

Risk Factors for Herpes Zoster Infection: A Meta-Analysis

Fawziah Marra, Kamalpreet Parhar, Bill Huang, and Nirma Vadlamudi[✉]

Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada

Background. The burden of herpes zoster (HZ) is significant worldwide, with millions affected and the incidence rising. Current literature has identified some risk factors for this disease; however, there is yet to be a comprehensive study that pools all evidence to provide estimates of risk. Therefore, the purpose of this study is to identify various risk factors, excluding immunosuppressive medication, that may predispose an individual to developing HZ.

Methods. The literature search was conducted in MEDLINE, EMBASE, and Cochrane Central, yielding case control, cohort, and cross-sectional studies that were pooled from January 1966 to September 2017. Search terms included the following: *zoster* OR *herpe** OR *postherpe** OR *shingle** AND *risk* OR *immunosupp** OR *stress* OR *trauma* OR *gender* OR *ethnicity* OR *race* OR *age* OR *diabetes* OR *asthma* OR *chronic obstructive pulmonary disease* OR *diabetes*. Risk ratios (RRs) for key risk factors were calculated via natural logarithms and pooled using random-effects modeling.

Results. From a total of 4417 identified studies, 88 were included in analysis (N = 3, 768 691 HZ cases). Immunosuppression through human immunodeficiency virus/acquired immune deficiency syndrome (RR = 3.22; 95% confidence interval [CI], 2.40–4.33) or malignancy (RR = 2.17; 95% CI, 1.86–2.53) significantly increased the risk of HZ compared with controls. Family history was also associated with a greater risk (RR = 2.48; 95% CI, 1.70–3.60), followed by physical trauma (RR = 2.01; 95% CI, 1.39–2.91) and older age (RR = 1.65; 95% CI, 1.37–1.97). A slightly smaller risk was seen those with psychological stress, females, and comorbidities such as diabetes, rheumatoid arthritis, cardiovascular diseases, renal disease, systemic lupus erythematosus, and inflammatory bowel disease compared with controls (RR range, 2.08–1.23). We found that black race had lower rates of HZ development (RR = 0.69; 95% CI, 0.56–0.85).

Conclusions. This study demonstrated a number of risk factors for development of HZ infection. However, many of these characteristics are known well in advance by the patient and clinician and may be used to guide discussions with patients for prevention by vaccination.

Keywords. age; herpes zoster; immunocompromised; meta-analysis; risk factors.

Herpes zoster (HZ) or shingles, as its commonly known, results from reactivation of the varicella zoster virus (VZV), which lies dormant in the spinal and cranial sensory ganglia after primary infection in childhood [1–3]. Herpes zoster presents as a painful, erythematous, maculopapular rash in which lesions become fluid-filled before crusting over. Unique features that distinguish HZ from other dermatological rashes are unilateral presentation and restriction to a single dermatome [4]. Through various mechanisms, VZV is reactivated to cause HZ. Although treatment is available via antiviral therapy, there are many ophthalmic, vascular, visceral, and neurological complications of HZ [5, 6]. These complications lead to increased all-cause total healthcare cost and place financial burdens on patients [6]. The

major complication associated with HZ is postherpetic neuralgia, pain persisting for over 90 days after shingles onset, that occurs within 20% of HZ patients [7] with an estimated prevalence of 0.5–1 million [8].

It is clear from the literature that millions of individuals are affected each year by shingles or HZ infection around the globe; in the United States, more than 1 million new cases of HZ are reported every year [9]. The incidence of HZ ranges from 3 to 5 per 100 000 in North America, Europe, and Asia, but more importantly, the incidence seems to be increasing with time, and it is unclear to what this may be related [10, 11]. Numerous studies have identified risk factors associated with reactivation of VZV, many of which are related to a decrease in T-cell immunity, such as aging and immunosuppression, but some are related to family history or stress [12]. We have previously conducted a meta-analysis that pooled data from randomized clinical trials and observational studies to determine the magnitude of risk with different immunosuppressive regimens in patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and inflammatory bowel disease (IBD) [13]. This time, we have focused on pooling data from all studies evaluating the risk of developing HZ infection except those studies evaluating risk with taking immunosuppressive medications.

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Correspondence: Fawziah Marra, BSc (Pharm), PharmD, FCSHP, Professor of Pharmacy, University of British Columbia, 2405 Wesbrook Mall, Vancouver, British Columbia, Canada V6T 1Z3 (fawziah@mail.ubc.ca).

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METHODS

This systematic review and meta-analysis was reported according to the MOOSE guidelines for the reporting of observational studies, in accordance with the PRISMA guidelines for conducting a meta-analysis [14, 15].

Data Sources and Search Strategy

We conducted a search of MEDLINE, EMBASE, Cochrane Central, Cochrane Systematic Reviews, Web of Science, and CAB Direct for articles reporting on HZ infection and associated risk from January 1, 1966 to January 31, 2019. Search terms as keywords, Mesh terms and subject headings included the following: *zoster* OR *herpe** OR *postherpe** OR *shingle** AND *risk* OR *immunosupp** OR *stress* OR *trauma* OR *gender* OR *ethnicity* OR *race* OR *age* OR *diabetes* OR *asthma* OR *chronic obstructive pulmonary disease* OR *diabetes*. After pooling the articles and deleting duplicates, a manual review of titles was conducted screening for relevant topics and keywords. Another final manual review of article abstract was conducted on short-listed articles. The literature search was performed by an author (B.H.) and a university librarian, the article review was conducted by 2 authors (B.H. and N.V.), and uncertainty and revisions were resolved by consensus.

Inclusion and Exclusion Criteria

We included all English studies that evaluated the risk factors associated with HZ in the population. We excluded cases and case series reports and literature reviews. We also excluded all studies that used immunosuppressive medications, including biologics, disease-modifying antirheumatic drugs, and/or corticosteroids.

Data Extraction, Study Verification, and Quality Assessment

Data were extracted independently by 2 authors using a standardized abstraction form, with discrepancies being resolved through consensus. Data extracted from the studies included the author, date of the study, type of study, inclusion and exclusion criteria, risk factor, number of patients, confounders adjusted for, demographics, and study outcome data. Quality assessment of the studies was conducted by 2 authors independently using the Newcastle-Ottawa quality assessment scale [16].

Statistical Analysis

Pooled risk ratios (RRs) with 95% confidence intervals (CI) were calculated for the risk of HZ associated with key risk factors, using natural logarithm of reported effect estimates, and their corresponding CI. Because these observational studies were conducted in different geographic locations, the true effect estimate will likely vary and represent a random sample of effect estimates; therefore, pooled estimates were obtained using a random-effects model.

We compared the risk of HZ in those with the following: (1) innate risk factors, such as race, sex, age, and family history; (2)

immunosuppression (human immunodeficiency virus [HIV]/acquired immune deficiency syndrome or malignancy [AIDS]); (3) comorbidities including asthma, chronic obstructive pulmonary disease (COPD), cardiovascular diseases (CVDs), IBD, depression, diabetes, chronic renal disease, SLE; and (4) other studies (physical trauma, psychological stress, smoking).

We measured heterogeneity across studies using the I^2 statistic, with higher values reflecting increasing heterogeneity [17]. Sources of heterogeneity were assessed by subgroup analysis and by meta-regression [18]. Subgroup analyses included disease subtypes, mean age, sex ratio, and study type. Using funnel plots, publication bias was assessed, and asymmetry was assessed by conducting the Egger test [19]. Statistical analyses were conducted in R version 3.3.2. All analyses were 2 sided with $P < .05$ defining statistical significance.

RESULTS

Search Results, Trial Characteristics, and Risk of Bias

The literature and manual references search identified 4417 studies (Figure 1). The majority of these studies were excluded based on the title and/or abstract screening and removal of duplicate records ($N = 4192$). Two hundred twenty-five studies were included for a full article review and 88 studies were included, corresponding to 68 cohort studies [20–87], and 20 case-control studies [88–107]. Reasons for exclusion were mainly irrelevant topic, immunosuppressive therapy focus, study design, studies were evaluating herpes treatment and vaccine effect rather than risk factors, complications associated with HZ infection, or lack of quantitative data on the incidence of HZ associated with individual risk factors. One percent of the studies were published between 1965 and 1969, 5% were published from 1990 to 1999, 17% were published from 2000 to 2009, and 77% were published from 2010 to 2018.

A summary of the baseline characteristics of patients included for analysis are presented in Supplementary eTable 1. A total study population of 198 751 846 was included, with 3 768 691 HZ cases reported in the included studies. The age ranged from 3 months to 104 years, the percentage of women in studies ranged from 0% to 100%, and the follow-up duration ranged from 1 to 62 years. Most studies were conducted in North America (Canada and United States; $N = 35$), followed by Asia (China, Iran, Israel, Japan, South Korea, and Taiwan; $N = 31$), and Europe (Belgium, Denmark, France, Germany, Italy, Spain, Netherlands, and United Kingdom; $N = 20$). Overall quality of the included studies ranged from fair to good, based on the Newcastle Ottawa scale assessment, ranging from 6 to 9 for cohort studies and 4 to 9 for case-control studies (Supplemental eTables 2 and 3).

Risk of Herpes Zoster

The estimates are presented in (Figure 2), and detailed forest plots for each outcome can be found in Supplemental eFigure 1–18). Within our categorization of innate characteristics, 56 studies

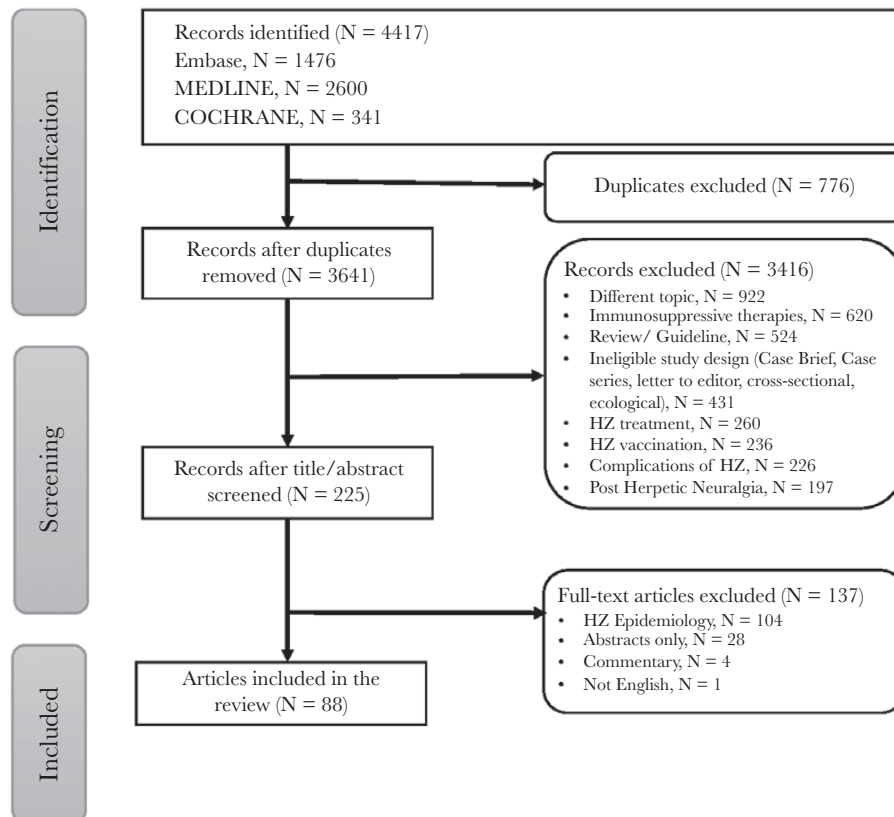


Figure 1. Screening of studies for inclusion into the study.

evaluated gender and 39 studies looked at age as potential risk factors for development of HZ. A smaller number of studies evaluated race (N = 17) and family history of zoster (N = 9). Family history was strongly associated with an increased risk of HZ than controls (RR = 2.48, 95% CI, 1.70–3.60; $I^2 = 94.4\%$) (Figure 2). Both older age (RR = 1.65, 95% CI, 1.37–1.97; $I^2 = 100\%$) and gender (odds ratio [OR] = 1.19, 95% CI, 1.14–1.24; $I^2 = 99.4\%$) were associated with an increased HZ risk, but less so than family history. Of note, a lower risk of HZ was associated with black race (RR = 0.69, 95% CI, 0.56–0.85; $I^2 = 97.2\%$).

We found 40 studies that reported risk of HZ from malignancies and 18 studies on HIV/AIDS. Human immunodeficiency virus/AIDS was strongly associated with an increased risk of HZ compared with controls (RR = 3.22; 95% CI, 2.40–4.33; $I^2 = 98.1\%$). Malignancies, such as lymphoma and leukemia, were also strongly associated with risk of HZ (RR = 2.17; 95% CI, 1.86–2.53; $I^2 = 99.6\%$). Numerous studies evaluated risk of HZ with various concurrent illnesses including diabetes (N = 34), chronic renal disease (N = 18), CVD (N = 16), depression (N = 14), COPD (N = 13), SLE (N = 13), asthma (N = 12), RA (N = 12), and IBD (N = 8). Most of these comorbidities increased risk of HZ, RR ranging from 2.08 to 1.23, particularly SLE (RR = 2.08; 95% CI, 1.56–2.78; $I^2 = 98.00\%$) and RA (RR = 1.51; 95% CI, 1.31–1.75; $I^2 = 99.10\%$).

Other nonmedical factors evaluated in studies included psychological stress (N = 8), physical trauma (N = 6), and smoking (N = 8); HZ was strongly associated with physical trauma (RR = 2.01; 95% CI, 1.39–2.91; $I^2 = 92.5\%$), but the rest were not significant.

A considerable amount of heterogeneity was found through visual inspection of funnel plot assessment (data not shown), but after evaluation with Egger's test only a handful of the risk factors (family history, SLE, psychological stress, and depression) were found to possess statistically significant heterogeneity. Most of the heterogeneity was found to be associated with study design, population, and geographic location.

DISCUSSION

This is the most comprehensive systematic review assessing risk factors for HZ infection. Our meta-analysis indicates that immunosuppression through HIV/AIDS or malignancy places individuals at significant risk of reactivating the latent viral suppression. Family history of zoster, physical trauma, and older age also significantly increased risk. Although the risk is present with female gender, psychological stress, or presence of comorbidities, such as diabetes, RA, CVDs, renal disease, SLE, and IBD, it was slightly less than the former risk factors.

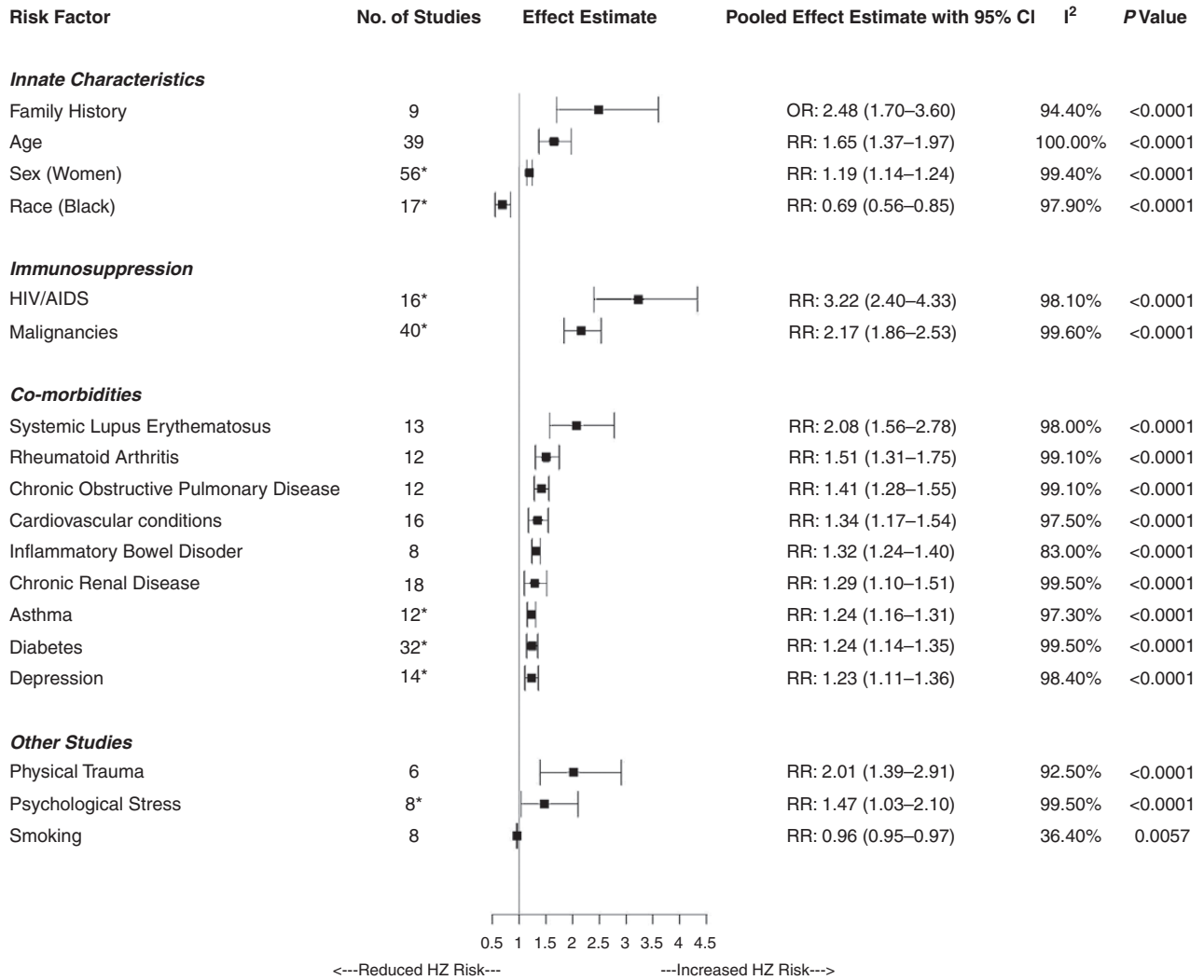


Figure 2. Pooled analysis of the risk of herpes zoster.

The elevated risk in the older patients is likely due to immunosenescence, in which the immune system progressively deteriorates as individuals age [108]. Varicella zoster virus is normally kept dormant in dorsal root sensory ganglia via specific cell-mediated immunity (CMI) [109, 110]. Cell-mediated immunity naturally declines over time, but it is normally boosted by exogenous and endogenous methods, thereby limiting VZV's ability to reactivate and cause HZ. Exogenous boosting occurs through repeated exposures to wild-type VZV causing subclinical infections that are immediately mediated by cellular processes [110]. Endogenously, subclinical reactivation of VZV stimulates CD4⁺ cells to release cytokines, including tumor necrosis factor (TNF)-alpha, interferon-gamma, and interleukin-2 (IL-2) [111, 112]. The latter agent enables T-helper cells to stimulate neutrophils and macrophages that phagocytize the zoster virus. In addition, IL-2 promotes CD8⁺ cells to release proteases, interferon-gamma, and lysins to destroy viral cells. Finally, CD4⁺ cells also play a role in memory B-cells

stimulation and immunoglobulin G-mediated B-cell proliferation [113]. In elderly patients with reduced immune function, VZV-specific T-cell immunity (CD4, CD8, and memory T cells) is below the clinical threshold of maintaining virus latency, thus placing this population at elevated risk of developing HZ [114]. In our meta-analysis, most of the studies were conducted in the population aged 60 years and over (N = 36), with only 1 study reporting HZ risk in those aged 40 years and over [29] and 2 studies reporting risk in individuals aged 50 years and above [22, 35]; the lack of data in these at-risk individuals meant we were unable to further characterize risk in these age groups.

It is well known that immunosuppressive conditions such as HIV/AIDS and malignancies [115] result in decreased CMI that increases the risk of viral infections, such as zoster. In general, these individuals have low CD4⁺ and CD8⁺ cells and impaired lymphocyte proliferation. We were not able to do a separate analysis according to CD4 count because most studies reported HZ in HIV patients with >350 CD4 cell count and at

the beginning of antiretroviral therapy. Immunosuppression also impacts recovery of CMI posttherapy, specifically towards IL-2 and CD4⁺, which play a significant role in limiting VZV reactivation to cause HZ [116]. Autoimmune diseases such as RA, IBD, and SLE also cause impaired CMI [115]. A study by Park et al [112] found lower CD4⁺ cell counts (including TNF-alpha and interferon-gamma) in patients with SLE, which they stated may place individuals at higher risk of HZ. Furthermore, a study conducted by Nagasawa et al [117] also discussed that SLE patients show altered immune function via tests for delayed hypersensitivity reactions, CD8⁺ activity, interferon production, and T-cell transformations. Elevated risk factors for both immunosuppressive conditions and autoimmune diseases were identified in our meta-analysis.

Only 1 other meta-analysis studied the impact of family history on developing HZ. Lai and Yew [118] evaluated this relationship, as well as dose-response relationships and whether the number of relatives affected HZ rates. They included 5 case-control studies (N = 4169) and identified a statistically significant increase in the risk of family history with first-degree relatives (OR = 3.03; 95% CI, 1.86–4.94) [118]. One proposed genetic mechanism, discussed by Lai and Yew [118], involves human leukocyte antigens (HLAs), specifically HLA-A, which is responsible for presenting peptides to CD8⁺ receptors to elicit an immune response. IE6862 is a VZV transcription factor protein and one of the main peptides responsible for eliciting CD8⁺ response; a study conducted by Meysman et al [119] found that patients in Belgium who had lower HLA-A presentation ability of IE62 protein had a 60% greater risk of HZ.

Our meta-analysis found female gender places individuals at a slightly higher risk of HZ, but there is no definite explanation for this difference. However, a review conducted by Fleming et al [34] proposed that gender biases during diagnosis may be a factor; another probable cause may be due to hormonal or biological differences between genders [120].

Black race was seen to be protective against HZ in comparison to white individuals. There are few documented reasons for this occurrence. A possible explanation is due to differences in household composition; black individuals may have elevated exposure to varicella, which boosts CMI [121]. Other explanations may lie in genetic variations, racial differences in reporting disease or the frequency of medical interactions [122]. Finally, it may also be related to lower rates of healthcare access among black individuals, which may be due to mistrust or lack of a consistent healthcare source, and this may contribute to lower numbers of patients seen with HZ by a healthcare professional [123, 124].

Currently, there are 2 vaccines on the market, Zostavax (a live vaccine) and Shingrix (a recombinant zoster vaccine) [125]. Both vaccines increase cellular mediated immunity. Zostavax is no longer the recommended vaccination for HZ because vaccine effectiveness after 3 years is only slightly above 50% and is further diminished to ≤24% after 4 years [126]. In addition,

Zostavax is less effective in older individuals and is contraindicated in immunosuppressive conditions (HIV/AIDs, malignancies), during immunosuppressive drug therapy and pregnancy [127]. Shingrix contains a recombinant VZV glycoprotein E and an adjuvant component that increase VZV-specific CMI and enhances specific humoral immunity, respectively [128, 129]. Shingrix is recommended to all adults ≥50 years old, in 2 separate intramuscular injections 2–6 months apart [130]. However, vaccination rates are still low and substantial efforts by healthcare professionals are required to increase uptake.

Our study was not without limitations. Most studies selected were observational (cohort or case-control studies) and, due to design, have a higher likelihood of bias. The potential for recall bias is possible in the studies that reported on family history and physical trauma [131]. Family history may have differential recall depending on various factors, such as the number of years since HZ events, variations in awareness of family history, or the strength of the relationships between families. Physical trauma can either impair patient's ability to recall events or strengthen their memory of coinciding events. Finally, selection bias may also be present in studies that collected HZ cases from specialist clinics such as those from dermatologists [131]. However, bias was accounted for via risk of bias assessment, in which all studies scored low. Due to study design, studies were also at risk of confounding, although most studies minimized the risk by adjusting for some of the variables such as age, sex, or other comorbidities. It is likely that a patient with multiple risk factors is at higher risk for HZ compared with someone with single risk factor; however, because of the differences in study design and population, we were not able to determine cumulative risk in our study. Administrative data was the preferred method of data collection by a majority of the studies selected. This form of data can be miscoded, incorrect, or vary between practitioners [132]. Most studies accounted for the possible error through various methods such as the following: only including patients with first diagnosis of HZ, selecting databases that were validated for correctness and accuracy, or incorporating various sources to confirm diagnosis (*International Classification of Diseases* codes + antiviral prescriptions) [89, 90, 103]. Heterogeneity was high, which may be attributed to variations in study design, differences in outcome ascertainment (record linkage, hospital records, diagnosis by physician), characteristics of populations (age, gender, size), and countries in which studies were conducted.

CONCLUSIONS

In conclusion, HIV/AIDS, immunosuppression, family history, older age, trauma, females, and presence of comorbid conditions place individuals at an increased risk of HZ. With 2 vaccinations available on the market, physicians and other healthcare providers can target patient education based on their risk factors and improve the uptake of zoster vaccination.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Author contributions. F. M. conceived and designed the study; B. H. conducted literature research; K. P., B. H., and N. V. acquired the data; N. V. performed data analysis; F. M., N. V., B. H., and K. P. interpreted the data; F. M., K. P., and N. V. wrote the first draft of the article; F. M., N. V., K. P., and B. H. critically revised the article for important intellectual content; and F. M., N. V., K. P., and B. H. approved the version to be published.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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