	132460 (13.0)
Lung disease	60746 (5.8)	52696 (5.0)	41074 (4.0)
Liver disease	22334 (2.1)	18338 (1.7)	13785 (1.4)
Diabetes	136639 (13.0)	104651 (9.9)	59096 (5.8)
<b>Number of outpatient visits<sup>i</sup></b>			
0–4	597908 (56.8)	652318 (61.8)	705044 (69.1)
5–10	267069 (25.4)	246076 (23.3)	198512 (19.5)
≥11	187385 (17.8)	157067 (14.9)	116778 (11.4)
<b>Number of emergency department visits<sup>i</sup></b>			
0	912897 (86.7)	925499 (87.7)	867645 (85.0)
1	98148 (9.3)	92490 (8.8)	104856 (10.3)
≥2	41317 (3.9)	37472 (3.6)	47833 (4.7)
<b>Number of hospitalization<sup>i</sup></b>			
0	964804 (91.7)	969071 (91.8)	936969 (91.8)
1	59844 (5.7)	58707 (5.6)	59299 (5.8)
≥2	27714 (2.6)	27683 (2.6)	24066 (2.4)
<b>Number of virtual encounters<sup>ij</sup></b>			

(Continued)

Table 1. (Continued).

	mRNA-1273-vaccinated	BNT162b2-vaccinated	Unvaccinated
0–10	954591 (90.7)	970159 (91.9)	949517 (93.1)
11–20	70051 (6.7)	60920 (5.8)	51336 (5.0)
≥21	27720 (2.6)	24382 (2.3)	19481 (1.9)

Note: <sup>a</sup>The study included KPSC members aged ≥16 years who received at least one dose of COVID-19 vaccine by 05/31/2021 with two doses >14 days apart.

<sup>b</sup>The index date was the date of the first dose of COVID-19 vaccine for vaccinated individuals; the same date was used for their matched unvaccinated counterparts.

<sup>c</sup>Includes other, multiple, or unknown race/ethnicity.

<sup>d</sup>Defined prior to index date.

<sup>e</sup>Defined between 04/01/2018 and index date.

<sup>f</sup>Defined prior to 6 months before the index date.

<sup>g</sup>Defined as HIV, leukemia, lymphoma, congenital immunodeficiencies, asplenia/hyposplenia, and transplant (including heart, kidney, liver, lung, pancreas, and bone marrow) prior to index date, or receipt of non-steroidal immunosuppressing medications overlapping with index date.

<sup>h</sup>Defined between 03/01/2020 and index date.

<sup>i</sup>Defined in one year prior to index date.

<sup>j</sup>Virtual encounters included e-mail, e-visit, telephone appointment visit, and video.

Abbreviations: COVID-19, coronavirus disease 2019; HZ, herpes zoster; KPSC, Kaiser Permanente Southern California; RZV, recombinant zoster vaccine; ZVL, zoster vaccine live.

the activation of VZV [7]. Elucidating the mechanism by which HZ occurs would be extremely beneficial as mRNA vaccine technology is being developed for use against other targets such as influenza. There is also a need to improve RZV vaccination rates among adults aged ≥50 years [22] as well as immunocompromised individuals aged ≥19 years [3]. The National Committee for Quality Assurance has added HZ vaccination to a new Adult Immunization Status Measure that will be publicly reportable in measurement year 2022 to encourage improvement in vaccination rates [23].

Our study has several strengths. We were able to focus on the effect of the primary series of the mRNA COVID-19 vaccine on HZ incidence with no interference from mRNA COVID-19 booster doses, or more virulent or transmissible strains of SARS-CoV-2. We were also able to utilize the diverse and stable population of a large integrated health-care system. In addition, we had a longer follow-up than previous studies to comprehensively monitor for HZ during the 90-day follow-up period, as timing of HZ occurrence post-mRNA vaccination is

not well established. We were also able to examine the risk of HZ after one and two doses of two distinct mRNA COVID-19 vaccines as previous work had shown that adverse events may occur at different rates following each dose [21,24]. Lastly, due to the comprehensive EHR system, we were also able to capture and control for past zoster vaccinations. There were also limitations to our study. Although we controlled for several factors, residual confounding from unmeasured factors could still be present. Misclassification of the HZ outcome is also possible as care-seeking behaviors varied during the COVID-19 pandemic, especially in the beginning when individuals may have avoided or postponed seeking care. Misclassification of HZ could have also occurred if the EHR did not accurately capture incidence of HZ; however, we captured HZ via ICD-10 code and antiviral medications to improve the specificity of the case definition [25]. Moreover, the sensitivity of this case definition likely improved through inclusion of the virtual care setting, which was more heavily utilized during the COVID-19 pandemic [26].

Table 2. Hazard ratio of herpes zoster up to 90 days after the first dose of mRNA COVID-19 vaccination, overall and by age group.

	Number of HZ cases <sup>a</sup>	N <sup>a</sup>	Hazard Ratio (95% CI) <sup>b</sup>	
			Unadjusted	Adjusted <sup>c</sup>
<b>All</b>				
mRNA-1273	529 vs. 942	1052362 vs. 1020334	1.45 (1.28–1.65)	1.08 (0.95–1.23)
BNT162b2	344 vs. 942	1055461 vs. 1020334	1.22 (1.06–1.41)	1.01 (0.87–1.17)
<b>Age at index date, years</b>				
<b>16–34</b>				
mRNA-1273	38 vs. 147	211912 vs. 420933	1.28 (0.86–1.90)	1.19 (0.80–1.77)
BNT162b2	41 vs. 147	290712 vs. 420933	1.31 (0.88–1.93)	1.25 (0.84–1.87)
<b>35–49</b>				
mRNA-1273	86 vs. 278	239360 vs. 275041	1.03 (0.78–1.35)	0.96 (0.73–1.28)
BNT162b2	73 vs. 278	260945 vs. 275041	1.05 (0.78–1.42)	0.99 (0.73–1.34)
<b>50–64</b>				
mRNA-1273	178 vs. 316	292754 vs. 217591	1.15 (0.92–1.43)	1.13 (0.91–1.41)
BNT162b2	118 vs. 316	258921 vs. 217591	1.11 (0.87–1.43)	1.11 (0.87–1.43)
<b>65+</b>				
mRNA-1273	227 vs. 201	308336 vs. 106769	0.99 (0.78–1.26)	1.04 (0.82–1.32)
BNT162b2	112 vs. 201	244883 vs. 106769	0.80 (0.61–1.06)	0.85 (0.64–1.12)

<sup>a</sup>mRNA-1273/BNT162b2 vs. unvaccinated.

<sup>b</sup>Reference group: unvaccinated.

<sup>c</sup>Cox proportional hazard model for HZ comparing individuals with and without mRNA COVID-19 vaccine, adjusted for all other variables in Table 1 except for age in age-stratified analyses.

Abbreviations: COVID-19, coronavirus disease 2019; HZ, herpes zoster.

**Table 3.** Hazard ratio of herpes zoster up to 90 days after the second dose of mRNA COVID-19 vaccination, overall and by age group.

	Number of HZ cases <sup>a</sup>	N <sup>a</sup>	Hazard Ratio (95% CI) <sup>b</sup>	
			Unadjusted	Adjusted <sup>c</sup>
<b>All</b>				
mRNA-1273	1484 vs. 942	959310 vs. 1020334	1.59 (1.46–1.72)	1.14 (1.05–1.24)
BNT162b2	1313 vs. 942	960843 vs. 1020334	1.40 (1.29–1.52)	1.12 (1.03–1.22)
<b>Age at index date, years</b>				
<b>16–34</b>				
mRNA-1273	90 vs. 147	179359 vs. 420933	1.38 (1.06–1.80)	1.31 (1.01–1.72)
BNT162b2	102 vs. 147	248722 vs. 420933	1.13 (0.88–1.45)	1.12 (0.87–1.45)
<b>35–49</b>				
mRNA-1273	251 vs. 278	213548 vs. 275041	1.11 (0.93–1.31)	1.07 (0.90–1.27)
BNT162b2	275 vs. 278	236321 vs. 275041	1.10 (0.93–1.30)	1.07 (0.91–1.27)
<b>50–64</b>				
mRNA-1273	498 vs. 316	269110 vs. 217591	1.18 (1.03–1.36)	1.17 (1.02–1.35)
BNT162b2	404 vs. 316	239539 vs. 217591	1.08 (0.93–1.25)	1.08 (0.93–1.25)
<b>65+</b>				
mRNA-1273	645 vs. 201	297293 vs. 106769	1.08 (0.92–1.27)	1.14 (0.97–1.34)
BNT162b2	532 vs. 201	236261 vs. 106769	1.12 (0.95–1.32)	1.20 (1.02–1.42)

Note: <sup>a</sup>mRNA-1273/BNT162b2 vs. unvaccinated.

<sup>b</sup>Reference group: unvaccinated.

<sup>c</sup>Cox proportional hazard model for HZ comparing individuals with and without mRNA COVID-19 vaccine, adjusted for all other variables in Table 1 except for age in age-stratified analyses.

Abbreviations: COVID-19, coronavirus disease 2019; HZ, herpes zoster.

**Table 4.** Hazard ratio of herpes zoster up to 90 days after the second dose of mRNA COVID-19 vaccination in individuals aged  $\geq 50$  years, by RZV or ZVL vaccination status.

	Number of HZ cases <sup>a</sup>	N <sup>a</sup>	Hazard Ratio (95% CI) <sup>b</sup>	
			Unadjusted	Adjusted <sup>c</sup>
<b>RZV or ZVL vaccinated</b>				
mRNA-1273	256 vs. 55	186274 vs. 44831	1.02 (0.76–1.37)	0.97 (0.72–1.30)
BNT162b2	217 vs. 55	152623 vs. 44831	1.06 (0.79–1.42)	1.03 (0.76–1.39)
<b>RZV and ZVL unvaccinated</b>				
mRNA-1273	887 vs. 462	380014 vs. 279529	1.32 (1.18–1.48)	1.18 (1.06–1.33)
BNT162b2	717 vs. 462	323064 vs. 279529	1.25 (1.12–1.41)	1.15 (1.02–1.29)

Note: <sup>a</sup>mRNA-1273/BNT162b2 vs. unvaccinated.

<sup>b</sup>Reference group: unvaccinated.

<sup>c</sup>Cox proportional hazard model for HZ comparing individuals with and without mRNA COVID-19 vaccine, adjusted for all other variables in Table 1 except for RZV or ZVL vaccination status.

Abbreviations: COVID-19, coronavirus disease 2019; HZ, herpes zoster; RZV, recombinant zoster vaccine; ZVL, zoster vaccine live.

## 5. Conclusions

In conclusion, we found a potential increased risk of HZ following mRNA COVID-19 vaccination based on a cohort study conducted within a large, diverse integrated health-care system. In addition, the increased risk was not observed in the zoster vaccinated population aged  $\geq 50$  years; this may also be true in the group aged 16–49 years. Thus, improving zoster vaccination coverage among the population aged  $\geq 50$  years could be beneficial, especially as uptake of mRNA COVID-19 vaccinations increases. To further evaluate the association between mRNA COVID-19 vaccination and risk of HZ, additional studies on the effect of COVID-19 vaccine doses beyond the 2-dose primary series are needed.

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## Declaration of interest

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## Author Contributions

Concept and design, or analysis and interpretation of data: AF, JW, LQ, BL, LSS, ICL, JHK, HFT. Drafting of the manuscript: AF. Critical revision of the manuscript for intellectual content: JW, LQ, BL, LSS, ICL, JHK, HFT. Statistical analysis: JW, LQ. Final approval of the version to be published: AF, JW, LQ, BL, LSS, ICL, JHK, HFT. All authors agree to be accountable for all aspects of the work.

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