ORIGINAL ARTICLE

Real-world evidence from over one million COVID-19 vaccinations is consistent with reactivation of the varicella-zoster virus

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Abstract

Background Reactivation of the varicella-zoster virus (VZV), which causes herpes zoster (HZ, synonym: shingles) in humans, can be a rare adverse reaction to vaccines. Recently, reports of cases after COVID-19 vaccination have arisen.

Objectives The aim of this study was to assess whether the frequency of HZ is found to increase after COVID-19 vaccination in a large cohort, based on real-world data. As a hypothesis, the incidence of HZ was assumed to be significantly higher in subjects who received a COVID-19 vaccine (Cohort I) vs. unvaccinated individuals (Cohort II).

Methods The initial cohorts of 1 095 086 vaccinated and 16 966 018 unvaccinated patients were retrieved from the TriNetX database and were matched on age and gender in order to mitigate confounder bias.

Results After matching, each cohort accounted for 1 095 086 patients. For the vaccinated group (Cohort I), 2204 subjects developed HZ within 60 days of COVID-19 vaccination, while among Cohort II, 1223 patients were diagnosed with HZ within 60 days after having visited the clinic for any other reason (i.e. not vaccination). The risk of developing shingles was calculated as 0.20% and 0.11% for cohort I and cohort II, respectively. The difference was statistically highly significant ($P < 0.0001$; log-rank test). The risk ratio and odds ratio were 1.802 (95% confidence interval [CI] = 1.680; 1.932) and 1.804 (95% CI = 1.682; 1.934).

Conclusions Consistent with the hypothesis, a higher incidence of HZ was statistically detectable post-COVID-19 vaccine. Accordingly, the eruption of HZ may be a rare adverse drug reaction to COVID-19 vaccines. Even though the molecular basis of VZV reactivation remains murky, temporary compromising of VZV-specific T-cell-mediated immunity may play a mechanistic role in post-vaccination pathogenesis of HZ. Note that VZV reactivation is a well-established phenomenon both with infections and with other vaccines (i.e. this adverse event is not COVID-19-specific).

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Introduction

Coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), rapidly became a pandemic, starting from the identification of the first cases. Globally, immense hope rests upon vaccination against COVID-19. Most available vaccines act by presenting the viral spike (S) protein to the host immune system, yielding an active immunization by the induction of a specific humoral response, followed by the formation of neutralizing anti-viral antibodies. The sera contain either (i) S protein-encoding mRNA embedded in lipid nanoparticles (LNPs), for example BioNTech/Pfizer's BNT162b2 or Moderna's mRNA-1273; (ii) adenovirus vectors,

such as Astra-Zeneca's ChAdOx1 nCoV-19, Johnson & Johnson's Ad26.COV2.S or Gam-COVID-19-Vac (Gamaleya National Centre of Epidemiology and Microbiology); or (iii) inactivated SARS-CoV-2 virions, as in Sinovac's CoronaVac. A broad spectrum of clinical studies conducted in different countries has shown high protection levels against COVID-19, especially as regards severe courses of the disease. Safety profiles were found to be acceptable despite the occurrence of minor adverse effects such as muscle aches (myalgia), fatigue and other flu-like symptoms.[1–10] Nevertheless, reports have recently emerged of very rare but severe adverse drug reactions (ADR) and adverse drug events (ADE). Specifically, eosinophilic lung disease, cerebral venous sinus thrombosis (CVST), pulmonary embolism, vaccine-induced immune thrombocytopenia (VITT) and myocarditis were found to be associated with COVID-19 vaccination.[11–18]

Because of the rapidity with which the first generation of COVID-19 vaccines had to be developed, tested, produced, delivered and finally utilized, there is an acute need to screen vaccinated cohorts for as yet unknown adverse reactions and undesirable effects; such data are also indispensable in continually refining next-generation vaccines. Although any scientific report of risks or complications can be misconstrued (the present work included), for example as part of anti-vaccine agendas, we believe that it is of fundamental ethical relevance that potential ADRs/ADEs are meticulously investigated and disclosed to the public. Note that many adverse events are known to occur both with infections (e.g. COVID-19 itself) and, in some cases, even with other (non-COVID) vaccines: that is, these adverse events are not necessarily specific side-effects of the various COVID vaccines. Any decision-making process—be it a population-wide policy recommendation or an individual/personal choice—is healthiest if it is balanced and data-informed, weighing the potential complications reported herein against the significant and well-established benefits of COVID-19 vaccination.[19]

Herpes zoster (HZ, synonym: shingles) is an infectious mucocutaneous disease caused by reactivation of the varicella-zoster virus (VZV). The initial infection, often contracted in childhood, emerges as a maculopapular rash (varicella, synonym: chickenpox). Despite clinical recovery, VZV persists in the bodies of neural cells located in the spinal dorsal root ganglia and the trigeminal ganglia.[20] Typically, shingles presents as a painful unilateral cutaneous or mucous rash consisting of confluent erosions following the formation of vesicles. The exanthema/enanthema typically corresponds to a dermatome or the innervation area of a sensory nerve. HZ is primarily diagnosed clinically and can be confirmed via polymerase chain reaction (PCR) and enzyme-linked immunosorbent assays (ELISA).[21] Herpes zoster can be treated with a family of nucleoside analogue compounds (aciclovir, valaciclovir and famciclovir) that inhibit the viral DNA polymerase. These virostatic agents require prompt administration, ideally within 72 h of onset of the rash. Furthermore, a VZV vaccine is available.[20]

Reactivation of herpesviridae, including VZV, has been reported to be potentially triggered by vaccines against, *inter alia*, yellow fever, hepatitis A, rabies and influenza.[22] An association of HZ with COVID-19 vaccination has been reported worldwide in case reports and case series,[23–35] as well as in a retrospective study focusing on the safety of BNT162b2. The latter found a risk ratio (RR) of 1.43 based on 15.8 events of HZ per 100.000 patients.[36] Iwanaga *et al.* published a narrative review on 399 patients who developed shingles after COVID-19 vaccination including two cases of oral HZ. Among those, 24 individuals reported a history of varicella/HZ. Twenty subjects had been vaccinated against VZV. BNT162b2 was most often associated with HZ.[37] Fathy *et al.* reviewed 35 cases of HZ after COVID-19 vaccination reported in the International Dermatology Registry. Shingles occurred in similar proportions after the use of BNT162b2 and mRNA-1273.[38]

Even though HZ can be sufficiently treated by prompt administration of nucleoside analogues, severe complications can occur. Of those, the most frequent ones are secondary infections, the development of subacute herpetic neuralgia and post-herpetic neuralgia, as well as zoster ophthalmicus including acute retinal necrosis, which can cause loss of vision.[20] Rather rare potential neurological complications are Hunt syndrome, Guillain–Barré syndrome, Bell's palsy, aseptic meningitis, peripheral motor neuropathy and myelitis.[45] Furthermore, VZV is known to increase maternal morbidity in pregnant individuals.[21]

The present work seeks to determine whether an association between COVID-19 vaccination and the eruption of herpes zoster can be found in a large international cohort, based on statistical analysis of real-world data. As a working hypothesis, we assumed that the incidence of HZ would be significantly (detectably) higher in individuals who were vaccinated against COVID-19, vs. those who remained unvaccinated. To gather subject data, the TriNetX Global Health Research Network was used. This database offers high volumes of real-world data aggregated from multiple centres; as of November 2021, TriNetX includes medical records of over 250 million individuals. The clinical data in the TriNetX biomedical research network are drawn from over 120 healthcare organizations (HCO) across 19 countries; it brings together HCOs, contract research sites and biopharmaceutical companies in order to exchange longitudinal clinical data and provide state-of-the-art analytics. The TriNetX resource was used recently for retrospective, real-world evidence (RWE) studies of other COVID-19-related topics.[39,40] Herein, we describe our findings for shingle-associated reactivation of VZV, based on a statistical survey of over 1 M COVID-19 vaccinations.

Materials and methods

Inclusion and exclusion criteria
The TriNetX database was accessed on 25 November 2021, and the eligibility period was limited to 2y backwards from the

access date. Thus, all patients who visited the respective HCO for evaluation and management services in this timeframe were eligible for inclusion. Subsequently, to construct the initial cohorts, the database was searched for (i) individuals who had received at least one intramuscular injection of mRNA LNP or adenovirus vector-based COVID-19 vaccine (giving Cohort I), and (ii) those who were not vaccinated against COVID-19 (giving Cohort II).

Matching process

In order to mitigate confounder bias via the method of propensity score matching, stratified and balanced sub-cohorts across current age and gender distributions were constructed from the initial cohorts, as shown in Fig. 1. One-to-one matching was conducted to replicate randomized conditions as closely as possible.

Statistical analysis

We defined the primary outcome as clinically diagnosed 'herpes zoster' (International Classification of Diseases [ICD] 10 code B.02) that condition being met either (i) within 1–60 days post-COVID-19 vaccination (for Cohort I) or (ii) within 1–60 days of a patient's visit to the HCO for any other reason (for Cohort II). Next, this framework was used to conduct a Kaplan–Meier analysis, and risk ratios (RRs) and odds ratios (ORs) were calculated. In addition, both cohorts were tested for distribution differences regarding the history of radiotherapy and/or chemotherapy, iatrogenic immunosuppression, as well as asymptomatic and symptomatic infection with human immunodeficiency virus (HIV; ICD-10 codes Z21 and B20). Statistical analyses were performed using the log-rank test, whereby the significance threshold was defined as $P \leq 0.05$.

Ethics approval

All methods were performed in compliance with relevant guidelines and regulations. All HCOs from which data were transferred to TriNetX obtained (written) informed consent from all patients and/or their legal guardians. TriNetX is compliant with the Health Insurance Portability and Accountability Act (HIPAA), which is the US federal law that protects the privacy and security of healthcare data. TriNetX is certified to the ISO 27001:2013 standard and maintains an Information Security Management System (ISMS) to ensure the protection of the healthcare data it has access to and to meet the requirements of the HIPAA Security Rule. Any data displayed on the TriNetX platform in aggregate form or any patient-level data provided in a data set generated by the TriNetX platform only contains de-identified data, per the de-identification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. The process by which the data are de-identified is attested to through a formal determination by a qualified expert as defined in Section §164.514(b) (1) of the HIPAA Privacy Rule. This formal determination by a qualified expert, refreshed in December 2020, supersedes the need for TriNetX's previous waiver from the Western Institutional Review Board (IRB). The TriNetX network contains data provided by participating healthcare organizations (HCOs), each of which represents and warrants that it
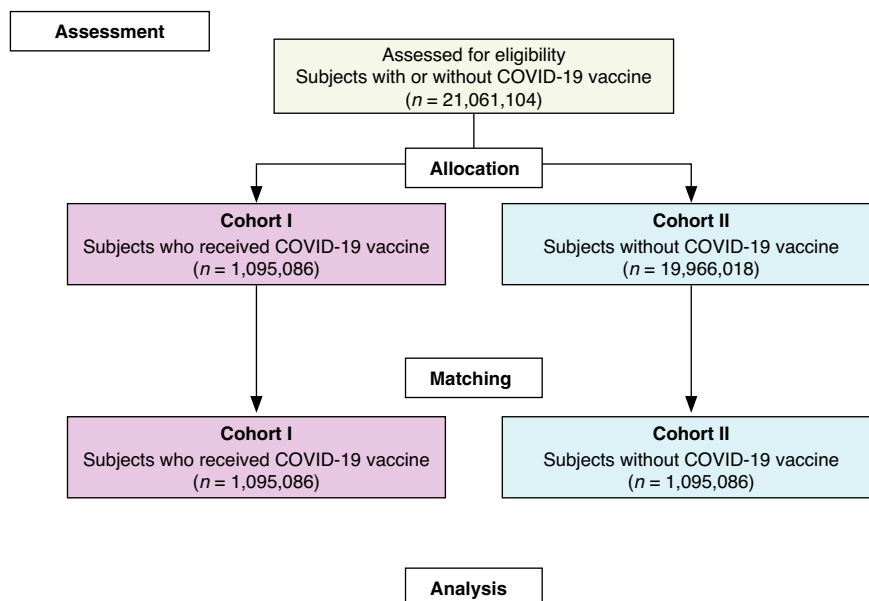

Figure 1 CONSORT flow chart.

has all necessary rights, consents, approvals and authority to provide the data to TriNetX under a business associate agreement (BAA), so long as their name remains anonymous as a data source and their data are utilized for research purposes. The data shared through the TriNetX platform are masked to ensure that they do not include sufficient information to facilitate the determination of which HCO contributed which specific information about a patient.[41]

Results

Based on the inclusion and exclusion criteria, 1 095 086 and 16 966 018 patients were eligible to comprise Cohorts I and II, respectively. After the matching process, each Cohort accounted for 1 095 086 individuals. The demographic characteristics of the included subjects are shown in Table 1, and the frequencies of the vaccines applied within Cohort I are presented in Table 2.

Among the individuals in Cohort I, 2204 subjects developed HZ within 60 days of COVID-19 vaccination (Fig. 2). Meanwhile, in Cohort II we found 1223 patients were diagnosed with HZ within 60 days of having visited an HCO for any other reason. The risk of developing shingles was calculated as 0.20% vs. 0.11% for Cohorts I and II, respectively. The underlying risk difference of 0.09% was statistically highly significant ($P < 0.0001$; 95% confidence interval [CI] = 0.079%; 0.100%). Computed RR and OR values (Fig. 2) were 1.802 (95% CI = 1.680; 1.932) and 1.804 (95% CI = 1.682; 1.934), respectively.

Patient data on a history of radiotherapy and chemotherapy, iatrogenic immunosuppression, as well as asymptomatic and

Table 2 Types of COVID-19 vaccines applied in Cohort I

Vaccine type	Patients (n)
BNT162b2 (30 μg/0.3 mL)	**970 465 (88.62%)**
First dose	511 186 (46.68%)
Second dose	459 279 (41.49%)
mRNA-1273 (100 μg/0.5 mL)	**108 085 (9.87%)**
First dose	56 397 (5.15%)
Second dose	51 688 (4.72%)
Ad26.COV2.S [5 x 10^10 viral particles/0.5 mL; single-dose]	**16 536 (1.51%)**

Percentage are of the total number from among the 1 095 086 patients within the cohort. Bold values are absolute numbers.

symptomatic infection with HIV (ICD-10 codes Z21 and B20), were available for 641 277 subjects from both cohorts. The frequencies of histories of radiotherapy or chemotherapy were significantly higher among Cohort II, with the differences being (for Cohort I vs. II): radiotherapy = 10 vs. 41; chemotherapy = 1020 vs. 2219 subjects ($P \leq 0.05$). As regards the use of immunosuppressants and the prevalence of the HIV-related ICD-10 codes (Z21 and B20), no significant differences were detected ($P > 0.05$).

Discussion

The present study sought to determine whether the frequency of herpes-zoster diagnoses was higher among patients who received COVID-19 vaccines (Cohort I) vs. those who were not vaccinated (Cohort II). We anticipated that the incidence of HZ might be detectably higher in Cohort I vs. Cohort II,

Table 1 Patient characteristics before and after matching of cohorts I (ICD-10 code B.02 after COVID-19 vaccination) and II (ICD-10 code B.02 without COVID-19 vaccination)

Patients (n)	Before matching				After matching			
	Cohort I	Cohort II	P-value	Standardized mean difference	Cohort I	Cohort II	P-value	Standardized mean difference
Total	1 095 086	16 966 018			1 095 086	1 095 086		
Female	638 242 (58.28%)	9 278 596 (54.69%)	<0.0001	0.0725	638 242 (58.28%)	638 242 (52.28%)	1.0	0
Male	456 687 (41.72%)	7 682 275 (45.31%)	<0.0001	0.0722	456 687 (41.72%)	456 687 (41.72%)	1.0	0
Mean current age (years)	54.74	40.31	<0.0001	0.6420	54.74	54.74	1.0	0
Standard deviation	20.20	24.53			20.20	20.20		0
Minimum	12	0			12	12		
Maximum	90	90			90	90		
Mean age at diagnosis (years)	54.10	40.00	<0.0001	0.6736	54.10	54.10	1.0	0
Standard deviation	20.16	24.49			20.16	20.16		
Minimum	7	0			7	7		
Maximum	90	90			90	90		

Abbreviation: ICD, International Classification of Diseases.
Percentage refers to gender distribution within the respective cohorts. *P*-value refers to comparison between both cohorts (log-rank test).
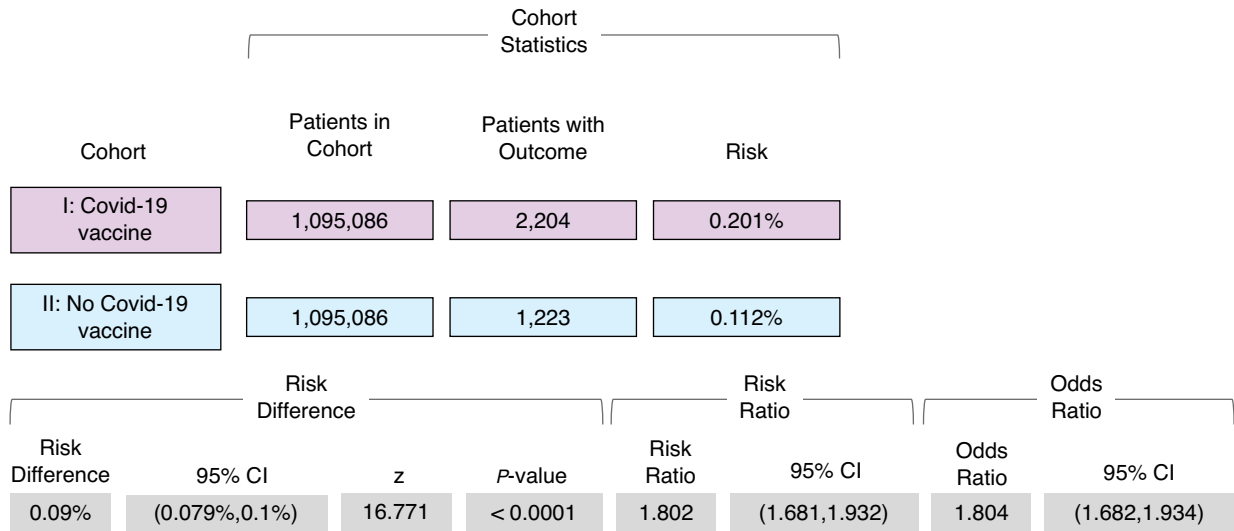
Figure 2 Cohort statistics after 1:1 matching.

based on prior reports by others and what is generally known about *herpesviridae* reactivation phenomena. The hypothesis was confirmed, based on comparative analysis of a 60-day period after vaccination (for Cohort I) vs. the same time period after a visit to the HCO for any other reason (Cohort II). Accordingly, reactivation of the varicella-zoster virus appears to be a potential ADR to COVID-19 vaccines, at least for mRNA LNP-based formulations. This finding concurs with recent reports (cited in the Introduction), a significant difference being that the present work is on a broader scale (volume of cases and distributed internationally) vs. what was sampled in other recent reports. However, we cannot draw conclusions from our analysis of the vector-based (*vs* mRNA-based) vaccines, as only 1.51% of the subjects in Cohort I received Ad26.COV2.S.

Intriguingly, a generally increased incidence of herpes virus infections has been reported since the COVID-19 pandemic began.[42,43] The possibility has been raised that *herpesviridae* reactivation may be triggered by suppressive effects of SARS-CoV-2 on a host immune system; furthermore, pandemic-related psychological stress has been noted to potentially play a causal role, too.[31] On the other hand, vaccination against COVID-19 seems to potentially raise the risk of precipitating HZ. While the specific molecular mechanisms that cause VZV to reactivate remain unknown, certain risk factors have been identified—including stress, elevated age, usage of immunosuppressants, chemotherapy and radiotherapy. A unifying thread among these conditions is that they correspond to a decreased immune competence, in terms of immunoglobulins, CD4+ and CD8+ T lymphocytes and memory T cells.[44] In the context of the present

study, we note that innate- or cell-mediated immune failures, caused by a host's response to COVID-19 vaccination, have been raised as potentially causative factors for VZV reactivation.[38] Psichogiou *et al.* postulated a temporary incapacity of VZV-specific CD8+ T cells, allowing VZV to reactivate and thereby cause HZ.[25]

Both the probability of severe courses of disease, as well as the risks of the listed complications, are heightened with increasing age because of adaptive immunosenescence[45]; concerningly, immunosenescence has been found to be associated not only with an increased susceptibility to viral infections but also with a decreased response to vaccination[46]. This raises an issue that is a potentially beneficial source of information (on a patient-by-patient basis): those who show reactivation of VZV following COVID-19 immunization might have a lower protection rate against COVID-19. Furthermore, it may be worth considering whether vaccination for VZV, or even prophylactic use of nucleoside analogue drugs, could be applied in patients at high risk of VZV reactivation, especially for patients above the age of 60 years. Given all of the above, we reiterate that, on the balance, the general benefits of COVID-19 vaccination far outweigh potential risks for a vast preponderance of the population.

Beyond the constraints that are inherent to its retrospective nature (e.g. unavailability of a placebo arm/control cohorts), the study reported here is not without certain limitations; future work can seek to address these issues. For example, data on psycho-emotional stress levels, history of VZV vaccination and history of chickenpox could be highly valuable to include in this type of analysis. Similarly, data on the use of immunosuppressants or the presence of general diseases which cause

immunodeficiency (especially HIV infection), and histories of chemotherapy and/or radiotherapy were provided for a limited number of patients, but detailed background information was unavailable for inclusion in the present analysis. To overcome these limitations, future studies might consider using a standard prospective design (placebo-controlled, randomized, double-blinded) in order to both assess and extend the results reported here.

Acknowledgements

Data availability statement
Data available on request from the authors.

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