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ORIGINAL RESEARCH ARTICLE

GP Consultations for Herpes Zoster After COVID-19 Vaccination: A Self-Controlled Cohort Study Based on Electronic Health Record Data from the Netherlands

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Abstract

Background and Objective Several systematic reviews and meta-analyses have been published with conflicting results on the risk of herpes zoster after coronavirus disease 2019 (COVID-19) vaccination. We aimed to study the risk of herpes zoster after COVID-19 vaccination using electronic health record data of general practices, from a large cohort in the Netherlands.

Methods Persons aged ≥ 12 years who received at least one COVID-19 vaccination and were registered in the general practice databases of PHARMO and Nivel Primary Care Database were included. This study used a self-controlled design comparing the risk of herpes zoster in the risk period (28 days after COVID-19 vaccination) with the control period. Poisson regression was used to calculate incidence rate ratios, adjusting for severe acute respiratory syndrome coronavirus 2 infection.

Results There were 2,098,683 COVID-19 vaccinated persons aged ≥ 12 years included, of whom 1,058,646 (50.4%) were female. An increased risk for herpes zoster was found after all the doses grouped together and the third dose of all COVID-19 vaccination (adjusted incidence rate ratio: all doses 1.07, 95% confidence interval [CI] 1.02–1.13 and third dose 1.21, 95% CI 1.05–1.38). After stratification on vaccine type, all doses and the third dose of messenger RNA vaccination (adjusted incidence rate ratio: all doses 1.06, 95% CI 1.00–1.12 and third dose 1.21, 95% CI 1.05–1.40) showed an increased risk.

Conclusions Our study showed a slight increased risk of herpes zoster when taking into account all doses and all types of vaccines. After stratification on vaccine type, no increased risk of herpes zoster after the primary vaccination series and a slightly elevated risk after the third/booster vaccination with a messenger RNA vaccine were found.

Key Points

Combining two large general practice databases in the Netherlands increased statistical power and ensured broader representativeness, enabling a more comprehensive analysis of coronavirus disease vaccination's effect on shingles occurrence.

Studies have shown conflicting results on the risk of herpes zoster after coronavirus disease 2019 vaccination.

Our study showed no increased risk of herpes zoster after the primary vaccination series and a slightly elevated risk after the third/booster vaccination for the combined messenger RNA vaccines.

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1 Introduction

In 2020, the world was taken by surprise by the coronavirus disease 2019 (COVID-19) pandemic. New vaccines were developed at a rapid pace. In a few months, four vaccines (from manufacturers Pfizer/BioNTech, Moderna, AstraZeneca, and Janssen), based on two vaccine types (messenger RNA [mRNA] and viral vector), became available in the Netherlands [1].

The vaccination campaign commenced on 6 January, 2021, with two doses of Pfizer/BioNTech, Moderna, or AstraZeneca, or one dose of Janssen (or one dose of Pfizer/BioNTech, Moderna, or AstraZeneca in the case of a prior COVID-19 infection). Nuvaxovid only became available in December 2021. For immunocompromised patients, a third dose was offered following the initial series with the invitation sent out from October 2021. The booster vaccination campaign began in November 2021. Starting on 19 November, 2021, individuals aged 80 years and over were invited to receive their booster vaccination. The aim was to ensure that as many seniors as possible received a booster before the end of 2021. Care home residents aged 18 years and over were also invited, along with healthcare workers and social support workers who work directly with patients and clients. From 3 December, 2021, invitations were sent out for individuals with Down syndrome. After these groups had received their booster vaccinations, invitations were extended to everyone aged 60 years and over, in descending age order. Everyone eligible for a booster vaccination was offered an mRNA vaccine, either Pfizer/BioNTech or Moderna, regardless of the vaccine they had previously received. For the Moderna booster, a half-dose was administered [2].

Although the safety of COVID vaccines has been studied worldwide, not all possible adverse events following immunization are fully mapped. One of these possible adverse events following immunization is an increase in the risk of herpes zoster or shingles that is caused by reactivation of the varicella-zoster virus. In most instances of acute herpes zoster reactivation, the rash and pain typically resolve. However, in some cases, post-herpetic neuralgia (PHN) develops. Postherpetic neuralgia is characterized by ongoing nerve pain in the affected area and this condition can lead to considerable impairments in quality of life [3].

Primary infection with varicella-zoster virus occurs mainly during childhood and causes varicella (chickenpox), after which the virus establishes a lifelong latency in the body. Reactivation of the virus, causing herpes zoster, is usually caused by decreased immunity because of older age, stress, immunosuppressive medication, or diseases that weaken the immunity such as HIV infection or malignancy [4, 5]. The most common complication of herpes zoster is PHN, which is characterized by severe pain in the areas that were affected by herpes zoster that persist for 3 months or longer [4, 5]. In the Netherlands, the incidence of herpes zoster, based on general practice (GP) records, was 5.4 per 1000 inhabitants in 2021, with a higher incidence among female individuals (6.3 per 1000 persons) compared with male individuals (4.4 per 1000 persons). The incidence of herpes zoster increases with age, in which an incidence of 4.7 per 1000 persons was seen among individuals aged 50–54 years. This increased to 8.1 per 1000 persons among individuals aged 60–64 years, and further increased to an incidence of 16.4 per 1000 persons among persons aged 85 years and older [6]. The prevalence of PHN varies between 5 and 30% among patients with herpes zoster [7].

Several systematic reviews and meta-analyses have been published that describe the risk of herpes zoster after COVID-19 vaccination, which show conflicting results [8–12]. These systematic reviews focus mainly on the mRNA vaccines (Pfizer/BioNTech and Moderna). While several of the underlying studies stratified the results according to vaccination doses, this was limited to the first two doses [10, 13–17]. However, it cannot be ruled out that receiving a third vaccination dose may alter the risk of herpes zoster. This information is essential, as in the current and future periods, COVID-19 vaccination campaigns will rely on booster vaccinations. Furthermore, little is known about potential risk groups with increased risks of herpes zoster after COVID-19 vaccination. Finally, knowledge about a potentially increased risk in the Dutch population is not yet available but is necessary to be taken into account as part of the risk/benefit assessment in the decision-making process during future vaccination rounds.

This study was part of a larger project in which an infrastructure was built that enabled us to perform in-depth analyses based on electronic health record data from GPs to investigate potential adverse drug reactions of COVID-19 vaccination. The aim of our study was to assess the risk of herpes zoster following COVID-19 vaccination and to determine whether specific groups experienced an increased risk, using data from GP records.

2 Methods

2.1 Setting

For this study, two GP databases and a database containing vaccination data were used. The PHARMO GP database encompasses around 20% of the Dutch population, while the Nivel GP database (Nivel Primary Care Database, Nivel-PCD) covers approximately 8–10% [18, 19]. In 2021, data of about 5% of the individuals aged ≥ 12 years were present in

both the PHARMO and Nivel GP databases. For these overlapping individuals, data from the PHARMO database were used, as it includes free-text fields that may provide more detailed and complete information. To obtain COVID-19 vaccination data, the national COVID Vaccination Information and Monitoring System (CIMS) database has been used, which is maintained by the National Institute for Public Health and the Environment (RIVM). The CIMS database includes COVID-19 vaccination data from all persons in the Netherlands who gave consent to share their data in the CIMS. It is estimated that approximately 6% of the Dutch vaccinated persons did not consent to share their data [20]. In this study, only those patients were included for which data were present in the CIMS.

2.2 Study Population

Persons aged 12 years and older with data available in the Nivel-PCD or PHARMO GP database from 1 January, 2016 and who had received a minimum of one COVID-19 vaccination in 2021 were included. Persons who consulted their general practitioner for herpes zoster in the 5 years prior to cohort entry (between 2016 and 2020) were excluded. See the Electronic Supplementary Material (ESM) for a description of the GP databases and the vaccination database used and data extraction.

2.3 Study Design

A retrospective self-controlled cohort study was performed, in which the association between a COVID-19 vaccination and the occurrence of herpes zoster was evaluated within the same individuals over time. The incidence of herpes zoster during a risk period post-vaccination (exposed period) was compared to the incidence during a control period (non-exposed period).

All persons had the same cohort-entry date, i.e., 1 January, 2021. The cohort exit date could be different for each person and could be reached at the deregistration date at the GP in 2021, or the maximum follow-up date, i.e., 31 December, 2021. The time from the cohort-entry date to the cohort-exit date was the follow-up time. For each person's follow-up time, the exposed period and non-exposed period were calculated, in which the exposed period was a maximum of 28 days after each vaccination and the non-exposed period was all the remaining time. If two vaccination doses were given in less than 28 days, the exposed period of the prior vaccination was truncated at the time the consecutive vaccination was administered. All persons depicted in the cohort have been vaccinated. The cohort includes persons who had herpes zoster *before* they were vaccinated with a COVID-19 vaccine.

The COVID-19 vaccination campaign involved two types of vaccines: mRNA vaccines and vector vaccines, with different brands available for each type. The vaccine brands Pfizer/BioNTech and Moderna belonged to the group of mRNA vaccines and Johnson & Johnson and AstraZeneca to the group of vector vaccines. Individuals may have received either the same or different types or brands of vaccines over time. These are referred to as homogeneous and heterogeneous vaccination schemes, respectively. For example, if a person received two different brands that belong to the same vaccine type, such as Pfizer/BioNTech and Moderna, this would be classified as a homogeneous scheme based on the vaccine type but a heterogeneous scheme based on the vaccine brand. Vaccines varied not only in their composition but also in the populations to which they were administered. As a result, the analysis was conducted for both vaccine type and brand.

2.4 Outcome

The following International Classification of Primary Care (ICPC) version I codes were collected from the GP databases to define the outcome herpes zoster: S70 Herpes zoster, S70.01 Herpes zoster, and S70.02 Post-herpetic neuralgia. Only the first general practitioner consultation for herpes zoster in the study period (which could be either ICPC codes) was included in this study.

2.5 Analyses

Incidence rates per 100,000 person-years were calculated for the exposed period and the non-exposed period. The incidence rate ratio (IRR), including its 95% CI, was then calculated by dividing the incident rate in the exposed period by the incidence rate in the non-exposed period, by using Poisson regression. Unadjusted IRRs (95% CI) were calculated, as well as adjusted IRRs (95% CI) by adjusting for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as a time-varying confounder during the follow-up period in 2021. SARS-CoV-2 infection was defined based on the ICPC codes R83.03 SARS-CoV-2 (COVID-19) [see ESM]. Forest plots were used to visualize the results. *P* values below 0.05 were defined as statistically significant (see ESM).

Analyses were carried out on three levels. First, all COVID-19 vaccines were analyzed together (including unknown COVID-19 brands), then they were stratified by vaccine type (mRNA versus vector vaccines), and finally by vaccine brand. In the case of fewer than 28 days between vaccinations, it is difficult to determine which vaccine type/brand was associated with herpes zoster. Therefore, for the analyses by vaccine type

Table 1 Characteristics of the study population

	Total study population $N = 2{,}098{,}683$
Source population, *n* (%)	
PHARMO database	1,844,865 (87.9%)
Nivel-PCD database	253,818 (12.1%)
Sex, *n* (%)	
Male	1,040,037 (49.6%)
Female	1,058,646 (50.4%)
Age, median (IQR)	51 (32)
Age in categories, years, *n* (%)	
12–18	179,027 (8.5%)
19–39	505,899 (24.1%)
40–59	691,604 (33.0%)
≥ 60	722,153 (34.4%)
Comorbidity, *n* (%)	
Cardiovascular disease	539,134 (25.7%)
Chronic lung disease	341,747 (16.3%)
Type 1 and 2 diabetes mellitus	152,396 (7.3%)
Malignancy	113,953 (5.4%)
Psoriasis	47,460 (2.3%)
Obesity	34,561 (1.6%)
Inflammatory bowel disease	14,547 (0.7%)
HIV	3279 (0.2%)
Chronic kidney disease	2575 (0.1%)
Number of persons with outcome (by ICPC code) during the follow-up, *n* (%)	10,385 (0.5%)
S70 Herpes Zoster	8242 (0.4%)
S70.01 Herpes Zoster	2052 (0.1%)
S70.02 Post-herpetic neuralgia	91 (0.0%)
Follow-up time during the study period in 2021, *n* (%)	
≤ 3 months	27,361 (1.3%)
Between 3 and ≤ 6 months	29,426 (1.4%)
Between 6 and ≤ 9 months	27,424 (1.3%)
Between 9 and ≤ 12 months	2,014,472 (96%)
Number of COVID-19 vaccination doses per person, *n* (%)	
1 dose	227,646 (10.8%)
2 doses	1,145,212 (54.6%)
3 doses	725,759 (34.6%)
4 doses	66 (0.0%)
Total COVID-19 vaccinations per vaccine brand, *n* (%)	
Pfizer/BioNTech	3,250,831 (69.2%)
Moderna	870,031 (18.6%)
AstraZeneca	444,879 (9.5%)
Johnson & Johnson	119,243 (2.5%)
Unknown brand	10,627 (0.2%)
Total number of persons with a heterogeneous/homogeneous sequential vaccination regimen based on vaccine type (mRNA vs vector), *n* (%)	
Heterogeneous	178,453 (8.5%)
Homogeneous	1,920,230 (91.5%)
Total number of persons with a heterogeneous/homogeneous sequential vaccination regimen based on vaccine brand (Pfizer/BioNTech, Moderna, AstraZeneca, Johnson & Johnson), *n* (%)	
Heterogeneous	592,969 (28.3%)
Homogeneous	1,505,714 (71.7%)

COVID-19 coronavirus disease 2019, *HIV* human immunodeficiency virus, *ICPC* International Classification of Primary Care, *IQR* interquartile range

and vaccine brand, only persons with a homogeneous sequential vaccination regimen were included.

The design of this study was a self-controlled cohort design. The characteristics mentioned in Table 1 were automatically corrected for in this design, as their presence remained stable before and after vaccination. Nonetheless, they may have acted as effect modifiers. For this reason, results were also stratified by age (12–18, 19–39, 40–59, ≥60 years) and sex (male/female) to investigate whether they were at a higher risk to develop herpes zoster after COVID-19 vaccination. These risk groups were based on the known increased risk of herpes zoster with increasing age and for female individuals, as described in the introduction [6]. In the overview of characteristics of the study population, we also show general comorbidities describing the nature of the cohort. Because of the low prevalence of these comorbidities, additional stratification based on conditions that may influence the occurrence of herpes zoster, such as disorders associated with a weakened immune response, was not considered meaningful. All data cleaning, data analysis, and data visualization was performed in RStudio version 4.2.2.

2.6 Privacy and Ethical Approval

All data were anonymized before they were received for data analyses. For observational studies containing no directly identifiable data, informed consent from patients or approval by a medical ethics committee is not required (Dutch Civil Law, Article 7: 458). The study was approved according to the governance code of Nivel-PCD (nr. NZR-00322.008) and by the Institutional Review Board of STIZON, Utrecht, the Netherlands (nr. CC2022-13).

3 Results

The total study population included 2,098,683 COVID-19 vaccinated persons aged 12 years and older, of which 1,058,646 (50.4%) were female. The median age was 51 years (interquartile range: 32 years). The two most common comorbidities were cardiovascular disease (n = 539,134, 25.7%) and chronic lung disease (n = 341,747, 16.3%). The majority of persons received two COVID-19 vaccinations (n = 1,145,212, 54.6%), in which Pfizer/BioNTech was the most administered vaccination brand (n = 3,250,831, 69.2%) followed by Moderna (n = 870,031, 18.6%). See Table 1 for an overview of the characteristics of the study population.

3.1 Risk of Herpes Zoster by COVID-19 Vaccination Dose, Vaccine Type, and Vaccine Brand

The analyses showed an increased risk for herpes zoster in the exposed period versus the non-exposed period after all doses of all COVID-19 vaccination grouped together and third dose of COVID-19 vaccination (adjusted IRR: all doses 1.07, 95% CI 1.02–1.13 and third dose 1.21, 95% CI 1.05–1.38), see Fig. 1. After stratification on vaccine type, all doses and third dose of mRNA vaccination (adjusted IRR: all doses 1.06, 95% CI 1.00–1.12 and third dose 1.21, 95% CI 1.05–1.40) showed an increased risk. The increased risk after the third dose of COVID-19 vaccination only includes persons who received three doses of an mRNA vaccine, as there were no persons who received three doses of a vector vaccine (see Fig. 1).

3.2 Risk of Herpes Zoster by Sex, Age, Vaccine Type, and Vaccine Brand

For male individuals of all ages, there was a significant risk of herpes zoster after vector vaccines (adjusted IRR: 1.38, 95% CI 1.02–1.87). For the mRNA vaccines, the risk was not significantly increased for both female and male individuals of all ages (female-adjusted IRR: 0.81, 95% CI 0.99–1.15 vs male-adjusted IRR: 1.04, 95% CI 0.95–1.13). No increased risk of herpes zoster after COVID-19 vaccination was shown after further stratification, neither for female and male individuals, see Fig. 2.

4 Discussion

This large cohort study among more than 2 million COVID-19 vaccinated persons aged ≥12 years showed an increased risk for herpes zoster in the exposed period versus the non-exposed period after all doses of all COVID-19 vaccination grouped together and a third dose of all COVID-19 vaccination. The third dose solely includes persons who received three doses of an mRNA vaccine, as there were no persons who received three doses of a vector vaccine. After stratification on receiving either a homogenous vaccination with an mRNA or vector vaccine, all doses grouped together and a third/booster dose of mRNA vaccination showed an increased risk. However, when further stratifying mRNA vaccination on brands, this increased risk is no longer significant for Pfizer/BioNTech. Currently, only the Pfizer/BioNTech vaccine is still used in the Netherlands for additional vaccination campaigns, making data at the brand level particularly informative. Stratification on subgroups of age and sex only showed a significant risk of herpes zoster after vector vaccines for male individuals of all ages. For other subgroups, there were no significant effects found.

There is conflicting evidence in the literature on the relationship between COVID-19 vaccination and herpes zoster. For instance, a self-controlled case series analysis on electronic health records and COVID-19 vaccination records in Hong Kong found an increased adjusted IRR of 5.23 (95%

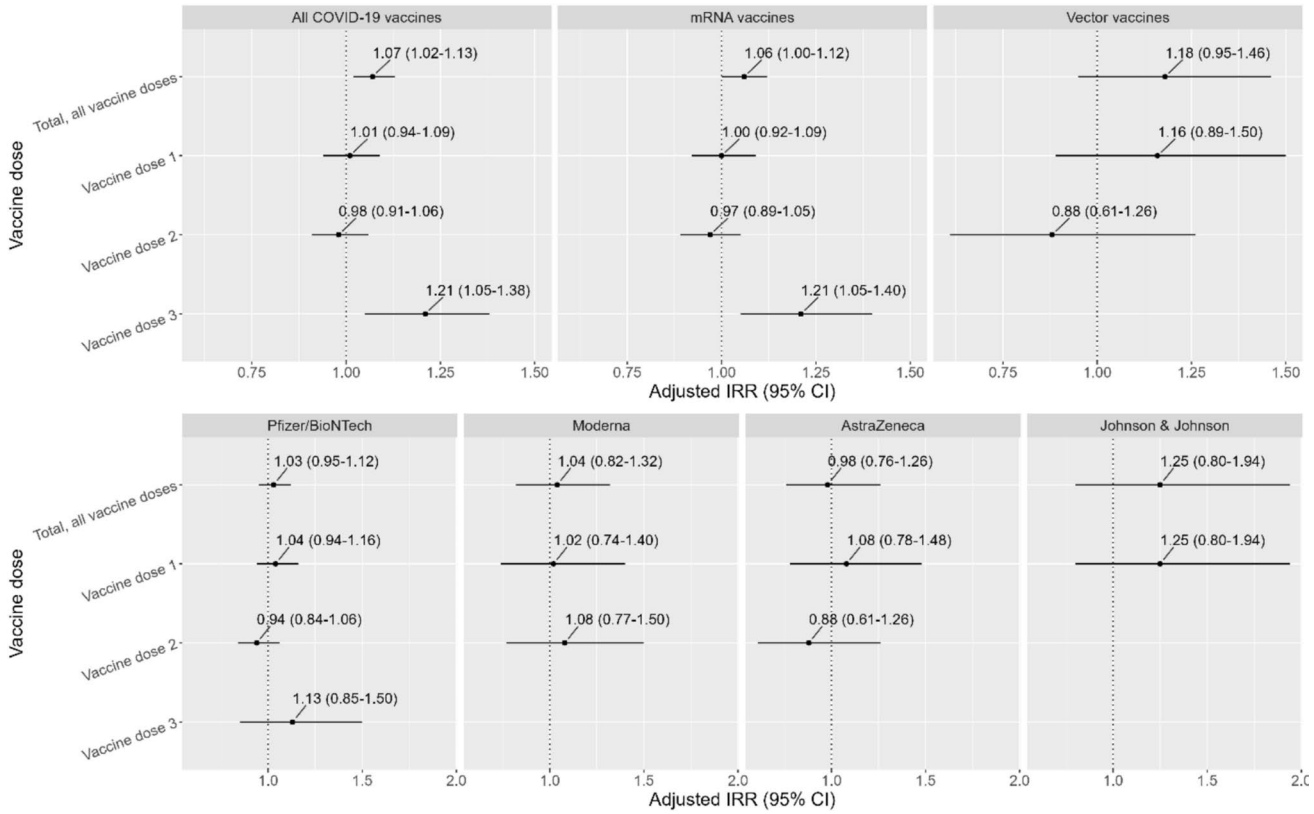

Fig. 1 Adjusted incidence risk ratios (IRRs) of herpes zoster after coronavirus disease 2019 (COVID-19) vaccination, for all COVID-19 vaccines, for homogenous dose regimen per vaccine type and per vaccine brand, stratified by vaccine dose. Blank results represent cell counts below 5 and are not shown. *CI* confidence interval, *mRNA* messenger RNA

CI 1.61–17.03) for herpes zoster-related hospital admission after 0–14 days after the first dose and an adjusted IRR of 5.14 (95% CI 1.29–20.47) at 0–14 days after the second dose of Pfizer/BioNTech [13]. However, a self-controlled risk interval analysis cohort study in a US healthcare claims database found no increased risk of IRR for herpes zoster after COVID-19 vaccination [IRR of 0.91 (95% CI 0.82–1.01)]. In a supplementary cohort analysis, COVID-19 vaccination was not associated with a higher risk of herpes zoster compared with influenza vaccination in the pre-pandemic period [16]. The self-controlled approaches applied in both studies closely resemble the approach used in our study. It is not clear to what extent the patients in both studies can be compared, given that the study from Hong Kong concerned patients requiring hospitalization. Our findings are in line with the study conducted in the USA, which used data from a medical claims database and probably also included non-hospitalized patients. In the Netherlands, herpes zoster is usually treated in the first line and hospital admission is exceptional.

Three systematic/narrative reviews including a variety of study designs and data sources showed an increased risk of herpes zoster after both mRNA vaccination and vector vaccination [8, 10, 11]. The majority of the underlying studies from these systematic/narrative reviews focused on the mRNA vaccinations. Parikh et al. [10] showed that some, but not all, included retrospective cohort studies showed an increased risk of herpes zoster after a Pfizer/BioNTech vaccination (the majority of the studies only included this particular vaccine). Parikh et al. [10] also described the results of a previous meta-analysis of 16 studies performed by Chen et al. [8], which showed an increased risk of herpes zoster after COVID-19 vaccination (odds ratio 1.32; 95% CI 1.09–1.62) compared with controls as well as an increased risk of herpes zoster after mRNA vaccination compared with vector vaccination (odds ratio 1.67; 95% CI 1.19–2.35).

In contrast, a systematic review and meta-analysis by Wang et al. [12], which pooled the results of 16 studies, did not find an increased risk of herpes zoster after COVID-19 vaccination [relative risk of 1.08 (95% CI 0.84–1.39) after COVID-19 vaccination compared with controls]. There was a very limited overlap between included studies in this meta-analysis and the study by Parikh et al. [10].

The slightly increased risk found in our study after the third/booster mRNA vaccination could be the result of a short-term decrease in immunity after COVID-19

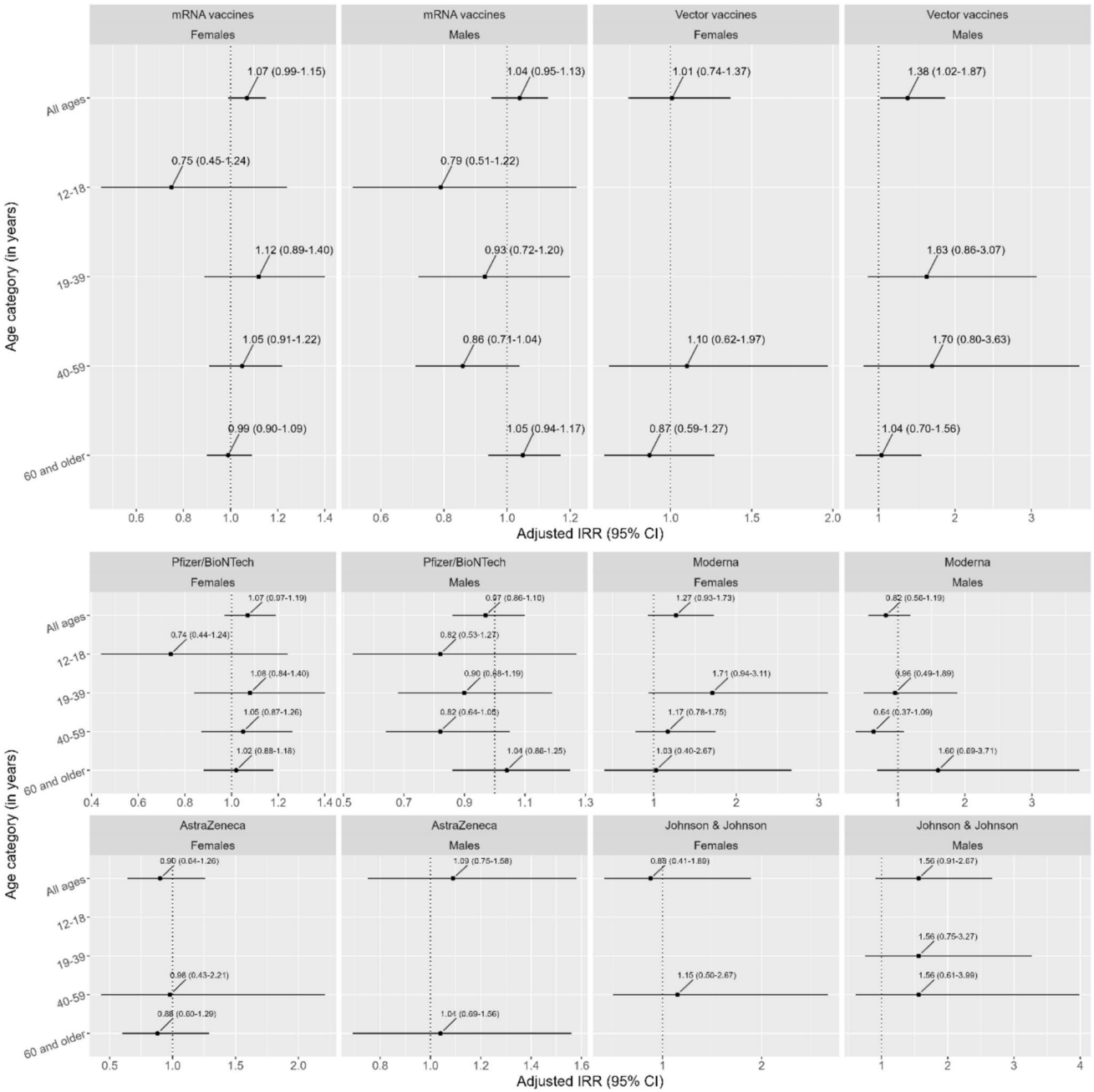

Fig. 2 Adjusted incidence risk ratios (IRRs) of herpes zoster after coronavirus disease 2019 vaccination, by homogenous dose regimen for vaccine type, and by homogenous dose regimen for vaccine brand, all stratified by age in categories and sex. Blank results represent cell counts below 5 and are not shown. *CI* confidence interval

vaccination [11, 14, 21]. This is possibly due to a shortage of lymphocytes or reduced function of the lymphocytes that are needed to keep the latent varicella-zoster virus in check. It is possible that this effect is stronger after repeated vaccination. To our knowledge, there are no studies that investigated the risk of herpes zoster after three or more doses/booster doses of COVID-19 vaccination in the general population. This makes it difficult to compare our results with other studies. Only one study among patients with cancer under active treatment included a booster vaccination and showed that all cases of herpes zoster occurred within 30 days after the third Pfizer/BioNTech vaccination, which was shown to be associated with impaired T-helper and T cytotoxic cell counts [22]. A clinical trial study among 45 healthy adults showed in the 1–3 days after dose 1 of the Pfizer/BioNTech vaccination, a decrease in the lymphocyte count in 8.3%, 45.5%,

and 50.0% of participants who received 10 µg, 30 µg, and 100 µg of the vaccine, respectively [23]. The lymphocyte count returned to normal in the 6–8 days after vaccination. Unfortunately, the study did not show the short-term (1–3 days) results after dose 2 of the Pfizer/BioNTech vaccination, and no data were available on the third/booster dose. A prospective observational study among 36 patients with cancer showed an optimal cellular response after two doses of the Moderna vaccine, but a decrease of specific interferon-γ production after the third dose, suggesting T-cell exhaustion due to repetitive vaccination [24]. It is unclear whether the same pattern could apply for patients without cancer.

4.1 Methodological Considerations

An exposure-anchored self-controlled cohort study was performed. This design shares conceptual foundations with Self-controlled Crossover Observational PharmacoEpidemiologic (SCOPE) studies [25, 26].

For the selection of cases of herpes zoster, both ICPC codes for herpes zoster and PHN have been used. Given the specific characteristics of this disorder, misclassification is unlikely. The number of codes for PHN is significantly lower than that for herpes zoster (see Table 1), as compared with previous studies that report the occurrence of this complication to be between 5 and 30% [7]. However, as general practitioners are likely to code for herpes zoster initially, PHN may not have been coded separately when it developed afterwards.

In this study, two databases were utilized to increase the coverage of GPs included in the analysis. The use of two databases was necessary because not all GP information systems transmit their data to the same repository. In our analysis, we carefully discussed and examined the data specifications of the GP information systems in the Netherlands, and there were no major differences in data quality, structure, or coding.

As a large number of statistical tests were carried out, it cannot be ruled out that type I errors may have occurred as a result. One method to correct for this is applying a multiplicity correction. The downside of applying this correction is that it increases the risk of type II errors (false negatives). This means that true effects may go undetected, as the threshold for statistical significance is raised to reduce the likelihood of type I errors (false positives). As a result, statistical power may be reduced, and conclusions become more conservative, making it harder to identify and report potential associations [27]. As this study involves exploratory analyses aimed at detecting possible signals, a strict correction could cover up findings that warrant further investigation. Therefore, it was decided not to apply this approach.

The COVID-19 vaccinations in the Netherlands were administered over specific time periods. For example, the primary series of vaccinations—two doses for the mRNA vaccines and AstraZeneca, and one dose for Janssen—were administered approximately between March and June 2021. The first booster doses were administered between mid-November 2021 and February 2022 [28]. If herpes zoster follows a seasonal pattern, the timing of vaccination might have coincided with changes in the background incidence of herpes zoster. Information regarding the seasonality of herpes zoster is conflicting [27]. A study based on hospital data in Italy found that the chance of herpes zoster infection increased during the onset of summer [28]. Bakker et al. analyzed shingles notification data from Thailand and found a pronounced seasonal pattern in incidence, with ambient ultraviolet radiation levels showing a strong correlation with herpes zoster reactivation [29]. However, other studies have not found seasonal effects in the incidence of herpes zoster [30]. For our study, we did not take seasonality into account as a time-varying confounder. To our knowledge, data on the possible seasonality of herpes zoster in the Netherlands are not available. However, a time series analysis study in a claims database in the USA, a country that shares similar seasonal fluctuations with Western Europe, found that herpes zoster may peak between March and October [29]. We observed a relatively high reporting rate associated with the third vaccination, administered in the fall and winter. If herpes zoster would also follow a similar seasonal pattern in the Netherlands, the association might be more obvious. The third vaccinations were all administered in a relative short time span as a result of which the exposed period fell in mostly fall and winter in contrast to the control period, which may have dampened the effect.

4.2 Strengths and Limitations

Our study has several strengths. First, the use of GP data is a valid and reliable data source to investigate the outcome herpes zoster. Because herpes zoster is a painful condition, it is expected that the majority of herpes zoster patients consult their general practitioner. Additionally, misclassification of the diagnosis by the general practitioner is unlikely, as herpes zoster symptoms are highly specific and accompanied by typical lesions. Therefore, we expect that under-reporting is limited and the use of ICPC codes to define herpes zoster is valid [4]. Second, combining two large GP databases from the Netherlands allowed for more statistical power, a more representative geographic distribution and representativeness of the Dutch population [30, 31]. Third, the use of a self-controlled cohort design allowed for all fixed and unknown/unmeasured confounders to be automatically corrected for.

Our study also has several limitations. First, SARS-CoV-2 infection, which we controlled for as a time-varying confounder, is likely under-reported in GP databases as a person needs to give permission to share the results of the polymerase chain reaction test carried out by Public Health Services with their general practitioner. In addition, a positive SARS-CoV-2 test taken at home may not always have been confirmed with a polymerase chain reaction test (carried out by Public Health Services) and is thus not available in the GP database. Second, there could be selection bias in who consented to share their COVID-19 vaccination data in the national CIMS COVID-19 database, as the CIMS misses around 6% of vaccinated persons who did not consent to share their data [20]. As the characteristics of these persons are not known, the impact on the results of this study cannot be estimated.

In the Netherlands, the initial point of contact for people who have a health-related question is their general practitioner. During the first wave of the pandemic, the total number of general practitioner visits between March and June 2020 was on average 11% lower compared with the same period in 2019. During the summer of 2020, the number of consultations returned to 'pre-pandemic' levels, i.e., levels similar to the same period in 2019. However, a shift was noted from fewer physical consultations to shorter telephone calls or video calling. General practitioners indicated that they also spoke to patients physically less often in 2021 [32]. It cannot be ruled out that this affected the number and nature of diagnoses recorded in GP systems over time. As the timing of the successive doses of vaccinations in 2021 was somewhat aligned, the nature and number of ICPC codes recorded could have been a time-dependent confounder. It cannot be ruled out that the fluctuating accessibility of primary care may have influenced the outcomes.

In our study population, 8.5% had a heterogenous regimen based on the vaccine type. It is possible that selection bias may have occurred because of differences in the characteristics of individuals who received a homogeneous vaccination compared with those who received a heterogeneous vaccination. However, within the heterogeneous vaccination group, various types and brands of vaccines have been used in small subgroups and therefore we did not stratify our findings for these individual subgroups [2].

We cannot fully exclude that that an episode of herpes zoster (e.g., shortly after a first dose of vaccine) might affect the uptake of second or third doses or cause a delay in subsequent vaccination. As such, we cannot fully exclude the possibility of selection bias (healthy vaccinee effect); however, a potential association between herpes zoster with COVID-19 vaccines was not known during the vaccination campaign and received no major media attention unlike other associations such as pericarditis and myocarditis, thrombosis, and menstrual disorders [1, 33]. One might also argue that the presence of a HZ infection, which has also been associated with a decreased immunological response, may have prompted patients to be vaccinated.

Herpes zoster can occur recurrently and having a first episode increases the probability of future episodes. Therefore, only the first episode of herpes zoster was treated as the outcome of interest in this study by excluding persons who consulted their general practitioner for herpes zoster in the 5 years prior to cohort entry. Investigating the risk of recurrence of herpes zoster after COVID-19 vaccination was not part of our study design.

Finally, we do not have data on the vaccination grade against herpes zoster in our cohort. Although there is currently no nationwide program for herpes zoster vaccination in the Netherlands, clear guidelines exist regarding eligibility for reimbursement. Individuals aged 60 years and older, as well as adults with certain immune-related conditions, can largely access vaccination depending on the reimbursement criteria. However, the majority of older adults were not eligible for reimbursement in 2021. Because of the cost of the vaccine, uptake was very limited in previous years until 2025 when more persons became eligible for reimbursement [34].

5 Conclusions

Our study showed a slight increased risk of herpes zoster when taking into account all doses and all types of vaccines. After stratification on vaccine type, no increased risk of herpes zoster after the primary vaccination series and a slightly elevated risk after the third/booster vaccination with an mRNA vaccine were found.

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Declarations

Conflict of interest The authors Rana Jajou, Erik Mulder and Agnes Kant have no conflicts of interest. Karik Hek received funding from Pfizer for research (starting per 01 December 2024) not related to this study. Jetty Overbeek is an employee of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related health care authorities and several pharmaceutical companies. Florence van Hunsel and Eugène van Puijenbroek are Editorial Board members of *Drug Safety*. These authors were not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethics approval All data were anonymized before it was received for data-analyses. For observational studies containing no directly identifiable data, it is not obligated to obtain approval by a medical ethics

committee (Dutch Civil Law, Article 7: 458). The study was approved according to the governance code of Nivel-PCD (nr. NZR-00322.008) and by the institutional review board of STIZON, Utrecht, the Netherlands (nr. CC2022-13).

Informed consent For observational studies containing no directly identifiable data, it is not obligated to obtain informed consent from patients (Dutch Civil Law, Article 7: 458).

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and materials Data for this study are not publicly available in order to protect patient privacy . Inquiries about the data used can be sent to the corresponding author.

Code availability R codes cannot be made available due to the data protection policy for this study.

Author's contributions All authors (RJ, EP, JO, KH, EM, FH and AK) contributed to the design of the study; RJ and EM performed the data-analysis. All authors contributed to the interpretation of data for the work; FH and RJ drafted the work; All authors contributed to reviewing it critically for important intellectual content; All authors read and approved the final version; All authors are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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