**Short Communication**

**Association study between herpes zoster reporting and mRNA COVID-19 vaccines (BNT162b2 and mRNA-1273)**

**Running title: Herpes zoster and mRNA COVID-19 vaccines**

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**What is already known about this subject**

* Several cases of herpes zoster (HZ) following mRNA COVID-19 vaccination have been reported
* First epidemiological evidences suggest an increased risk of HZ after mRNA COVID-19 vaccination
* HZ infection characteristics are not known so far and this risk has not yet been assessed at a global level

**What this study adds**

* HZ may occur shortly after mRNA COVID-19 vaccination, at higher frequency than reported with influenza vaccination
* This risk of HZ reporting was reduced among under 40-year-old persons compared to older
* HZ reactions following mRNA COVID-19 vaccination remain usually mild and rare as mirrored to the billions doses administered so far

**Abstract**

Several cases of herpes zoster (HZ) following mRNA COVID-19 vaccination (BNT162b2 and mRNA-1273) have been reported, and first epidemiological evidences suggest an increased risk.

We used the worldwide pharmacovigilance database VigiBase to describe HZ cases following mRNA COVID-19 vaccination. We performed disproportionality analyses (case/non-case statistical approach) to assess the relative risk of HZ reporting in mRNA COVID-19 vaccine recipients compared to influenza vaccine recipients and according to patient age.

Until 30th June 2021, of 716,928 reports about mRNA COVID-19 vaccines, we found 7,728 HZ cases. When compared to influenza vaccines, mRNA COVID-19 vaccines were associated with a significantly higher reporting of HZ (reporting odds-ratio 1.9, 95%CI [1.8-2.1]). Furthermore, we found a reduced risk of reporting HZ among under 40 year-old persons compared to older persons (reporting odds-ratio 0.39, 95%CI [0.36-0.41]).

For the first time, we could assess at a global level the risk of HZ after mRNA COVID-19 vaccination.

**Introduction**

Vaccination is the cornerstone of coronavirus disease-19 (COVID-19) prevention. Two mRNA vaccines, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), have been approved. (1,2). Although these vaccines have a very good safety profile, post-marketing monitoring is key during mass immunizations (3). Several cases of herpes zoster (HZ) following mRNA COVID-19 vaccination have been reported (4–6). A safety signal has been raised by the French National Medicine Agency (ANSM) in March 2021 (<https://ansm.sante.fr/actualites/point-de-situation-sur-la-surveillance-des-vaccins-contre-la-covid-19-9>). An increased risk of HZ infection have been observed in BNT162b2 mRNA vaccine recipients, while infection characteristics are not known so far (7). The aim of this analysis was to describe HZ cases following mRNA COVID-19 vaccination at a global level, and to appraise this risk.

**Methods**

We used VigiBase (<https://www.who-umc.org/vigibase/vigibase/>), the WHO global individual case safety report database, which contains about 27 million spontaneous reports of suspected adverse drug reactions collected by national drug authorities in more than 130 countries. This unique database provides a powerful tool to assess relative risk of adverse effect usingdisproportionality analyses (8)*.* This pharmacovigilance statistical approach, also called case/non-case study, is similar to case–control study nested in a large cohort and estimates the differential proportion of a specific adverse drug reaction reported in a specific group (e.g. according to drug exposure or patient age) with the proportion of the same adverse drug reaction for a control group. The association is expressed using the Reporting Odds Ratio (ROR) and its 95% confidence interval (CI), which is similar in concept to the odds ratio in case-control studies.

Cases are reports registered in VigiBase up to June 30th, 2021 containing a HZ reaction with BNT162b2 or mRNA-1273, identified using ad-hoc terms from the Medical Dictionary for Regulatory Activities (**Table S1**), whereas non-cases are reports including all other adverse reactions with these vaccines. Cases were categorized by clinical presentation, such as skin rash, herpes zoster ophtalmicus and oticus, and central nervous system (CNS) injuries. First disproportionality analysis was to assess the risk of HZ reporting compared to influenza vaccine (J07BB using the Anatomical Therapeutic Chemical Classification System) recipients, given the similarity of the vaccine recipients, especially in the first months of the campaign in early 2021. Second, disproportionality analysis was to assess a possible increased risk of HZ reporting in people under 40 year-old compared to older people, among mRNA COVID-19 vaccine recipients. We further performed sensitivity analyses, by restricting our disproportionality analysis to serious cases only and to cases reported by healthcare professionals.

**Results**

Of 26,246,383 reports, 716,928 reports concerned mRNA COVID-19 vaccines, among which we observed 5,931 HZ cases with BNT162b2 and 1,797 with mRNA-1273 (**Table 1**). Of these 7,728 cases, 5,135 (66.4%) concerned female patients. Median (IQR) age was 59.1 (46-72) years. A mRNA COVID-19 vaccine was the only suspected drug in all except 62 (0.8%) cases. Most cases (7,494, 97.0%) were skin rash, with a median time to onset of 7 (2-15) days and requiring hospitalization in 173/7,494 (2.3%). Herpes zoster ophtalmicus and oticus involved respectively 197 (2.5%) and 60 (0.8%) cases. Central nervous system involvement, such as meningitis, meningoencephalitis or meningoradiculitis accounted for 0.3% of cases for each mRNA vaccine. The time to onset was 17.5 (12.5-29) days following vaccination in this setting, with 14 (56%) vaccine recipients requiring hospitalization. No HZ-related death was reported.

When compared with influenza vaccines, mRNA COVID-19 vaccines were associated with an increased HZ reporting for BNT162b2 (ROR 95%CI, 2.0 [1.8-2.2]), mRNA-1273 (ROR 95%CI, 1.5 [1.2-1.8]) and overall (ROR 95%CI, 1.9 [1.8-2.1]) (**Table 2**). Furthermore, among mRNA COVID-19 recipients, we found a reduced risk of reporting HZ among under 40 year-old persons compared to older persons (ROR 95%CI, 0.39 [0.36-0.41]) (**Table 2**). These results were consistent with further sensitivity analyses restricted to serious reports and to reports originating from a healthcare provider (**Table S2, Table S3**). Finally, we also found a slightly increased in HZ reporting for BNT162b2 compared to mRNA-1273, however not being confirmed by our sensitivity analyses (**Table S4**).

**Discussion**

Our study first describes the occurrence of HZ after mRNA COVID-19 vaccination at a global level and evidence an increased relative risk of HZ reporting in mRNA COVID-19 vaccine recipients as compared to influenza vaccine recipients. Furthermore, as expected acknowledging the classical epidemiology of HZ reactions, this risk was reduced in patients under 40 year-old. HZ reactions were mostly skin rash, and occurred at all age groups. Time to HZ onset following mRNA COVID-19 vaccination of one week after injection seems to be similar to that of HZ occurring as a consequence of COVID-19 infection (9). Some cases of CNS injuries were also observed with a later onset and noteworthy no fatal outcome were reported. A significant different risk for HZ reporting between BNT162b2 and mRNA-1273 appears unlikely.

Herpes zoster (HZ) may occur in patients previously infected with varicella-zoster virus, especially in patients with cellular immune defects or older people (10). It mainly presents as shingles, cranial nerve palsy, meningitis, myelitis, retinitis, or hepatitis. Recently, Barda et al. found an excess of HZ infection of 15.8 (from 8.2 to 24.2) events per 100,000 persons during the 21 days following BNT162b2 vaccination compared to non-vaccinated people (7). This national study did not bring detailed description of HZ cases. Our study shows that patients were younger in vaccine-associated HZ as compared to HZ in general population, suggesting a specific pathophysiology, although we did not find an increased risk in people under 40 years. Mechanisms involved in post-vaccination HZ are not fully understood but might imply toll-like receptors (TLRs) 3 and 7 stimulation by mRNA vaccines (11,12) as discussed by others (4). Noteworthy, other neurological disorders have been reported following COVID-19 vaccination such facial-nerve palsy (13). The hypothesis of a mechanism involving Type I interferons has been discussed with a possible role of HZ infection as potential trigger for facial palsy (7,14).

Several limitations must be acknowledged. First, VigiBase is based on spontaneous reports, which will likely feature under-reporting of total real-world cases and variable data quality, all of which are inherent to any pharmacovigilance system. However, VigiBase, covering more than 90% of the world’s population, provides a unique opportunity to analyze rare adverse events at a global scale. Furthermore, disproportionality analysis on VigiBase has proven its value in detecting increased risk of events. Their estimates correlate well with relative risks calculated from meta-analyses of the same intervention (8). Second, disproportionality studies are subject to notoriety bias and to residual confounders. To address these issues, we restricted the study period to a time frame that limited these biases, and selected an active comparator based on influenza vaccine recipients (15). Last, the available data did not allow us to investigate whether the risk of HZ was greater after the first or second dose of vaccine.

Overall, our study shows that HZ may occur shortly after mRNA COVID-19 vaccination, at higher frequency than reported with influenza vaccination. HZ reactions following mRNA COVID-19 vaccination remain usually mild, without reported case-related mortality, and rare as mirrored to the billions doses administered so far. Further clinical data are needed to confirm this signal, that should not hamper the use of mRNA COVID-19 vaccines, whose benefits dramatically overweight this risk.

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**Ethical approval information and data sharing statement:** Vigibase is a fully anonymized database of spontaneous reports from WHO, access is granted for national or regional pharmacovigilance centers, as our team. The information within VigiBase, the WHO global pharmacovigilance database, comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases. The present analysis does not represent the opinion of the UMC or the World Health Organization and only reflects the authors opinion.

**Author Contributions**

Concept and design: Préta, Contejean, Chouchana

Acquisition, analysis, or interpretation of data: Préta, Contejean, Chouchana

Drafting of the manuscript: Préta, Contejean

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**Table 1. Characteristics of herpes zoster cases reported with mRNA COVID-19 vaccines in the WHO global safety database**

|  |  |  |  |
| --- | --- | --- | --- |
| **Reporting characteristics** | **BNT162b2 (n=5931)** | **mRNA-1273 (n=1797)** | **Overall**  **(n=7728)** |
| Continent of reporting  Africa  Asia-Oceania  Europe  North America  South America | 13 (0.2%)  112 (1.9%)  3616 (61.0%)  2173 (36.6%)  17 (0.3%) | -  1 (0.1%)  358 (19.9%)  1438 (80.0%)  - | 13 (0.2%)  113 (1.5%)  3974 (51.4%)  3611 (46.7%)  17 (0.2%) |
| Type of reporter  Pharmacist  Physician  Other health professional  Consumer  Unknown | 162 (2.7%)  1431 (24.1%)  252 (4.2%)  1869 (32.5%)  2217 (37.4%) | 19 (1.1%)  192 (10.7%)  5 (0.3%)  144 (8.0%)  1437 (80.0%) | 181 (2.3%)  1623 (21.0%)  257 (3.3%)  2013 (26.0%)  3654 (47.3%) |
| Sex – female | 3903 (65.8%) | 1232 (68.6%) | 5135 (66.4%) |
| Age – years | 59.7 (46-73) | 57.0 (44-70) | 59.1 (46-72) |
| Age – ranges  < 12 years  12 - 17 years  18 - 39 years  40 - 64 years  65 - 74 years  ≥ 75 years  Unknown | 10 (0.2%)  13 (0.2%)  831 (14.0%)  2230 (37.6%)  1188 (20.0%)  1200 (20.2%)  459 (7.7%) | -  1 (0.1%)  312 (17.4%)  780 (43.4%)  374 (20.8%)  288 (16.0%)  42 (2.3%) | 10 (0.1%)  14 (0.2%)  1143 (14.8%)  3010 (38.9%)  1562 (20.2%)  1488 (19.3%)  501 (6.5%) |
| Type of injury: skin rash\*  Age - years  Time to reaction onset – days  Requiring hospitalization | 5733 (96.6%)  61 (46-73)  7 (2-14)  131 (2.3%) | 1761 (98.0%)  57 (44-70)  7 (2-16)  42 (2.4%) | 7494 (97.0%)  60 (45-72)  7 (2-15)  173 (2.3%) |
| Type of injury: ophtalmicus  Age - years  Time to reaction onset – days  Requiring hospitalization | 165 (2.8%)  68 (56-78)  8 (2.75-15)  21 (12.7%) | 32 (1.8%)  69 (56.5-75.5)  4 (2-13.8)  2 (6.0%) | 197 (2.5%)  68 (56-77.5)  7 (2-14.75)  23 (11.7%) |
| Type of injury: oticus  Age - years  Time to reaction onset – days  Requiring hospitalization | 47 (0.8%)  57 (44.5-66.5)  5 (2-12)  6 (12.8%) | 13 (0.7%)  47 (40-59)  3 (1-11)  - | 60 (0.8%)  57 (41.75-66.25)  4 (1.75-11.75)  6 (10%) |
| Type of injury: central nervous system  *Meningitis*  *Meningoencephalitis*  *Meningoradiculitis*  *Unspecified neurological infection*  Age - years  Time to reaction onset – days  Requiring hospitalization | 19 (0.3%)  *9 (47.4%)*  *5 (26.3%)*  *2 (10.5%)*  *3 (15.8%)*  65 (55-78)  18 (2.5-30)  11 (57.9%) | 6 (0.3%)  *3 (50%)*  *2 (33.3%)*  *-*  *1 (16.7%)*  47.5 (33-72.5)  17 (13-21)  3 (50%) | 25 (0.3%)  *12 (48%)*  *7 (28%)*  *2 (8%)*  *4 (16%)*  65 (47-77)  17.5 (12.5-29)  14 (56%) |
| Cases with another suspected reported drug | 45 (0.8%) | 17 (0.9%) | 62 (0.8%) |
| Month of reporting  December  January  February  March  April  May  June | 5 (0.1%)  151 (2.5%)  370 (6.2%)  542 (9.1%)  728 (12.3%)  1680 (28.3%)  2455 (41.4%) | 0  5 (0.3%)  24 (1.3%)  86 (4.8%)  129 (7.2%)  660 (36.7%)  893 (46.7%) | 5 (0.1%)  156 (2.0%)  394 (5.1%)  628 (8.1%)  857 (11.1%)  2340 (30.3%)  3348 (43.3%) |

*Footnote:* Data are presented as N (%) or median (IQR)

As patients could develop more than one type of lesion, the number of type of injury exceed the number of cases

\* including seven genital injuries for BNT162b2 and none for mRNA-1273.

**Table 2. Herpes zoster reporting and Reporting Odds Ratios for mRNA COVID-19 vaccines within the WHO global safety database**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Cases** | **Non-cases** | **ROR [95% CI]** |
| **First analysis - compare to influenza vaccines** | | | |
| **Both mRNA COVID-19 vaccine recipients** | 1449 | 228,489 | 1.9 [1.8-2.1] |
| **BNT162b2 recipients** | 1292 | 196,365 | 2.0 [1.8-2.2] |
| **mRNA-1273 recipients** | 157 | 32,124 | 1.5 [1.2-1.8] |
| **Influenza vaccine recipients** | 665 | 201,452 | ref |
| **Second analysis - according to age** | | | |
| **≤ 40 years mRNA COVID-19 vaccine recipients** | 1262 | 233,937 | 0.39 [0.36-0.41] |
| **> 40 years mRNA COVID-19 vaccine recipients** | 5964 | 431,063 | ref |

*Abbreviations:* ROR: Reporting Odds-Ratio, 95% CI: 95% confidence interval.

*Footnote:* Cases are reports containing a herpes zoster reaction (Table S1), whereas non-cases are reports including all other adverse reaction with these vaccines. ROR [95% CI] are calculated as ROR= , where *a* is the number of herpes zoster cases in a group of interest, *b* is the number of other reaction cases in a group of interest, *c* is the number of herpes zoster cases in a comparator group and *d* is the number of other reaction cases in a comparator group.

First analysis: group of interest was mRNA COVID-19 vaccine recipients and comparator group was any influenza vaccine recipients. Reports that involved any influenza vaccine or varicella-zoster virus vaccine in addition to mRNA COVID-19 vaccine were excluded. To avoid a notoriety bias, a longstanding known bias in disproportionality studies which is related to an inflation reporting following a scientific communication, this analysis was restricted to reports recorded in VigiBase before April 12th, 2021 (corresponding to the date of first publication of herpes zoster following mRNA vaccination case series (<https://doi.org/10.1093/rheumatology/keab345>). For influenza vaccine, analysis included reports registered after January 1st, 2011 (coinciding after the H1N1 mass immunization).

Second analysis: group of interest was mRNA COVID-19 vaccine recipients being under 40 years and comparator group was mRNA COVID-19 vaccine recipients being over 40 years. Of note, patient age is not known in some reports, that were not considered in this analysis.