Epidemiology of herpes simplex virus type 2 in China: Systematic review, meta-analyses, and meta-regressions

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Abstract

Background: Herpes simplex virus type 2 (HSV-2) infection is prevalent and a significant public health problem. Understanding its epidemiology will help assess the current HSV-2 prevention efforts and inform future interventions in China. **Methods:** We followed Cochrane and PRISMA guidelines for a systematic review and included publications published in Chinese and English bibliographic systems until March 18 th, 2023. We synthesized seroprevalence, sero-incidence, and proportions of HSV-2 isolated in genital ulcer disease (GUD) and genital herpes data. We used random-effects models for meta-analyses and conducted meta-regression to assess the association between population characteristics and seroprevalence. **Results:** Overall, 21,849 articles were identified, and 457 publications (1,051,035 participants) were included. A total of 429 studies reported the overall seroprevalence rates (939 stratified measures), 5 reported seroincidence rates, 4 reported overall proportions of HSV-2 isolation in GUD (8 stratified proportions), and 24 reported overall proportions of HSV-2 isolation in genital herpes (59 stratified proportions). Pooled HSV-2 seroprevalence among overall populations was 14.9% (95% confidence interval (CI): 13.8-16.1%) and was 7.9% (95% CI: 6.9-8.8%) among the general population. Seroprevalence was highest among key populations (e.g., female sex workers and men who have sex with men) (32.1% (95% CI: 27.8-36.5%)). Among the general population, we found northeastern regions had a higher HSV-2 seroprevalence (12.4%, 95% CI: 7.8-17.9%). HSV-2 seroprevalence also increased with age. The pooled HSV-2 seroincidence rate was 4.3 per 100 person-years (95% CI: 1.0-7.6). Pooled HSV-2 seroprevalence among GUD and genital herpes were 45.2% (95% CI: 29.0-61.9%) and 52.8% (95% CI: 46.6-59.0%), respectively. We also found higher HSV-2 seroprevalence estimates in publications published in English bibliographic databases than those in Chinese databases (20.5% *vs.* 13.6%, risk ratio=1.10 (1.05-1.14)), indicating a potential existence of language bias in publication. **Conclusion:** Around 1 in 12 among the general population and 1 in 7 among all included populations were infected with HSV-2. The data revealed vulnerability to HSV-2 infection among higher-risk populations calling for expanding the intervention to prevent HSV-2 infection. It also revealed heterogeneities in synthesized HSV-2 prevalence results, suggesting the necessity to include Chinese bibliographic databases in conducting systematic reviews and meta-analyses of this topic.

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Abstract

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Results: Overall, 21,849 articles were identified, and 457 publications (1,051,035 participants) were included. A total of 429 studies reported the overall seroprevalence rates (939 stratified measures), 5 reported seroincidence rates, 4 reported overall proportions of HSV-2 isolation in GUD (8 stratified proportions), and 24 reported overall proportions of HSV-2 isolation in genital herpes (59 stratified proportions). Pooled HSV-2 seroprevalence among overall populations was 14.9% (95% confidence interval (CI): 13.8-16.1%) and was 7.9% (95% CI: 6.9-8.8%) among the general population. Seroprevalence was highest among key populations (e.g., female sex workers and men who have sex with men) (32.1% (95% CI: 27.8-36.5%)). Among the general population, we found northeastern regions had a higher HSV-2 seroprevalence (12.4%, 95% CI: 7.8-17.9%). HSV-2 seroprevalence also increased with age. The pooled HSV-2 seroincidence rate was 4.3 per 100 person-years (95% CI: 1.0-7.6). Pooled HSV-2 seroprevalence among GUD and genital herpes were 45.2% (95% CI: 29.0-61.9%) and 52.8% (95% CI: 46.6-59.0%), respectively. We also found higher HSV-2 seroprevalence estimates in publications published in English bibliographic databases than those in Chinese databases (20.5%*vs* . 13.6%, risk ratio=1.10 (1.05-1.14)), indicating a potential existence of language bias in publication.

Conclusion: Around 1 in 12 among the general population and 1 in 7 among all included populations were infected with HSV-2. The data revealed vulnerability to HSV-2 infection among higher-risk populations calling for expanding the intervention to prevent HSV-2 infection. It also revealed heterogeneities in synthesized HSV-2 prevalence results, suggesting the necessity to include Chinese bibliographic databases in conducting systematic reviews and meta-analyses of this topic.

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Introduction

Herpes simplex virus type 2 (HSV-2) is an incurable and recurring sexually transmitted infection.[1] Often asymptomatic, people with HSV-2 can transmit the virus to their sexual partners without awareness of their infection.[2] It also increases the risk of acquiring and transmitting the Human immunodeficiency virus (HIV).[3,4] Given its contingency and impact on life quality and well-being,[5]understanding the epidemiology of HSV-2 is essential for informing future prevention. Also, considering its synergy with HIV, reducing HSV-2 infection is beneficial to the goal of ending STI epidemics as major public health concerns by 2030.[6]

The latest estimate of HSV-2 global prevalence in 2016 was 13.2% (491 million) among people aged 15-49 worldwide.[7] Recent meta-reviews have reported a wide range of prevalence estimates from different geographical regions, including 37.3% in sub-Saharan Africa,[8] 20.6% in Latin America,[9]15.4% in Canada, Australia, and New Zealand,[10] 12.4% in Europe,[11] 12.1% in Asia,[12] and 5.1% in the Middle East and North Africa among the general population.[13] Seroprevalences of HSV-2 among key populations such as male sex workers(MSW), men who have sex with men (MSM), and female sex workers (FSW) are substantially higher across regions, ranging from 20.6% to 74.8% for FSW and from 18.3% to 54.6% for MSM and MSW.[8-13]

Despite the existing literature, a comprehensive overview of HSV-2 epidemiology and trends among different populations in China is limited, calling for a systematic review and meta-analysis. A meta-analysis in Asia reported a pooled HSV-2 seroprevalence of 9.3% among the general population.[12] However, it only included literature identified from English bibliographic databases, which may incur language bias.[14] We also identified two additional meta-analyses that focused on specific populations in China, such as the MSM population with a pooled prevalence of 9.4%, [15]and the FSW population with a 15.8% HSV-2 prevalence.[16] These reviews included a small portion of the existing studies, which is quite limited. Our study aims to fill this gap and provide a more comprehensive and up-to-date estimate of the HSV-2-related outcomes (e.g., prevalence and incidence) among various populations in China by synthesizing literature published in Chinese and English and generating estimates by different groups and subpopulations.

Methods

The study protocol was registered in PROSPERO (PROSPERO ID: CRD42023408108).

Data sources and search strategy

This systematic review was conducted under the guidance of the Cochrane Collaboration Handbook.[17] We reported the findings following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[18] We included four bibliography databases, including PubMed, Embase, China National Knowledge Infrastructure (CNKI), and Wanfang, as the sources. Considering the limited publication coverage in Chinese in PubMed and Embase, we included two major Chinese bibliography databases, CNKI and Wanfang.[19] We searched the publications till March 18th, 2023.

Eligibility criteria

We included the publications that reported primary data related to HSV-2 for any of the four outcomes (1) seroprevalence, which was defined by the proportion of the included population who tested HSV-2 seropositive; (2) seroincidence or seroconversion, defined as the occurrence of HSV-2 infections per person-time; (3) the proportion of genital ulcer disease (GUD) cases in which HSV-2 was isolated as its cause; (4) the proportion of genital herpes cases in which HSV-2 was isolated as its cause.

We excluded case reports, case series, commentaries, reviews, and publications without access to the full text. We also excluded the studies that involved less than 10 participants. Those studies reporting HSV-related

outcomes (including both HSV-1 and HSV-2) were excluded if we could not extract HSV-2 outcomes. If one study only reported HSV-2 prevalence from infants younger than six months, we excluded it due to the parental source antibody.[20]

Literature screening and data extraction

For each publication, any two of the eight reviewers (FL, AW, XY, YW, SH, YD, HX, CF) independently screened thetitles, abstracts, and full texts and identified eligible publications for data extraction. In case of disagreements between the two reviewers, a third reviewer (WT and YW) was consulted for reconciliation if an agreement was not reached.

We extracted the variables containing information on publication year, data collection time, methods, testing assay, study population type, age, sex, sample size, and relevant study outcomes. We used pre-defined population types and risk factors to conduct stratified analyses of our study outcomes. The definition of population type and risk factors was included in the supplementary materials (Supplementary Box S1 and S3).

Quality assessment

We referred to a previously published study in assessing the study quality.[21] WT (University of North Carolina at Chaple Hill) is the team's leading HSV-2 assay analysis assessment expert. Study precision was categorized into high and low based on the sample size (low: <200 vs. high [?]200). The risk of bias was assessed based on the sampling method (probability-based vs. non-probability-based) and response rate (low: <80% vs. high [?]80%). We consider studies using existing medical records as non-probability-based studies and of high response rates.

Meta-analyses

We used the random-effects model to conduct the meta-analyses and to pool the proportions of HSV-2 positive cases.[22] We used the Freeman-Tukey double arcsine transformation by specifying the command sm="PFT" in the analysis.[23] We presented Cochran's Q statistic to assess the effect size heterogeneity.[24] I^2 was used to measure the between-study heterogeneity. We also presented prediction intervals, defined as the 95% confidence interval of the distribution of true HSV-2 seroprevalence around the estimation.

The pool results were stratified by different characteristics, including age groups, gender, year of data collection, and study sites. We mapped the pooled seroprevalence in the unit of provinces in China to demonstrate the geographic difference in the HSV-2 disease burden.

Meta-regression

We conducted univariate and multivariable random-effects meta-regression analyses to assess the association between log-transformed seroprevalence and pre-decided factors. All variables in the univariate model whose p-value was less than 0.1 were included in the multivariable analyses. A P -value < 0.05 (two sides) in the multivariable analysis indicated a statistically meaningful association.

Language bias assessment

To compare the synthesized HSV-2 prevalence between the studies published in Chinese and English bibliographic databases, we stratified the study population into the general, intermediate-risk, and higher-risk populations. We used the meta-regression to assess the association between HSV-2 seroprevalence and language of the bibliography systems using relative risk as the measure. We hypothesize there would be a difference in HSV-2 seroprevalence estimation between the studies identified from Chinese and English bibliographic databases suggesting the existence of publication bias.[25]

"Publication" refers to a document reporting any outcome measure, while a "study" refers to details of a specific outcome measure. One publication might contain multiple study outcome measures (e.g., subgroup analyses). Duplicate or overlapping studies were included only once.

Literature screening was completed by Covidence.[26]Publication management was completed by Endnote X9.[27]Data extraction was completed by Microsoft Office Excel 2016. Meta-analyses, meta-regression, and mapping were conducted in R, version 4.3.0, using the 'meta' and 'metafor' packages.[28,29]

Results

Search results and scope of evidence

We identified 21,849 publications from four bibliographic databases (PubMed 1,125, Embase 14,243, CNKI 2,387, and Wanfang 4,094). After excluding duplicate references, 20,830 publications remained. Based on the abstract and title screening, 19,643 publications were further excluded. As 16 publications were not retrieved for full text, 1,171 publications entered full-text screening. Of these, an additional 714 publications were excluded, leaving the rest 457 publications that met eligibility criteria. The majority of the studies were conducted in Central Southern China (30.6%), Southeastern (28.7%), and Southwestern China (17.5%).

In total, 429 included publications reported the overall seroprevalence rates (939 stratified measures), 5 reported seroincidence rates, four reported the overall proportions of HSV-2 isolation in GUD (8 stratified proportions), and 24 reported the overall proportions of HSV-2 isolation in genital herpes (59 stratified proportions). The PRISMA flowchart of article selection is summarized in **Figure 1** . For study settings, 80.0% of the studies involved more than 200 participants, and 91.2% used non-probability-based methods. About two-thirds of studies had more than 80% response rates.

Seroincidence overview

Seroincidence rates are summarized in Table S1. More than half of the studies were longitudinal cohort studies (n=4; 80.0%) with follow-up durations ranging from 6 months to 12 months. In all populations, HSV-2 seroincidence ranged between 3.8 to 21.9 per 100 person-years, with the highest reported seroincidence among FSWs. The pooled seroincidence rate was 4.3 per 100 person-years (95% CI: 1.0-7.6).

Seroprevalence overview

More than 80% of the studies reporting seroprevalence measures (n=429) were published after 2005 (n=352, 82.1%). Most studies used convenience sampling (n=374, 87.2%). All seroprevalence measures are summarized in Table 1 and Table 2. Most studies collected data during the 21st century (2000-2010: 42.0%; after 2010: 42.4%).

Pooled means of HSV-2 seroprevalence among overall populations was 14.9% (n=947, 95% confidence interval (CI): 13.8%-16.1%). Pooled mean HSV-2 seroprevalence was lowest at 7.8% (n=10, 95% CI: 2.6%-15.2%) among other populations, followed by 7.9% (n=256, 95% CI: 6.9%-8.8%) among the general population, 16.7% (n=16, 95% CI: 12.7%-21.1%) among intermediate-risk populations, 23.1% (n=73, 95% CI: 20.5%-25.8%) among STI clinic attendees and symptomatic populations, and 26.0% (n=14, 95% CI: 20.0%-32.4%) among people living with HIV (PLWH) and their couples, and 32.1% (n=80, 95% CI: 27.8%-36.5%) among those at high risk. Across all populations except for HIV-positive and individuals in HIV-discordant couples, women had higher pooled mean seroprevalence than men (**Table 1**).

Table 2 shows stratified subpopulations in the general populations and their range of seroprevalence. Pooled mean seroprevalence was higher in the Northeast region at 12.4% (n=18, 95% CI: 7.8-17.9%), followed by the Central-southern region at 10.5% (n=126, 95% CI: 8.4-12.7%). The pooled mean seroprevalence increased with age from the age group 20-29 years. Pooled mean seroprevalence was 5.6% (95% CI: 4.0-7.3%) among 20-29-year-olds (n=74), followed by 8.2% (95% CI: 6.0-10.6%) among 30-39-year-olds (n=50), 8.9% (95% CI: 5.1%%-13.5%) in those aged 40-49 years (n=60), 15.3% (95% CI: 12.0-19.0%) in those aged 50-59 years (n=14), and 20.0% (95% CI: 9.9-32.3%) in those aged [?]60 years (n=9). Pooled mean seroprevalence decreased with the year of data collection and year of publication. Pooled mean seroprevalence was 15.1% (95% CI: 8.3-23.4%) for data collected in 2000 and earlier (n=30), followed by 6.9% (95% CI: 5.6-8.3%) during 2001-2010 (n=205) and 6.7% (95% CI: 5.7-7.8%) after 2010 (n=231). For year of publication, pooled

mean seroprevalence was 10.7% (95% CI: 7.2-14.7%) in 2005 and earlier (n=71), followed by 8.1% (95% CI: 6.7-9.6%) during 2006-2015 (n=258) and 6.5% (95% CI: 5.6-7.4%) after 2015 (n=175).

High and significant heterogeneity was found between studies (p-value <0.001, I^2>50%). Forest plots of different meta-analyses are displayed in Figure S1-S2.

The heatmap in **Figure 2** shows that HSV-2 seroprevalence varied across different provinces in China, with higher HSV-2 seroprevalence in Jilin, Liaoning, and Yunnan Provinces.

Meta-regression results

The results of univariate and multivariable meta-regression analyses are summarized in Table 3. We performed two multivariable models, the second multivariable model replacing the categorical variable of "year of data collection" in the first multivariable model with another temporal variable of "year of publication".

The first multivariable model explained 47.7% of the variation in seroprevalence (Table 3). Compared to general populations, FSWs had the highest HSV-2 seroprevalence with an adjusted risk ratio (ARR) of 1.66 (95% CI: 1.58-1.75), followed by drug users (ARR=1.53, 95% CI: 1.39-1.70), PLWH and HIV-negative individual in HIV discordant couples (ARR=1.22, 95% CI: 1.12-1.32), STI clinic attendees (ARR=1.20, 95%CI: 1.15-1.25), intermediate-risk populations (ARR=1.13, 95% CI: 1.05-1.22) and MSM/MSWs (ARR=1.09, 95% CI: 1.03-1.16).

Compared to those aged <20 years, HSV-2 seropositivity increased with age and was highest in those aged [?]60 years (ARR=1.22, 95% CI: 1.11-1.36). People living in the Northeast have the highest risk of HSV-2 (ARR=1.30, 95% CI: 1.21-1.40) than those living in the North, followed by the Southwest (ARR=1.10, 95% CI: 1.04-1.16) and Central-southern regions (ARR=1.10, 95% CI: 1.04-1.16). Men have a similar HSV-2 seroprevalence as women (ARR=0.96, 95% CI: 0.92-1.01). Studies that used PCR as an assay reported lower HSV-2 seroprevalence than those using ELISA.

Studies with larger sample sizes and non-probability sampling reported lower seroprevalence. Studies with lower response rates reported higher seroprevalence. Compared to data collected before 2000, data collected during 2001-2010 (ARR=0.88, 95% CI: 0.83-0.94) and after 2010 (ARR=0.91, 95% CI: 0.85-0.96) had lower HSV-2 seroprevalence.

The second model explained 45.7% of the variation in HSV-2 seroprevalence, yielding similar results to the first model. The seroprevalence did not vary by year of publication (**Table 3**).

HSV-2 isolation in GUD and genital herpes

The proportions of people with HSV-2 virus isolation in clinically diagnosed cases of genital ulcer disease and genital herpes are presented in **Table 4** . Most studies on HSV isolation in GUD (n=3, 75.0%) and in genital herpes (n=17, 70.8%) were published after 2005.

In patients with GUD (n=8), HSV-2 seroprevalence ranged from 12.1% to 70.9%, with a median of 55.3 %. Pooled seroprevalence was 45.2% (95% CI: 29.0-61.9%), with 48.2 % (95% CI: 22.0-74.9%) among women and 42.2% (95% CI: 21.1-64.8%) among men.

In genital herpes cases (n=59), HSV-2 seroprevalence ranged from 15.4 % to 100.0%, with a median of 48.3%. Pooled seroprevalence was 52.8% (95% CI: 46.6-59.0%), with 55.2 % (95% CI: 40.1-69.8%) among women and 47.5% (95% CI: 31.8-63.5%) among men.

Significant heterogeneity was found between studies (P -value <0.001, I^2>95%). Forest plots of the proportion of HSV-2 isolated in GUD and genital herpes are presented in Figure S2.

Language bias between publications identified in Chinese and English bibliographic databases

Table 5 summarizes the differences in pooled HSV-2 seroprevalence between publications identified in Chinese and English bibliographic databases. More publications were collected in Chinese bibliographic

databases (371 identified in CNKI and Wanfang *vs* . 58 identified in PubMed and Embase). HSV-2 seroprevalence in Chinese publications ranged from 0.0% to 85.3%, with a median of 11.3%, and in English publications ranged from 0.0% to 88.0%, with a median of 15.6%. Pooled HSV-2 seroprevalence was higher among studies identified in English than in Chinese (20.5% *vs* . 13.6%).

For intermediate-risk populations and drug users, we observed a higher synthesized seroprevalence in publications published in Chinese than in English bibliographic databases (22.1% *vs* . 9.6%, 63.1%*vs* . 35.5%, respectively). The results of the meta-regression analysis also supported this observation (RR=0.84, 95% CI: 0.76-0.93, RR=1.11, 95% CI: 1.04-1.20, respectively). Within FSWs and MSM/MSWs, HSV-2 seroprevalence was significantly higher in publications published in English compared to those published in Chinese (RR=1.21, 95% CI: 1.10-1.33, RR=1.11, 95% CI: 1.04-1.20, respectively). However, within general populations, STI clinic attendees and symptomatic populations, and HIV-positive individuals and individuals in HIV-discordant couples, there was no significant difference in HSV-2 seroprevalence between publications identified from Chinese and English bibliographic databases.

Quality assessment

Table S12 summarizes the quality assessment of 429 seroprevalence studies. Of these, 356 studies (83.0%) had high precision, 30 studies (7.2%) had low ROB in the sampling method domain, and 290 studies (67.6%) had low ROB in the response rate domain. Only 17 studies (4.0%) had low ROB in both quality domains, and 126 studies (29.4%) had high ROB in both quality domains.

Discussion

This is a comprehensive systematic assessment of HSV-2 epidemiology in China. We included publications in Chinese and English major bibliography databases and involved over one million study participants. This study has added to the existing literature by providing a most up-to-date, comprehensive picture of HSV-2 epidemiology in China, mapping the Chinese provincial level of HSV-2 seroprevalence differences, and investigating language bias between publications identified from Chinese and English databases. Around 1 out of 12 people in the general population were infected by HSV-2. Stratified by study populations and geographic regions, we observed higher HSV-2 disease burden among higher-risk populations such as FSW and participants from northeastern China, calling for more preventive interventions for these populations. By comparing the HSV-2 prevalence synthesized from Chinese and English databases, we found a higher overall HSV-2 prevalence from English bibliographic databases than Chinese, indicating the existence of language bias and implying the importance of including both Chinese and English publications in the review.

The HSV-2 seroprevalence among the general population is 7.9% (6.9-8.8%), similar to the overall prevalence of HSV-2 in Asia,[21] lower than in Europe, Sub-Saharan Africa, and Australia but higher than the Middle East and North Africa.[8,10,12,13,30] With other regions whose prevalence was flat[8] or increasing[10,11], we observed the HSV-2 prevalence in China reduced by about 2% every five years, which could be attributed to better STI clinic access and improved STI education among the general population nationwide.[31,32] Stratified by sex, we observed comparable HSV-2 prevalence between men and women. However, among other populations, we found a higher HSV-2 seroprevalence among women than men, especially higher-risk populations, with the seroprevalence significantly higher among FSW than MSM (52.1% *vs* . 12.2%), which revealed on the one hand, sustained HSV-2 transmission among this population[33] and on the other hand, the importance of continuing healthcare and behavioral intervention to reduce HSV-2 infection among the populations vulnerable to HSV-2 infection. Geographically, we found that the Northeastern region (Liaoning, Jilin, and Heilongjiang) had the highest HSV-2 prevalence due to the high proportion of STI clinic attendees with suspected genital herpes symptoms and MSM living with HIV within this sample (10,202/15,904, 64.1%). Stratified by age group, we observed a steady increase of HSV-2 prevalence with age, consistent with increasing cumulative exposure risk to the virus over the sexual life span and incurability of HSV-2. The assessment of HSV-2 risk factors through meta-regression confirmed the observations in synthesized seroprevalences: populations of higher vulnerability to HSV-2 had higher HSV-2 prevalence as earlier studies had higher HSV-2 prevalence than later studies.

We found heterogeneities in HSV-2 seroprevalence estimation and study population composition between English and Chinese bibliographic databases, indicating language bias. First, from the estimation perspective, the overall HSV-2 seroprevalence was significantly higher from English databases than Chinese databases (20.5% *vs* . 13.6%, RR=1.10 (1.05-1.14)). Stratified by risk levels, although we found comparable HSV-2 seroprevalence estimation among the general population, the HSV-2 seroprevalence estimation was significantly higher among higher-risk populations such as FSW and MSM/MSM in English databases. Second, the composition of the study population significantly differed between the publications identified from English and Chinese databases. The sample size of general populations in publications from Chinese databases is more than 15-fold that from English bibliography databases, mainly attributable to the large-scale toxoplasmosis, rubella cytomegalovirus, herpes simplex, and HIV (TORCH) screening among pre-pregnancy and pregnancy women in clinical and community settings. Meanwhile, the sample size of the higher-risk population in English databases accounted for one-third of the overall identified sample size, compared to around 3% in Chinese databases. Third, Chinese publications were more geographically diverse, providing HSV-2 seroprevalence not just in southern China (e.g., Guangdong and Yunnan) but around the country. These observations might be due to several reasons. First, the regular TORCH screening results among the general population were harder to be published in journals published in English bibliographic databases than in Chinese databases.[34] Second, higher-risk populations had higher HSV-2 vulnerabilities and potentially higher public health significance.[35] Investigators promoted their results in journals published in English databases for wider attention and higher citation.[36] Interestingly, on the other hand, we found lower HSV-2 prevalence estimation among intermediate-risk populations and drug users. The sample sizes and numbers of the study were much lower than those of higher-risk populations, which indicates an unmet study need for these populations. These observations indicate a potential existence of language bias by only including publications published in English bibliography databases in the review. Considering the huge quantity and varying quality, most Chinese journals have yet to be published in English bibliographic databases.[37] The synthesized results might be distorted by restricting publications to English-language only in literature searching.[38] Previous studies have shown that positive results in randomized controlled trials are more likely to be published and published in English bibliographic databases, potentially leading to overestimating the drugs' effectiveness. The Cochrane Handbook for Systematic Reviews and the United States Institute of Medicine Guidelines for Systematic Reviews recommends including non-English-language literature published in English bibliographic databases in the review.[17,39] Our study revealed that this might not be enough to eliminate the language bias if not including non-English bibliographic databases in the review. As a result, it could y lead to misinterpretation of the disease's unmet needs and a suboptimal distribution of public health resources in HSV-2 prevention across different populations.

There are some limitations to be noted. First, we should have included all Chinese bibliographic databases in the literature search scope. There are other databases, such as Weipu Database. However, we have included the two most popular Chinese bibliographic databases in this review and have yet to observe differences regarding the impact of journals published in different Chinese databases. Thus, the potential publication bias of excluding other Chinese databases is minimal. Second, due to heterogeneities in variable categorization (such as age group), some studies' subgroups cannot be extracted and are categorized into the mixed group or other populations. These studies' information was not fully utilized. However, the synthesized results did not differ significantly from the categorized groups' results. The overall estimation should be robust to these heterogeneities in variable categorization. Third, the current included studies, 29.4% of them had high ROB in both quality domains, and only 4.0% of the studies had low ROB in both domains, which implies a space for future studies to employ probability-based sampling methods to improve study quality. Fourth, we only presented the synthesized results for studies across different regions. However, there were heterogeneities regarding the study population. For example, in some regions, we identified more studies among higher-risk populations than in other regions, which could inflate the HSV-2, which calls for caution in interpreting the current results prevalence in this region.

Conclusion

Around 1 in 12 among the general population and 1 in 7 among all included populations were infected with

HSV-2, which calls for more education to increase HSV-2 awareness and preventive intervention to curb the transmission of HSV-2. Regarding the language bias of HSV-2 epidemiology, it is necessary to include Chinese bibliographic databases in the reviewing scope to obtain a more comprehensive picture of HSV-2 infection for various populations and geographic regions and to extract these figures to reduce the language bias of this topic.

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