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REVIEW

The Impact of the COVID-19 Pandemic on the Incidence of Herpes Zoster: A Narrative Literature Review

Raunak Parikh · Mitra Yousefi · Desmond Curran · Robyn Widenmaier

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ABSTRACT

Coronavirus disease 2019 (COVID-19) has had a broad impact on health services and health outcomes. During the pandemic, there were numerous reports of herpes zoster (HZ) in people with COVID-19 and in COVID-19 vaccine recipients. The aim of this review is to elucidate the global effects of the COVID-19 pandemic on HZ. It is postulated that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection produces an immunosuppressive state that favours varicella zoster virus (VZV) reactivation. Three large cohort studies (a multinational study and studies from the USA and Spain) that excluded individuals vaccinated against HZ reported significantly increased risk of HZ following COVID-19 infection, especially in people aged ≥ 50 years. In contrast, a large study from Israel that did not consider HZ vaccination status reported no such increase. Cases of HZ following COVID-19 vaccination have been reported and may be the result of attenuated cell-mediated immunity. This phenomenon appears to vary by vaccine type. Some (but not all) large analyses have reported a significant positive relationship between receipt of mRNA vaccines for COVID-19 and development of HZ. These include analyses of health records databases in Israel and Hong Kong and of spontaneous case reports in the US Vaccine Adverse Event Reporting System (VAERS) database. Routine vaccinations, including shingles vaccine programmes, were disrupted by the COVID-19 pandemic. It is estimated that missed shingles vaccinations may have resulted in 63,117 avoidable HZ cases in the USA. Now that the World Health Organization has declared an end to the COVID-19 pandemic as a health emergency and routine vaccination services have resumed, there is a need to increase awareness of HZ and HZ vaccination.

Graphical abstract available for this article.

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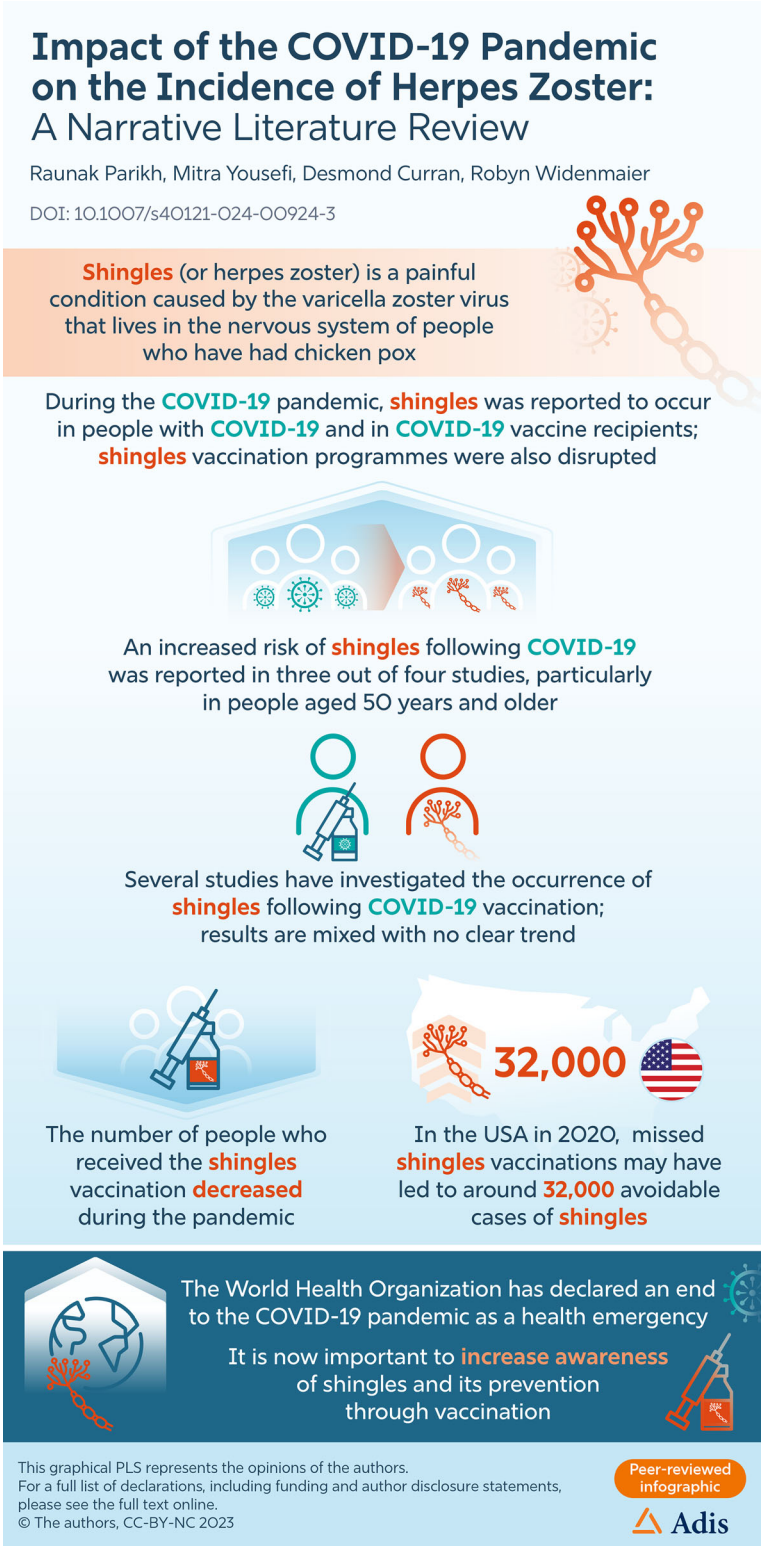
R. Parikh (✉) · D. Curran
GSK, Wavre, Belgium
e-mail: raunak.p.parikh@gsk.com

M. Yousefi · R. Widenmaier
GSK, Rockville, MD, USA

Graphical Abstract:



Keywords: COVID-19; Herpes zoster; Incidence; mRNA vaccine; SARS-CoV-2; Vaccination; Vaccine-preventable disease; Varicella zoster virus

Key Summary Points

During the COVID-19 pandemic, there were numerous reports of herpes zoster (HZ) in people with COVID-19 and in COVID-19 vaccine recipients.

Three large cohort studies that excluded individuals who had been vaccinated against HZ have reported an increased risk of HZ following COVID-19, especially in people aged ≥ 50 years; however, one study reported no such relationship, although the HZ vaccination status of study subjects was unknown.

Several studies have assessed the incidence of HZ following COVID-19 vaccination; some (but not all) studies reported that recipients of mRNA vaccines for COVID-19 were more likely to develop shingles than were control subjects who had not been vaccinated.

Routine vaccination programmes, including shingles vaccine programmes, were disrupted by the COVID-19 pandemic; however, now that the World Health Organization has declared an end to the COVID-19 pandemic as a health emergency, there is an important need to increase awareness of HZ and HZ vaccination.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.25273681

INTRODUCTION

Varicella zoster virus (VZV) results in two distinct diseases [1]. The primary infection, chicken pox, is a common self-limiting disease of childhood. During the primary infection, VZV migrates to sensory ganglia and enters a life-long latent phase [2]. Reactivation of latent VZV infection, usually decades after the primary infection, results in herpes zoster (HZ), which manifests as a painful vesicular rash with a dermatomal distribution. The most common complication of HZ is post-herpetic neuralgia, which persists after the acute episode. Other complications include ocular involvement, which can result in permanent impairment of vision, secondary bacterial cutaneous infections, nerve palsies and vasculopathies, such as transient stroke [3–6].

Reactivation of latent VZV infection is the result of decreased VZV-specific cell-mediated immunity; thus, major risk factors for development of HZ include increasing age and immunosuppression owing to disease or drug therapy [2]. The incidence of HZ appears to be increasing, although the reasons for this increase are not clear [7–9]. It is estimated that approximately 1 in 3 persons will experience HZ during their lifetime [1].

Coronavirus disease 2019 (COVID-19) has had a broad impact on health services and health outcomes. The substantial financial burden placed on health systems, the considerable psychosocial burden experienced by health professionals and the public, and the increase in morbidity and mortality rates are well known and have been widely discussed [10–12]. In contrast, the impact of COVID-19 on other vaccine-preventable diseases (VPDs) and on vaccination programmes in adults is not as well known. In addition to the direct impact of COVID-19, the pandemic affected the delivery of routine healthcare services, including vaccination. It is well established that the COVID-19 pandemic has disrupted routine childhood immunisation programmes [13–16], and the same is true for vaccines recommended for older adults [17].

At the same time, the onset of the COVID-19 pandemic led to a substantial decline in the incidence in adults of VPDs that are predominately spread via respiratory droplets (e.g. influenza and invasive pneumococcal disease [IPD]) [18–25]. These decreases are likely attributable to the widespread adoption of measures to interrupt the transmission of COVID-19, such as social distancing and mask-wearing, as they would be expected to prevent the transmission of other respiratory pathogens.

HZ is distinct from other VPDs in that the goal of vaccination is to prevent a disease that results from reactivation of latent infection rather than to prevent infection that results from transmission of a pathogen. Thus, in contrast to VPDs that are predominantly spread via the respiratory route/droplets in adults, social distancing would not be expected to reduce the incidence of HZ. There have been numerous reports of HZ in people with COVID-19 and after COVID-19 vaccination.

The aim of this review is to elucidate the global effects of the COVID-19 pandemic on HZ, including the impact of COVID-19 on the incidence of HZ, the impact of COVID-19 vaccination on the incidence of HZ and the impact of the COVID-19 pandemic on HZ vaccination rates.

METHODS

Searches of PubMed and Embase were performed on 25 April 2023 to identify papers and congress abstracts related to the incidence of HZ and its association with COVID-19 and vaccination.

The search string was ('herpes zoster'/exp OR 'herpes zoster') AND ('covid 19'/exp OR 'covid 19'). Papers and congress abstracts were manually reviewed to identify epidemiological studies that were relevant to the scope of this article. Reviews, case reports and case series were excluded.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Impact of COVID-19 on HZ

Evidence from Large Retrospective Database Studies

Three large retrospective cohort studies, including a multinational study and studies from the USA and Spain, have reported an increased risk of HZ following COVID-19 [26–28], whereas one further study from Israel has reported no increased risk of HZ following COVID-19 [29].

The multinational analysis included data from people aged ≥ 20 years with at least two healthcare visits documented between 1 January 2020 and 31 December 2021 in one of 74 healthcare organisations in four countries (USA, Brazil, Georgia and Taiwan) that were part of the TriNetX database, a global health research network [26, 30]. The analysis included a COVID-19 cohort that comprised 1,221,343 adults with confirmed COVID-19 and a control cohort that comprised 1,221,343 propensity-matched COVID-negative adults. The outcome of interest was the incidence of HZ between 3 and 12 months after the index date (all individuals had 12 months of follow-up data available). Importantly, the analysis excluded people who had previously received a zoster vaccine. During 1 year of follow-up, individuals in the COVID-19 cohort had a significantly higher risk of HZ (hazard ratio [HR] 1.59; 95% confidence interval [CI] 1.49–1.69 versus the control cohort). The risk of HZ was consistently higher in the COVID-19 cohort regardless of COVID-19 vaccination status, age, sex and the presence of certain comorbid medical conditions [26]. The risk of HZ was highest in people aged > 50 years (HR 1.77; 95% CI 1.64–1.91 versus the control cohort; Fig. 1) [26].

The two large retrospective cohort studies (one each from the USA and Spain) have reported a significant association between COVID-19 and HZ in people aged ≥ 50 years. Both studies excluded individuals who had previously received a vaccine against HZ or COVID-19 (Fig. 1) [27, 28]. The first of these studies included data from US commercial

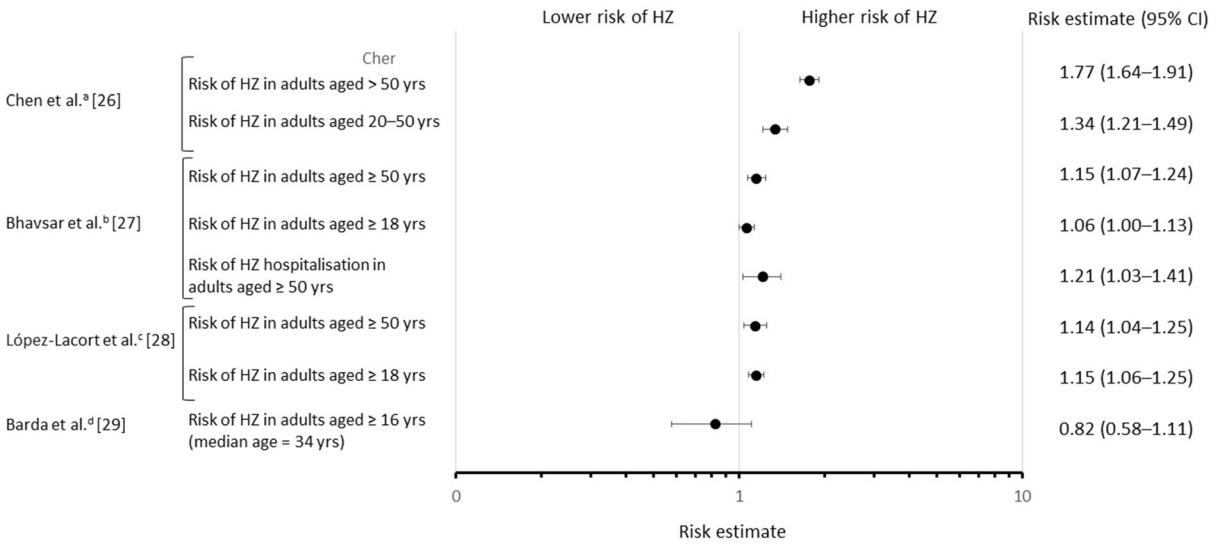


Fig. 1 Retrospective studies that have investigated associations between HZ following COVID-19. [a]Risk reported as hazard ratio; [b]risk reported as adjusted incidence rate ratio; [c]risk reported as adjusted relative risk; and [d]risk reported as risk ratio. *CI* confidence interval, *COVID-19* coronavirus disease 2019, *HZ* herpes zoster, *yrs* years

databases collected between March 2020 and February 2021 from 394,677 people with COVID-19 aged ≥ 50 years and 1,577,346 matched controls without COVID-19. A diagnosis of COVID-19 was associated with a 15% higher risk of developing HZ in individuals aged ≥ 50 years (adjusted incidence rate ratio [aIRR] 1.15; 95% CI 1.07–1.24; $p < 0.001$ versus controls without COVID-19; Fig. 1) [27]. The risk of developing HZ was significantly higher during the first 6 months after a COVID-19 diagnosis. Of note, the risk of developing HZ was not increased in individuals aged 18–49 years who had COVID-19 compared with those who did not (aIRR 0.89; 95% CI 0.79–1.01; $p = 0.07$) [27].

While none of the mentioned studies evaluated HZ risk based on the severity of COVID-19, Bhavsar et al. [27] did assess the incidence of HZ in patients aged ≥ 50 years who were hospitalised for COVID-19. This analysis showed that the differential risk was more pronounced in the adults who were hospitalised with COVID-19 compared with matched controls without COVID-19 (aIRR 1.21; 95% CI 1.03–1.41; $p = 0.02$) [27].

The large retrospective Spanish cohort study reported findings consistent with the USA study [27] by analysing data contained in the Valencia Healthcare Integrated Databases for the period November 2020 to October 2021 [28]. The cohort comprised 2,087,232 people aged ≥ 50 years, among whom 139,863 (6.70%) had confirmed COVID-19. A total of 555 and 10,156 cases of HZ occurred among individuals with and without COVID-19, respectively, which translates into incidence rates of 10.16 (95% CI 9.33–11.04) and 9.2 (95% CI 9.02–9.38) per 1000 person-years. The adjusted relative risk (aRR) of HZ in individuals with confirmed COVID-19 was 1.14 (95% CI 1.04–1.25; $p = 0.006$) [28]. A sensitivity analysis showed a similar risk in people aged ≥ 18 years (aRR 1.15; 95% CI 1.06–1.25). The risk of HZ was higher in women than in men and also increased with age, being 61%, 93% and 109% higher in people aged 60–69, 70–79 and ≥ 80 years compared with those aged 50–59 years. The risk of HZ was also higher in individuals with comorbid medical conditions than in those without [28].

In contrast to the above studies showing a positive association between COVID-19 and HZ, an analysis of a large Israeli database reported no increase in the risk of HZ in individuals who had tested positive for COVID-19 versus those who had tested negative. The analysis included

people with COVID-19 and matched controls without COVID-19 (median age [interquartile range] 34 years [24–47]). In 175,693 people in the HZ cohort, COVID-19 infection did not significantly increase the risk of HZ (relative risk [RR] 0.82; 95% CI 0.58–1.11; Fig. 1) [29]. This finding remained consistent when the analysis was stratified by age and sex, although the number of events was small in each stratum [31]. The HZ vaccination status of individuals included in this study is unknown.

Other Evidence

A cross-sectional analysis that included 889 adults with COVID-19 in the University of Florida patient registry also showed a significant relationship between COVID-19 and HZ when compared with adults with HZ alone (unadjusted odds ratio 5.26; 95% CI 3.10–8.93; $p < 0.001$) [32]. The prevalence of VZV infection in people with COVID-19 was 1.8% compared with the prevalence of VZV infection in the overall hospital population without COVID (0.43%). The difference remained significant after adjustment for sex, age, race and certain comorbidities (including endocrine disease, diabetes, neurological disease and circulatory disease) [32]. The 16 adults with COVID-19 and HZ were aged 45–74 years, 12 of whom were aged $\geq$ 55 years [32].

Further evidence comes from an analysis of data from the Brazilian Ministry of Health public database that demonstrated an increase in the number of HZ diagnoses during the COVID-19 pandemic. Specifically, there was a 35% increase in HZ diagnoses (crude reported rates) between March and August 2020 and a 53% increase between September 2020 and February 2020 when compared with the same periods in 2017–2019 [33, 34]. However, this should be interpreted with caution as the studies did not include an assessment of an association with COVID-19 disease or test results.

Impact of COVID-19 Vaccination on HZ

There are conflicting data on the risk of HZ after COVID-19 vaccination, including variation by vaccine type, as detailed below and shown in Fig. 2. For this reason, results are presented by vaccine type.

mRNA COVID-19 Vaccines

Several large retrospective analyses have reported a positive relationship between receipt of mRNA vaccines for COVID-19 and development of HZ. A retrospective analysis of a large Israeli database showed that the incidence of HZ increased significantly in 888,647 recent recipients of the BNT162b2 mRNA vaccine when compared with 888,647 unvaccinated individuals. Receipt of BNT162b2 was associated with a 43% higher risk of developing HZ within the first 42 days post vaccination (RR 1.43; 95% CI 1.20–1.73; risk difference 15.8 events per 100,000 individuals; 95% CI 8.2–24.2) [29], although the number of events in each stratum was low [31]. As noted above, the HZ vaccination status of individuals included in this analysis is unknown.

A retrospective population-based analysis using electronic health records in Hong Kong found an association between receipt of the BNT162b2 vaccine and HZ [35]. The study used a self-controlled case series (SCCS) as a main analysis and a nested case–control analysis as a confirmatory method. The analysis included 1,957,612 and 1,451,858 people who received first and second doses of BNT162b2, respectively, of whom 47 individuals were hospitalised with HZ between 23 February and 31 July 2021. HZ was documented in 454 unvaccinated individuals during the same period. The SCCS analysis showed that receipt of BNT162b2 vaccine was associated with a significantly increased risk of HZ-related hospitalisation after both doses in the series (0–13 days after the first dose: aIRR 5.23; 95% CI 1.61–17.03; 14–27 days after the first dose: aIRR 5.82; 95% CI 1.62–20.91; 0–13 days after the second dose: aIRR 5.14; 95% CI 1.29–20.47). In the nested case–control analysis, HZ-related hospitalisations were significantly higher after receipt of the first dose of BNT162b2 (0–13 days after the first dose: adjusted odds ratio [aOR] 2.60; 95% CI 1.29–5.25; 14–27 days after the first dose: aOR 3.93; 95% CI 1.50–10.26) but not after the second dose (0–13 days after the second dose: aOR 2.01; 95% CI 0.84–4.77;

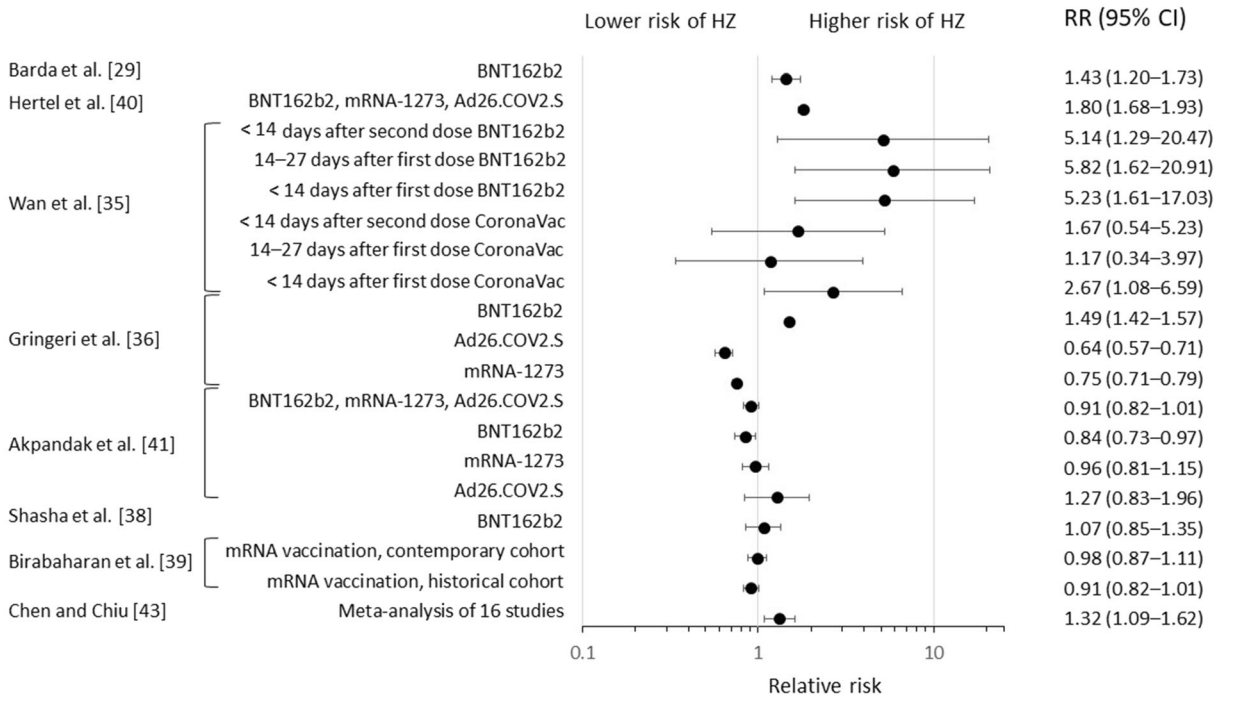


Fig. 2 Retrospective studies that have investigated associations between HZ following COVID-19 vaccination. *CI* confidence interval, *COVID-19* coronavirus disease 2019, *HZ* herpes zoster, *RR* relative risk

14–27 days after the second dose: aOR 0.70; 95% CI 0.16–3.14) [35].

A nested case–control analysis of the US Vaccine Adverse Event Reporting System (VAERS) database also showed that there was a higher risk of HZ following receipt of BNT162b2 [36]. This analysis included all individual case safety reports (ICSRs) submitted to the VAERS up to 3 December 2021 for an approved mRNA-based COVID-19 vaccine (including BNT162b2 and mRNA-1273). Among a total of 588,323 ICSRs that were included in the analysis, 5611 cases of HZ were associated with mRNA vaccines (BNT162b2, n = 3263; mRNA-1273, n = 2348). A disproportionality analysis showed a significantly higher reporting odds ratio (ROR) for developing HZ after receipt of BNT162b2 (1.49; 95% CI 1.42–1.57), but not after receipt of mRNA-1273 (ROR 0.75; 95% CI 0.71–0.79) [36]. Considering the total number of doses of BNT162b2 administered in the USA between 13 December 2020 and 3 December 2021 (N = 548,578,240), the vaccine-associated HZ incidence was estimated to be 0.59 cases per 100,000 doses.

A comparative analysis that matched US veterans who had received either BNT162b2 (n = 216,836) or mRNA-1273 (n = 216,836) showed that the incidence of HZ or herpes simplex within 38 weeks was similar in recipients of the two vaccines (43.2 events per 10,000 persons after receipt of BNT162b2; 95% CI 39.2–47.1; versus 41.4 events per 10,000 persons after receipt of mRNA-1273; 95% CI 37.7–44.9) [37]. The absence of a control group prevents any conclusion regarding the impact of vaccination on the relative incidence of HZ.

Despite some studies showing an increased risk of HZ in recipients of BNT162b2, other analyses have not demonstrated a similar association. A retrospective analysis of a database for a health maintenance organisation containing records for 1.2 million Israeli citizens found no significant association between BNT162b2 and HZ among enrollees who were vaccinated between 19 December 2020 and 12 February 2021 [38]. The analysis matched the records of 233,159 BNT162b2 recipients with unvaccinated recipients, among whom 151 and 141 cases of HZ were reported during the study

period, respectively (RR 1.07; 95% CI 0.85–1.35).

A study that utilised the TriNetX Global Health Research Network did not find an increase in risk of HZ among enrollees who had received an mRNA COVID-19 vaccine within 28 days compared with matched cohorts of unvaccinated individuals diagnosed with common dermatological conditions before (n = 555,256; RR 0.91; 95% CI 0.82–1.01) and after (n = 359,789; RR 0.98; 95% CI 0.87–1.11) the availability of COVID-19 vaccines [39].

Other Vaccines

In the study from Hong Kong described above, receipt of CoronaVac (an inactivated whole-virion vaccine) was also significantly associated with an increased risk of HZ-related hospitalisation [35]. A total of 1,269,574 and 982,255 people received first and second doses of CoronaVac, respectively, among whom 44 individuals were hospitalised with HZ after receiving the vaccine. The SCCS analysis showed that there was a significantly increased risk of HZ-related hospitalisation within 14 days after receipt of the first dose of CoronaVac (aIRR 2.67; 95% CI 1.08–6.59). This finding was confirmed in the nested case–control analysis (aOR 3.44; 95% CI 1.56–7.56).

The nested case–control analysis of the US VAERS database included, in addition to the cases of HZ after receipt of mRNA vaccines (described above), a small number of cases of HZ after receipt of the Ad26.COV2.S viral vector vaccine (n = 323/5934 cases overall, 5.4%) [36]. The disproportionality analysis showed that there was no significant increase in the ROR for HZ after receipt of Ad26.COV2.S (ROR 0.64; 95% CI 0.57–0.71).

Studies with Multiple Vaccine Types

Some studies have analysed outcomes for combinations of more than one type of vaccine. The risk of developing HZ was significantly higher in COVID-19 vaccine recipients than in unvaccinated individuals in a study that matched individuals 1:1 by age and sex (RR 1.80; 95% CI 1.68–1.93) [40]. It is likely that these results were driven by mRNA vaccines as only a small number of individuals received the Ad26.COV2.S viral vector vaccine (BNT162b2, 88.6%; mRNA-1273, 9.9%; Ad26.COV2.S, 1.5%). This analysis used data from 1,095,086 COVID-19 vaccine recipients and 16,966,018 unvaccinated individuals in the TriNetX Global Health Research Network [40].

No association between COVID-19 vaccination and HZ was observed in an analysis of data from a total of 2,039,854 enrollees in a US commercial claims database who received any dose of a COVID-19 vaccine (BNT162b2, 55.8%; mRNA-1273, 40.8%; or Ad26.COV2.S, 3.4%) from 11 December 2020 to 30 June 2021 [41]. The self-controlled risk analysis compared HZ incidence rates occurring 30 days after COVID-19 vaccination with those occurring after receipt of a previous non-COVID vaccine (n = 1451). The overall incidence rate ratio for HZ during the risk interval after COVID-19 vaccination versus the control interval was 0.91 (95% CI 0.82–1.01; p = 0.08) [41].

Similarly, no statistically significant difference was observed in the frequency of HZ diagnosed in the 3 months before (n = 716) or after vaccination (n = 781; p = 0.093) in an analysis of data from 596,111 individuals who received at least one COVID-19 vaccine (either an mRNA or a viral vector vaccine) between 12 January 2020 and 30 September 2021 within the New York University Langone Health system [42].

Meta-Analyses

A comprehensive meta-analysis of 16 cohort, case–control and randomised controlled studies showed that COVID-19 vaccination was associated with a significantly increased risk of HZ (odds ratio [OR] 1.32; 95% CI 1.09–1.62) when compared with controls and that receipt of an mRNA-based vaccine was associated with a higher risk of HZ compared with the adenovirus-based vaccine (OR 1.67; 95% CI 1.19–2.35) [43]. An earlier meta-analysis that included data from just three studies concluded that COVID-19 vaccination did not increase the risk of HZ (RR 1.06; 95% CI 0.91–1.24) [44].

Other Findings

Several studies, including pharmacovigilance studies, have reported associations between HZ and receipt of COVID-19 vaccinations; however, owing to a lack of comparative data in unvaccinated individuals, no comment can be made on whether HZ occurred at a higher rate than that in unvaccinated individuals.

When compared with influenza vaccine, mRNA-based COVID-19 vaccines were associated with a significantly higher incidence of HZ (ROR 1.9; 95% CI 1.8–2.1) in an analysis of 716,928 reports submitted to the World Health Organization (WHO) database of spontaneous safety reports (VigiBase) up to 30 June 2021 [45]. This analysis found a reduced risk of HZ reporting among individuals aged ≤ 40 years when compared with older individuals (ROR 0.39; 95% CI 0.36–0.41).

Several pharmacovigilance studies have reported dermatological reactions, including HZ, after receipt of COVID-19 vaccination. Approximately 10% (n = 41/405) of dermatological reactions occurring within 21 days of receipt of any COVID-19 vaccination (BNT162b2, 40.2%; mRNA-1273, 36.3%; AZD1222, 23.5%) were attributable to HZ according to a nationwide, multicentre, observational study endorsed by the Spanish Academy of Dermatology [46]. HZ was also the most common cause of sick leave after COVID-19 vaccination (25.9%; n = 15/58 cases) [46]. Of note, 34/41 cases of HZ occurred in individuals who received an mRNA vaccine, whereas 7/41 cases occurred following receipt of the AZD1222 viral vector vaccine [46]. Low incidences of HZ have been reported in smaller analyses of dermatological reactions in an international COVID-19 dermatology registry (0.5%, n = 4/803 [47] and 2.4%, n = 10/414 [48]) as well as in a multicentre Turkish study (4.4%, n = 8/183) [49].

Some analyses have reported an association between vaccination against COVID-19 and HZ ophthalmicus (HZO) [50–53]. Of note, the VAERS database received 983 and 180 reports of COVID-19-associated HZO and herpes simplex ophthalmicus, respectively, between 11 December 2020 and 1 July 2022 [53]. A majority of cases of HZO (61.3%) occurred within 2 weeks of vaccination. On the basis of these reports, the incidence of HZO and herpes simplex ophthalmicus in the USA was estimated to be 0.25, 0.22 and 0.47 cases per million doses for BNT162b2, mRNA-1273 and Ad26.COV2.S, respectively [53].

Trends in the Uptake of HZ Vaccines during the COVID-19 Pandemic

Routine vaccinations were disrupted by the COVID-19 pandemic. In the case of recombinant zoster vaccine (RZV), this is evidenced by comparing vaccination rates among US Medicare beneficiaries aged ≥ 65 years in 2020, after the onset of the pandemic, with vaccination rates during the same weeks in 2019, before the onset of the pandemic. Thus, when compared with 2019 data, an immediate 62% decrease in RZV vaccination rates was observed during the first week after the national declaration of the pandemic (13 March 2020), and a nadir of 89% below 2019 levels occurred from 12–18 April 2020 before rebounding to a rate that was 43% below 2019 levels during the week of 12 July 2020 [54]. The potential impact of this decrease in vaccination rates on HZ cases and complications was estimated by using a Markov model with the assumption that there was an overall 43% reduction in RZV use between April and December 2020 (i.e. 3.9 million persons missed initiating the RZV series). In 2020, the interruption in vaccination may have resulted in 31,945 avoidable HZ cases and 2714 cases of post-herpetic neuralgia [55]. These results highlight the potential impact of the pandemic on routine RZV vaccination, especially if a high proportion of individuals remained unvaccinated throughout 2020, although the impact would have been lower if actual vaccination rates continued to increase between July and December 2020. As such the hypothetical scenarios investigated in the model, including the estimated proportion of individuals remaining unvaccinated, may not have occurred in reality.

DISCUSSION

The epidemiological pattern of infectious diseases changed during the COVID-19 pandemic. The published evidence suggests that diseases that result from pathogens transmitted by aerosol transmission (e.g. influenza and IPD) occurred less frequently during compared with before the COVID-19 pandemic, likely as the result of COVID-19 preventative measures, such as social distancing and mask-wearing. However, unlike that of other adult VPDs, the rate of HZ during the COVID-19 pandemic remained stable or increased. Reasons for this include the likelihood that social distancing measures did not affect HZ, which occurs due to reactivation of latent VZV infection. The pandemic itself may have increased the incidence of HZ owing to the physical and emotional stress associated with the unprecedented circumstances of a global pandemic, and the COVID-19 disease itself may have increased the risk for HZ by an as yet undetermined mechanism [56, 57]

Important risk factors for the reactivation of latent VZV infection include increasing age and immune suppression owing to disease or drug therapy [4]. The results of the current review suggest that COVID-19 itself may cause a modest increase in the risk of HZ, as demonstrated in three large studies, especially in individuals aged $\geq$ 50 years and in those with comorbid conditions [26–28]. In contrast, a large study from Israel found no increase in the risk of HZ in individuals who had contracted COVID-19; however, the median age of individuals included in this analysis was 34 years, the number of cases of HZ was comparatively low, HZ vaccine status was not considered in the analysis and the duration of follow-up (42 days) was shorter than that in other studies [29]. Database studies, such as these, are subject to confounding. For example, there is no way to verify that matched controls in a database study have not previously contracted COVID-19. Such controls may have had COVID-19 but may not have been tested, either because the disease was mild or because the person was not hospitalised. Such mild, unreported cases may influence the results of such analyses.

There is some evidence to suggest that COVID-19 vaccination is associated with HZ, although there is no clear pattern across the different vaccine types and no causal association has been established. Pharmacovigilance studies have reported HZ after receipt of COVID-19 mRNA vaccines; however, this type of report does not include a comparator and, therefore, provides no evidence of causation. Several large-scale epidemiological analyses [29, 35, 36, 40] and a meta-analysis of 16 controlled studies [43] have reported a significant increase in the risk of HZ after exposure to COVID-19 vaccines, in particular after receipt of BNT162b2. It must be noted, however, that other large analyses have found no such association, particularly for non-mRNA-containing vaccines [36, 38, 39, 41]. Whether these between-study differences are influenced by differences in the age structure, number of HZ cases or HZ vaccination status is unclear. Moreover, it must be emphasised that the possible association between COVID-19 vaccination and HZ should not dissuade people from receiving COVID-19 vaccination, which significantly decreases the risk of hospitalisation, severe disease and death due to COVID-19, especially in elderly people [58, 59].

Another potential cause of increased rates of HZ during the COVID-19 pandemic is missed vaccination opportunities. The US Centers for Disease Control and Prevention recently reported that single dose coverage with any HZ vaccine among adults aged $\geq$ 50 years was slightly higher in 2021 (32.6%) when compared with 2020 (29.4%) [60]. However, the report did not include estimates of the impact of the pandemic on routine vaccination rates or the expected vaccine coverage had the COVID-19 pandemic not occurred. While vaccination rates may have increased since the nadir in April 2020, a 43% decrease in vaccination rates between 2019 and 2020 [54] (an assumption included in the Markov model of Curran et al. [55]) would have resulted in approximately 32,000 avoidable HZ cases in 2020, highlighting the potential impact of missed vaccinations. This reinforces the importance of routine vaccination of adults against HZ and other VPDs in counterbalancing age-related dysregulation, the decline of the

immune system in older age (i.e. immunosenescence) and the negative impact of comorbidities on the risk of serious illness [61, 62].

Until recently, the COVID-19 pandemic led to the prioritisation of healthcare services directed towards SARS-CoV-2 care, often at the expense of routine medical services, including vaccination. Now that the WHO has declared an end to the COVID-19 pandemic as a health emergency [63] and routine vaccination services have resumed, there is a need to focus on increasing coverage for recommended vaccines. Targeted catch-up strategies, for example, during regular preventative care visits, may be considered, especially in older adults [64]. Thus, vaccination of adults should be a priority for healthcare professionals.

CONCLUSIONS

Emerging data suggest that the COVID-19 pandemic may have increased the risk of HZ and negatively impacted HZ vaccine uptake. Therefore, there is an important need to increase awareness of HZ and HZ vaccination following the COVID-19 pandemic.

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Declarations

Conflict of Interest. Raunak Parikh, Mitra Yousefi, Desmond Curran and Robyn Widenmaier are employees of GSK. Raunak Parikh and Robyn Widenmaier hold stock/stock options in GSK.

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