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Epidemiology of Herpes Simplex Virus Type 2 in Canada, Australia, and New Zealand: Systematic Review, Meta-Analyses, and Meta-Regressions

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Background: This study characterized the epidemiology of herpes simplex virus type 2 (HSV-2) infection in Canada, Australia, and New Zealand.
Methods: Cochrane and PRISMA guidelines were followed to systematically review, synthesize, and report HSV-2-related data up to January 21, 2021. Meta-analyses and meta-regressions were performed.
Results: In Canada, pooled mean seroprevalence was 10.0% (95% confidence interval [CI], 7.8–12.4%) among general populations, 44.5% (95% CI, 20.0–70.5%) among sexually transmitted infection clinic attendees and symptomatic populations, and 60.7% (95% CI, 49.8–71.1%) among human immunodeficiency virus (HIV)-positive individuals and individuals in HIV-discordant couples. In Australia and New Zealand, combined, pooled mean seroprevalence was 15.4% (95% CI, 9.6–22.2%) among general populations, 27.8% (95% CI, 12.0–47.2%) among men who have sex with men, and 37.2% (95% CI, 23.7–51.8%) among sexually transmitted infection clinic attendees and symptomatic populations. Men had 0.64-fold (95% CI, 0.47–0.86) lower seroprevalence compared with women. No evidence was found for a decline in seroprevalence over time. Pooled mean proportion of HSV-2 isolation in laboratory-confirmed genital herpes was 62.1% (95% CI, 53.8–70.1%) in Canada and 71.9% (95% CI, 64.2–78.9%) in Australia and New Zealand. Proportion of HSV-2 isolation in genital herpes declined by 0.98-fold (95% CI, 0.97–0.99) per year. Pooled mean proportion of HSV-2 isolation in genital ulcer disease was 17.4% (95% CI, 4.0–37.1%) in these countries.
Conclusions: Over 10% of adults in these countries are infected, with no evidence for declining seroprevalence, unlike other global regions. Over 60% of genital herpes cases are caused by HSV-2 in these countries, yet HSV-2's role is declining by 2% per year.

Herpes simplex virus type 2 (HSV-2) infection is one of the most common sexually transmitted infections (STIs)[1,2] and causes genital ulcer disease (GUD) and genital herpes.[3,4] The infection is chronic, with frequent reactivations and subclinical shedding,[3–5] leading to high transmission potential to sexual partners.[6,7] Vertical mother-to-child transmission of this infection can cause neonatal herpes, a serious and sometimes fatal disease in newborns.[8,9] Herpes simplex virus type 2 infection is believed to increase acquisition and transmission of HIV,[10–12] potentially resulting in epidemiologic synergy between these 2 infections.[6,13,14] The World Health Organization's (WHO) "Global Health Sector Strategy on STIs" calls for elimination of STIs, as a main public health concern by 2030, through integrated, preventive, and therapeutic interventions.[15] The WHO and global partners are also leading efforts to develop an HSV-2 vaccine to address the global disease burden of this infection.[16,17]

This study's objective was to characterize the epidemiology of HSV-2 infection in Canada, Australia, New Zealand, and 22 Pacific Island nations. These countries share similar socioeconomic conditions, sociocultural attributes, and/or geography. Moreover, a large proportion of the population in these countries comprises immigrants from diverse nations.[18,19] This objective was accomplished by systematically reviewing and synthesizing publications on HSV-2 antibody prevalence (seroprevalence), HSV-2 seroincidence, the proportion of HSV-2 isolation (that is identification of the pathogen) in clinically diagnosed GUD, and the proportion of HSV-2 isolation in laboratory-confirmed genital herpes; by estimating pooled means for HSV-2 seroprevalence, the proportion of HSV-2 isolation in GUD, and the proportion of HSV-2 isolation in genital herpes; and by assessing population-level temporal trends of and associations with HSV-2 seroprevalence and proportion of HSV-2 isolation in genital herpes. The study was conducted to complement a series of studies for other global regions, as part of a project intended to characterize the global epidemiology of HSV-2 infection.[20–22]

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MATERIALS AND METHODS

The methodology implemented in this study was adapted from earlier systematic reviews of HSV-2 epidemiology in other regions.[20–22] Description of this methodology is provided in Box 1.

Data Sources, Search Strategy, Study Selection, and Eligibility Criteria

This systematic review was conducted following the Cochrane Collaboration Handbook[23] and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[24] guidelines (Supplementary Table S1, http://links.lww.com/OLQ/A799). The definition of Pacific Island countries was based on the United Nation geoscheme and was informed by WHO Pacific region definitions (Box 1).[25,26]

Search strategies are listed in Table S2 (http://links.lww.com/OLQ/A799). Details of the screening process and inclusion and exclusion criteria are in Box 1.

Data Extraction, Synthesis, and Quality Assessment

Four authors (S.A., U.S.F., M.H., and L.A.) independently extracted and double-extracted data from eligible articles. Data extraction was done using a standardized set of variables (Box 1).

Herpes simplex virus type 2 diagnostic assays have established limitations.[27,28] Therefore, assessment was made of the validity of each diagnostic method in each included study with support from Professor Rhoda Ashley-Morrow of the University of Washington, an expert in HSV-2 diagnostic methods who has investigated and evaluated the validity and reliability of different assays for over three decades. Only studies with sufficiently reliable and valid assays were included in this study, and these were appraised for precision and risk of bias (ROB), as informed by the Cochrane approach (Box 1).

Meta-Analyses

Meta-analyses were conducted using the DerSimonian-Laird random-effects model.[29] Proportions were transformed using the Freeman-Tukey double arcsine transformation,[30] after ensuring applicability of this transformation.[31s] Pooled mean estimates for HSV-2 seroprevalence and proportion of HSV-2 isolation in GUD and in genital herpes were calculated. Cochran's Q statistic, I^2, and prediction interval were calculated to quantify heterogeneity.[29,32s] Analyses were performed in R, version 4.0.4[33s] using the meta package[34s] (Box 1).

Meta-Regressions

Univariable and multivariable random-effects meta-regression analyses were conducted to investigate factors associated with HSV-2 seroprevalence and proportion of HSV-2 isolation in genital herpes, as well as to explain interstudy heterogeneity (Box 1). Factors of interest were established a priori. These analyses included all studies for Canada, Australia, and New Zealand, but the country name was explicitly included as a variable in the analysis. Analyses were applied to log-transformed proportion measures, and were implemented using Stata/SE version 16[35s] using the metareg package.[36s]

RESULTS

Search Results and Scope of Evidence

The study selection process, based on PRISMA, is illustrated in Figure 1. The initial search identified 1142 publications (PubMed: 358 and Embase: 784), of which 43 were found relevant. Four additional publications were identified by screening bibliographies of relevant articles.[37s–40s] Overall, 47 publications met the inclusion criteria. Only 1 study was identified in the 22 Pacific Island nations, in Vanuatu.[41s] Informed by the distribution of available data in these publications, the extracted data were analyzed for each of Canada and for the sister nations of Australia and New Zealand, combined.

Extracted HSV-2 measures encompassed 5 cumulative seroconversion rates (1 in Canada, 2 in Australia, and 2 in New Zealand), 2 seroincidence rates (1 in Canada and 1 in Australia), 22 overall seroprevalence measures in Canada (63 stratified measures by sex and/or age), 14 overall seroprevalence measures in Australia and New Zealand (35 stratified measures by sex and/or age), 5 overall proportions of HSV-2 isolation in GUD (5 stratified proportions; 1 in Canada and 4 in Australia), 7 overall proportions of HSV-2 isolation in genital herpes in Canada (27 stratified proportions by sex and/or age), and 9 overall proportions of HSV-2 isolation in genital herpes in Australia and New Zealand (19 stratified proportions by sex and/or age).

Cumulative Seroconversion and Seroincidence Overview

Cumulative seroconversion (cumulative seroincidence) and seroincidence rates are shown in Table S3 (http://links.lww.com/OLQ/A799). All studies were longitudinal cohorts [number of measures (n) = 5] with follow-up durations ranging from 6 months to 4 years. Herpes simplex virus type 2 cumulative seroconversion and seroincidence rates ranged between 0.25 to 39.0% and 1.5% to 17.1% per 100 person-years, respectively, among all population types.

Seroprevalence Overview

Overall seroprevalence measures in Canada (n = 22) are reported in Table S4 (http://links.lww.com/OLQ/A799). Majority of the studies were published after 2005 (n = 14; 63.6%) and used convenience sampling (n = 17; 77.2%). In Australia and New Zealand (n = 14; Table S5, http://links.lww.com/OLQ/A799), most of the studies were published before 2005 (n = 9; 64.3%), but also used convenience sampling (n = 11; 78.6%).

Stratified seroprevalence measures are summarized in Tables 1 and 2. In Canada, HSV-2 seroprevalence ranged from 0.0% to 46.6% with a median of 9.8% among general populations (n = 50), from 19.0% to 88.7% with a median of 42.3% among STI clinic attendees and symptomatic populations (n = 5), and from 48.2% to 86.3% with a median of 55.9% among HIV-positive individuals and individuals in HIV-discordant couples (n = 7).

In Australia and New Zealand, HSV-2 seroprevalence ranged from 1.6% to 72.1% with a median of 15.1% among general populations (n = 20), from 9.0% to 59.7% with a median of 28.3% among men who have sex with men (MSM) (n = 5), and from 11.7% to 64.7% with a median of 32.5% among STI clinic attendees and symptomatic populations (n = 8).

Descriptive statistics of HSV-2 seroprevalence in Canada and in Australia and New Zealand, by sex and by general population stratification, are in Tables 1 and 2, respectively.

Pooled Mean Estimates for HSV-2 Seroprevalence

Herpes simplex virus type 2 seroprevalence meta-analyses across population types and subpopulations are in Tables 1 and 2. In Canada, pooled mean seroprevalence was lowest in general populations at 10.0% (95% confidence interval [CI], 7.8–12.4%) and was highest in STI clinic attendees and symptomatic populations at 44.5% (95% CI, 20.0–70.5%), and in HIV-positive individuals and individuals in HIV-discordant couples at 60.7% (95% CI, 49.8–71.1%).

In Australia and New Zealand, pooled mean seroprevalence was lowest in general populations at 15.4% (95% CI, 9.6–22.2%) and was highest in MSM at 27.8% (95% CI, 12.0–47.2%) and in

STI clinic attendees and symptomatic populations at 37.2% (95% CI, 23.7–51.8%). Women generally had a higher pooled mean seroprevalence than men (Table 1).

Among general populations in Canada, pooled mean seroprevalence increased with age from 4.2% (95% CI, 2.6–6.1%) in younger than 20 years individuals, to 6.5% (95% CI, 3.9–9.7%) in 20- to 29-year-old individuals, 13.9% (95% CI, 11.0–17.1%) in 30- to 39-year-old individuals, 15.7% (95% CI, 10.6–21.5%) in 40- to 49-year-old individuals, and 18.8% (95% CI, 16.6–21.2%) in 50 years or older individuals (Table 2).

Similarly, in Australia and New Zealand, pooled mean seroprevalence increased from 3.7% (95% CI, 1.1–7.3%) in younger

BOX 1. Methodology Employed in this Study

Methodology	Detailed Description
Data source and search strategy	–Search conducted on January 21, 2021 in PubMed and Embase. –Search strategies included exploded MeSH/Emtree terms and broad terms with no language or time restrictions. –The definition of Canada, Australia, New Zealand, and Pacific Islands region included 25 countries and territories: ○ Canada, Australia, New Zealand, American Samoa, Cook Islands, Fiji, French Polynesia, Guam, Kiribati, Marshall Islands, Micronesia, Nauru, New Caledonia, Niue, Northern Mariana Islands, Palau, Pitcairn, Samoa, Solomon Islands, Tokelau, Tonga, Tuvalu, Vanuatu, Wallis and Futuna islands.
Study selection and inclusion and exclusion criteria	–Search results were imported into the reference manager Endnote (Thomson Reuters, USA). –Screening was performed in four stages: (1) Duplicate publications were identified and excluded. (2) Titles and abstracts were screened for relevant and potentially relevant publications. (3) Full texts of relevant and potentially relevant publications were retrieved and screened for relevance. (4) Bibliographies of relevant publications and reviews were checked for additional potentially relevant publications. –Inclusion criteria were any publication reporting primary data on any of the following outcome measures (with a minimum sample size of 10): (1) HSV-2 antibody seroincidence as detected by a type-specific diagnostic assay. (2) HSV-2 antibody seroprevalence as detected by a type-specific diagnostic assay. (3) Proportion of HSV-2 in GUD as isolated by standard viral detection and subtyping methods. (4) Proportion of HSV-2 in genital herpes (as opposed to HSV-1), as isolated by standard viral detection and subtyping methods. –Exclusion criteria were: ○ Case reports, case series, reviews, editorials, commentaries, and qualitative studies. ○ Measures reporting seroprevalence in infants <6 months old as their antibodies can be maternal in origin. –In this study, the term "publication" refers to a document reporting one or several outcome measures. "study" or "measure" refers to a specific outcome measure and its details.
Data extraction and data synthesis	–Extracted variables included: author(s), publication title, year(s) of data collection, publication year, country of origin, country of survey, city, study site, study design, study sampling procedure, study population and its characteristics (e.g., sex and age), sample size, HSV-2 outcome measures, and diagnostic assay. –Overall outcome measure and their stratified measures were extracted, provided the sample size in each stratum is ≥10. –For studies including overall sample size, but no individual strata sample sizes, the sample size of each stratum was assumed equal to overall sample size divided by the number of strata in the study. –Stratification hierarchy for seroincidence and seroprevalence in descending order of preference was: (1) Population type as defined in Box S1 (http://links.lww.com/OLQ/A799). (2) Sex (3) Age group classified as (groups optimized to best fit reported data): ○ <20 y ○ 20–29 y ○ 30–39 y ○ 40–49 y ○ ≥50 y ○ Mixed age bands. –Stratification hierarchy for GUD and genital herpes included genital herpes episode status and study site: (1) Genital herpes episode status classified as: ○ First episode genital herpes. ○ Recurrent genital herpes. (2) Study site stratification classified as: ○ Hospital. ○ Sexually transmitted disease clinic. –Measures reporting any HSV-2 outcome among children <15 years old were only reported but not included in the analyses.
Quality assessment	The Cochrane's approach for ROB assessment included: –Study's precision classification into low versus high based on the sample size (<200 vs ≥200). –Study's appraisal into low vs high ROB was determined using two quality domains: ○ Sampling method: probability-based versus non-probability based. ○ Response rate: ≥80% versus <80% or unclear.

Continued next page

BOX 1. *(Continued)*

Methodology	Detailed Description
Meta-analyses	–Meta-analyses were conducted using DerSimonian-Laird random-effects models with inverse variance weighting. The variance of each outcome measure was stabilized using the Freeman-Tukey arcsine square-root transformation. –Pooled mean HSV-2 seroprevalence was estimated for Canada and for Australia and New Zealand by population type and sex, and for general populations by age group, year of data collection category, and year of publication category. –Pooled proportions of HSV-2 isolation in GUD were estimated by sex. Pooled proportions of HSV-2 isolation in genital herpes were estimated for Canada and for Australia and New Zealand by sex, age group, year of data collection category, and year of publication category. –Heterogeneity assessment was based on three complementary metrics: ○ Cochran's Q statistic to assess existence of heterogeneity in effect size ($P < 0.1$ indicated heterogeneity). ○ I^2 heterogeneity measure to assess the percentage of between-study variation in effect size that is due to actual differences in effect size rather than chance. ○ Prediction interval to describe the distribution of true outcome measures around the pooled mean.
Meta-regressions	–Univariable and multivariable random-effects meta-regression analyses using log-transformed proportions were carried out to identify predictors of HSV-2 seroprevalence and proportion of HSV-2 isolation in genital herpes. –Factors in the univariable model with a $P < 0.1$ were included in the multivariable analysis. –Factors in the multivariable model with a $P \leq 0.05$ were deemed to be significant predictors. –Variables included in the univariable meta-regression model for HSV-2 seroprevalence were: ○ Population type. ○ Age group. ○ Sex. ○ Country. ○ Assay type (Western blot, ELISA, and others*). ○ Sample size. ○ Sampling method. ○ Response rate. ○ Year of data collection. ○ Year of publication. ○ Year of publication category (≤2005; >2005)†. ○ Year of data collection category (≤2000; >2000). –Variables included in the univariable meta-regression model for proportion of HSV-2 isolation in laboratory-confirmed genital herpes were: ○ Age group. ○ Sex. ○ Country. ○ Sample size. ○ Year of publication. ○ Year of publication category (≤2005; >2005). – The year of data collection had a few missing entries that were imputed by adjusting the year of publication using the median difference with the year of data collection across all studies.

*Other assay type is radioimmunoassay.

†The categories were set based on the observed median time between the year of publication and year of data collection of 5 years.

ELISA, enzyme-linked immunosorbent type-specific assay.

than 20 years individuals, to 10.4% (95% CI, 7.1–14.2%) in 20- to 29-year-old individuals, and 17.4% (95% CI, 13.7–21.5%) in 30 years or older individuals (Table 2).

The majority of meta-analyses showed strong evidence for heterogeneity ($P < 0.001$) that was confirmed by I^2 greater than 50% and wide prediction intervals (Tables 1 and 2). Thus, heterogeneity was due to true differences in seroprevalence across studies, instead of random chance. Forest plots by population type can be found in Figure S1 for Canada and Figure S2 for Australia and New Zealand (http://links.lww.com/OLQ/A799).

Associations with Increased HSV-2 Seroprevalence

Results of univariable and multivariable meta-regression models for HSV-2 seroprevalence are presented in Table 3. The first model, including population type, age group, sex, and year of publication as a categorical term, explained 60.1% of seroprevalence variation (Table 3). Compared with general populations, seroprevalence was highest in HIV-positive individuals and individuals in HIV-discordant couples, with an adjusted risk ratio (ARR) of 5.50 (95% CI, 3.20–9.46), followed by STI clinic attendees and symptomatic populations, intermediate-risk populations, and higher-risk populations.

Compared with individuals younger than 20 years, seroprevalence increased gradually with age, peaking in those 50 years or older with an ARR of 3.61 (95% CI, 1.48–8.82). Men had a lower seroprevalence than women with an ARR of 0.64 (95% CI, 0.47–0.86). No evidence was found for a statistically significant variation in seroprevalence over time.

The second model, which included the year of publication as a continuous variable, explained 59.3% of seroprevalence variation and produced similar findings to the first model (Table 3). Sensitivity analysis, including year of data collection instead of year of publication, confirmed the same findings (Table S6, http://links.lww.com/OLQ/A799).

HSV-2 Isolation in GUD and in Genital Herpes

Stratified proportions of HSV-2 isolation in clinically diagnosed GUD and in laboratory-confirmed genital herpes are summarized in Table 4. A list of the studies overall measures

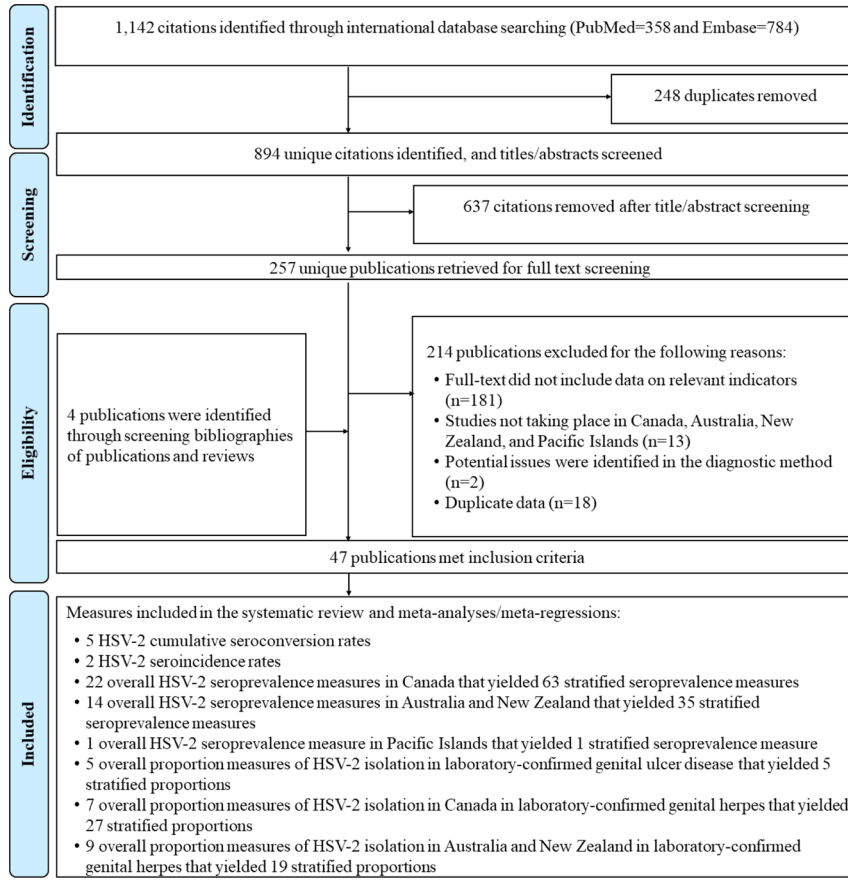

Figure 1. Flowchart of article selection for systematic review of HSV-2 infection in Canada, Australia, New Zealand, and Pacific Islands, per PRISMA guidelines.[24]

is shown in Table S7 (http://links.lww.com/OLQ/A799). The proportion of HSV-2 isolation in GUD (n = 5) in Canada and Australia, combined (no studies from New Zealand), ranged from 1.6% to 53.3% with a median of 22.1% and a pooled mean of 17.4% (95% CI, 4.0–37.1%) (Table 4).

The proportion of HSV-2 isolation in genital herpes in Canada (n = 27) ranged from 24.2% to 99.0% with a median of 64.6% and a pooled mean of 62.1% (95% CI, 53.8–70.1%). Among women, the proportion ranged between 24.2% and 95.5% with a median of 55.8% and a pooled mean of 56.1% (95% CI, 40.7–71.0%). Among men, it ranged between 45.0% and 85.7% with a median of 71.0% and a pooled mean of 63.7% (95% CI, 54.8–71.2%).

In Australia and New Zealand (n = 19), the proportion of HSV-2 isolation in genital herpes ranged from 33.9% to 94.4% with a median of 70.0% and a pooled mean of 71.9% (95% CI, 64.2–78.9%). Among women, the proportion ranged between 33.9% and 81.0% with a median of 67.5% and a pooled mean of 65.8% (95% CI, 54.7–76.1%). Among men, it ranged between 59.8% and 94.4% with a median of 79.1% and a pooled mean of 79.2% (95% CI, 68.9–87.9%). Additional summary statistics are shown in Table 4.

Heterogeneity was confirmed in most meta-analyses ($P < 0.001$, $I^2 > 50\%$, and wide prediction intervals). Forest plots are presented in Figure S3 (http://links.lww.com/OLQ/A799).

Associations with Increased HSV-2 Isolation in Genital Herpes

Results of univariable and multivariable meta-regression models for the proportion of HSV-2 isolation in genital herpes are shown in Table 5. The first model, including year of publication as a categorical term, explained 68.7% of the variation. Compared with individuals younger than 20 years, the proportion of HSV-2 isolation in genital herpes was highest in those 50 years or older with an ARR of 2.67 (95% CI, 1.91–3.72). Compared to women, men had a higher proportion of HSV-2 isolation with an ARR of 1.21 (95% CI, 1.06–1.38). Data published after 2005 had a lower proportion of HSV-2 isolation than those published before 2005 with an ARR of 0.82 (95% CI, 0.72–0.93).

The second model, including year of publication as a linear term, explained 75.9% of the variation, and showed similar results to the first model. There was evidence for a statistically significant decline in the proportion of HSV-2 isolation in genital herpes over time with an ARR of 0.98 (95% CI, 0.97–0.99) per year.

Quality Assessment

Out of 49 publications that included seroprevalence measures, 47 were included in the systematic review, and only 2 were excluded due to potential issues in the validity of the diagnostic method (Fig. 1). Findings of the quality assessment are presented in Table S8 (http://links.lww.com/OLQ/A799). In summary, 34 studies (91.9%) had high precision, 8 studies (21.6%) had low ROB in the sampling method domain, and 4 studies (10.8%) had low ROB in the response rate domain. Three studies (8.1%) had low precision, 29 studies (78.4%) had high ROB in the sampling method domain, and 9 studies (24.3%) had high ROB in the response rate domain. Only 1 study (2.7%) had low ROB in both quality domains, whereas 5 studies (13.5%) had high ROB in both

TABLE 1. Pooled Mean Estimates for HSV-2 Seroprevalence in Canada and in Australia and New Zealand

	Outcome Measures	Samples	HSV-2 Seroprevalence (%)		Pooled Mean HSV-2 Seroprevalence	Heterogeneity Measures		
Population Type	Total, n	Total, N	Range	Median	Mean (%) (95% CI)	Q* (*P*)	$I^{2\dagger}$ (%) (95% CI)	Prediction Interval‡ (%)
Canada								
General populations	50	11,140	0.0–46.6	9.8	10.0 (7.8–12.4)	878.2 (< 0.001)	94.4 (93.3–95.3)	0.1–30.5
Women	35	8154	0.0–46.6	11.0	11.1 (8.2–14.3)	720.9 (< 0.001)	95.3 (94.2–96.1)	0.1–34.0
Men	15	2986	0.0–21.3	7.0	7.8 (5.0–11.1)	151.3 (< 0.001)	90.7 (86.4–93.7)	0.1–24.3
Higher-risk populations	1§	144	—	—	38.2 (30.4–46.3)	—	—	—
MSM	1§	144	—	—	38.2 (30.4–46.3)	—	—	—
STI clinic attendees and symptomatic populations	5	8648	19.0–88.7	42.3	44.5 (20.0–70.5)	868.0 (< 0.001)	99.5 (99.4–99.6)	0.0–100.0
Women	1§	195	—	—	88.7 (83.9–92.8)	—	—	—
Mixed sexes	4	8453	19.9–46.8	33.2	32.5 (19.7–46.7)	481.0 (< 0.001)	99.4 (99.1–99.6)	0.0–93.5
HIV-positive individuals and individuals in HIV-discordant couples	7	1522	48.2–86.3	55.9	60.7 (49.8–71.1)	87.8 (< 0.001)	93.2 (88.4–96.0)	22.6–92.4
Women	2§	298	—	—	79.1 (62.8–91.7)	—	—	—
Men	3	894	48.2–55.9	50.5	51.3 (46.3–56.4)	4.3 (0.117)	53.4 (0.0–86.6)	7.3–94.1
Mixed sexes	2§	330	—	—	55.5 (50.1–60.8)	—	—	—
Australia and New Zealand								
General populations	20	10,655	1.6–72.1	15.1	15.4 (9.6–22.2)	597.4 (< 0.001)	96.8 (96.0–97.5)	0.0–53.9
Women	16	8081	2.9–72.1	15.5	15.8 (9.4–23.4)	434.8 (< 0.001)	96.6 (95.5–97.4)	0.0–54.3
Men	4	2574	1.6–43.8	11.5	14.0 (1.9–34.3)	134.8 (< 0.001)	97.8 (96.2–98.7)	0.0–100.0
Intermediate-risk populations¶	2§	747	—	—	38.3 (8.1–74.7)	—	—	—
Women	1§	118	—	—	57.6 (48.6–66.4)	—	—	—
Men	1§	629	—	—	21.1 (18.0–24.4)	—	—	—
Higher-risk populations	5	1371	9.0–59.7	28.3	27.8 (12.0–47.2)	120.3 (< 0.001)	96.7 (94.4–98.0)	0.0–95.2
MSM	5	1371	9.0–59.7	28.3	27.8 (12.0–47.2)	120.2 (< 0.001)	96.7 (94.4–98.0)	0.0–95.2
STI clinic attendees and symptomatic populations	8	1181	11.7–64.7	32.5	37.2 (23.7–51.8)	221.7 (< 0.001)	96.8 (95.3–97.9)	1.1–86.5
Women	2§	150	—	—	41.0 (18.0–66.3)	—	—	—
Men	5	851	22.0–64.7	35.0	41.8 (25.1–59.5)	125.6 (< 0.001)	96.8 (94.7–98.1)	0.0–97.2
Mixed sexes	1§	180	—	—	11.7 (7.4–16.8)	—	—	–
Pacific Islands								
General populations	1§	535	—	—	30.0 (25.7–33.6)	—	—	—
Mixed sexes	1§	535	—	—	30.0 (25.7–33.6)	—	—	—

*Q: The Cochran's Q statistic is a measure assessing the existence of heterogeneity in pooled outcome measures, here HSV-2 seroprevalence.

†I^2: A measure that assesses the magnitude of between-study variation that is due to actual differences in HSV-2 seroprevalence across studies rather than to chance.

‡Prediction interval: A measure that estimates the distribution (95% interval) of true HSV-2 seroprevalence around the estimated mean.

§No meta-analysis was done due to the small number of studies (n < 3).

¶Intermediate-risk populations included prisoners from correctional centers.

quality domains. Risk of bias assessment for the response rate domain was "unclear" for 24 studies (64.9%).

DISCUSSION

This study provided a thorough, systematic investigation of HSV-2 epidemiology in Australia, Canada, and New Zealand. The HSV-2 seroprevalence in the general population was estimated at 10% in Canada and 15% in the sister nations of Australia and New Zealand, levels that are similar to those found at present in the United States[42s–45s] and in Asia,[20] but lower than the seroprevalence in Africa at 37%[21] and in Latin America and the Caribbean (LAC) at 21%.[22] While HSV-2 seroprevalence in Canada at 10% is similar to that in the United States, estimated most recently at 12%,[42s] the estimate for Canada is based on seroprevalence studies conducted over the last two decades, including times in which seroprevalence in the United States was higher and approached 20%.[42s–45s] It appears thus that HSV-2 seroprevalence in Canada has been lower than that in the United States, perhaps because Canada was less affected by the cohort effect of high incidence between 1960 and mid-1980s that was described recently for the United States.[44s]

Unlike as in Africa,[21] Asia,[20] LAC,[22] and the United States,[42s–45s] there was no evidence for declining HSV-2 seroprevalence in these countries. It is not known whether this lack of decline compared with other world regions could be a consequence of recent migration into these countries from countries with higher seroprevalence than in these countries. One of the reviewed studies suggested that immigrants tend to have higher seroprevalence than those born in these countries.[46s]

Remarkably, HSV-2 infection (as opposed to herpes simplex virus type 1 [HSV-1] infection) was the etiological cause of 62% and 72% of genital herpes cases in Canada and in Australia and New Zealand, respectively. The contribution of HSV-2 to genital herpes in these countries is thus lower than that in Africa at 97%,[21] LAC at 91%,[22] and Asia at 76%.[20] Moreover, the contribution of HSV-2 to genital herpes is declining by about 2% per year (Table 5). This is consistent with increasing HSV-1 infection in

TABLE 2. Pooled Mean Estimates for HSV-2 Seroprevalence in the General Populations in Canada and in Australia and New Zealand

	Outcome Measures	Sample Size	HSV-2 Seroprevalence (%)		Pooled Mean HSV-2 Seroprevalence	Heterogeneity Measures		
Population Classification	Total, n	Total, N	Range	Median	Mean (%) (95% CI)	Q* (*P*)	$I^{2\dagger}$ (%) (95% CI)	Prediction Interval‡ (%)
Canada								
Age group, y								
<20	10	1105	0.0–9.0	3.6	4.2 (2.6–6.1)	17.6 (0.041)	48.8 (0.0–75.2)	0.6–10.3
20–29	13	2518	0.7–16.3	7.5	6.5 (3.9–9.7)	80.9 (< 0.001)	85.2 (76.2–90.7)	0.0–21.0
30–39	10	1251	7.0–21.5	12.6	13.9 (11.0–17.1)	18.1 (0.034)	50.4 (0.0–75.9)	6.4–23.5
40–49	8	865	5.7–28.1	15.6	15.7 (10.6–21.5)	37.3 (< 0.001)	81.2 (63.9–90.2)	2.2–37.4
≥50	2§	1083	—	—	18.8 (16.6–21.2)	—	—	—
Mixed	7	4318	2.6–46.6	16.0	14.8 (5.9–26.9)	514.7 (< 0.001)	98.8 (98.4–99.1)	0.0–66.0
Year of publication category¶								
≤2005	40	4909	0.0–28.1	9.3	9.2 (7.1–11.5)	283.8 (< 0.001)	86.3 (82.2–89.4)	0.4–26.1
>2005	10	6231	2.6–46.6	13.5	13.4 (6.8–21.6)	593.2 (< 0.001)	98.5 (98.0–98.8)	0.0–51.3
Year of data collection category								
≤2000	40	4909	0.0–28.1	9.3	9.2 (7.1–11.5)	283.8 (< 0.001)	86.3 (82.2–89.4)	0.4–26.1
>2000	10	6231	2.6–46.6	13.5	13.4 (6.8–21.6)	593.2 (< 0.001)	98.5 (98.0–98.8)	0.0–51.3
All studies	50	11,140	0.0–46.6	9.8	10.0 (7.8–12.4)	878.1 (< 0.001)	94.4 (93.3–95.3)	0.1–30.5
Australia and New Zealand								
Age group, y								
<20	2§	182	—	—	3.7 (1.1–7.3)	—	—	—
20–29	3	2065	8.3–15.5	9.7	10.4 (7.1–14.2)	6.9 (0.032)	70.9 (1.2–91.5)	0.0–72.0
≥30	5	2226	13.8–27.6	18.1	17.4 (13.7–21.5)	18.8 (0.001)	78.8 (49.3–91.1)	6.3–32.5
Mixed	10	6182	1.6–72.1	15.6	17.8 (7.1–31.9)	508.4 (< 0.001)	98.2 (97.6–98.7)	0.0–77.0
Year of publication category¶								
≤2005	10	4130	1.6–19.9	9.0	8.7 (5.0–13.2)	125.8 (< 0.001)	92.8 (88.9–95.4)	0.0–28.4
>2005	10	6525	7.6–72.1	20.3	23.4 (12.9–35.9)	409.6 (< 0.001)	97.8 (97.0–98.4)	0.0–73.6
Year of data collection category								
≤2000	8	3498	4.3–19.9	11.8	11.2 (7.7–15.3)	51.3 (< 0.001)	86.3 (75.2–92.5)	1.8–26.6
>2000	12	7157	1.6–72.1	16.8	18.6 (9.2–30.4)	538.1 (< 0.001)	98.0 (97.3–98.4)	0.0–71.1
All studies	20	10,655	1.6–72.1	15.1	15.4 (9.6–22.2)	597.4 (< 0.001)	96.8 (96.0–97.5)	0.0–53.9

*Q: The Cochran's Q statistic is a measure assessing the existence of heterogeneity in pooled outcome measures, here HSV-2 seroprevalence.

†I^2: A measure that assesses the magnitude of between-study variation that is due to actual differences in HSV-2 seroprevalence across studies rather than to chance.

‡Prediction interval: A measure that estimates the distribution (95% interval) of true HSV-2 seroprevalence around the estimated mean.

§No meta-analysis was done due to the small number of studies (n < 3).

¶The categories were set based on the observed median time between the year of publication and year of data collection of 5 years.

genital herpes in these countries, as in Western countries including the United States,[47s,48s] and Europe,[49s–53s] as well as in parts of Asia.[54s] Meanwhile, sexual transmission of HSV-1 infection still appears to be limited in Africa,[55s] LAC,[56s] and possibly in the Middle East and North Africa.[57s]

Herpes simplex virus type 2's role in genital herpes was higher among older persons (Table 5), consistent with increased HSV-1 sexual transmission mainly among young persons, a pattern well-documented in several Western countries.[48s–52s,58s] Herpes simplex virus type 2 genital herpes seems to affect men more than women (Table 5), but this may reflect the ease of clinically diagnosing this condition in men compared with women and/or disproportional contribution of genital herpes among MSM.[59s] Herpes simplex virus type 2 seems to play a minor role in GUD, at only 17% (Table 4), lower than that found in Africa at 51%,[21] Asia at 48%,[20] and LAC at 41%.[22] However, only 5 GUD studies were identified in these countries; thus, they may not be representative of the true contribution of HSV-2 to GUD in these countries.

These findings support the existence of generic patterns in the global epidemiology of HSV-2 infection. Just as in Africa,[21] Asia,[20] and LAC,[22] seroprevalence increased steadily with age and varied immensely by population sexual-risk classification (Table 3). Age and risk group alone explained over half of the seroprevalence variation across studies (Table 3). Women had 60% higher seroprevalence than men (Table 3), attesting to women's higher bio-anatomical susceptibility to this infection.[60s,61s]

This study had some limitations. Only 1 study was available for Pacific Island nations. There was heterogeneity in study methods, study quality, and implemented diagnostic assay. Most studies did not use probability-based sampling, nor did they report the response rate, thereby increasing the likelihood of bias. Despite these limitations, there was no evidence of a statistically significant effect on HSV-2 seroprevalence for assay type, sample size, sampling method, and response rate (Table 3). A considerable volume of data was available to allow a range of analyses to be completed. Most of the observed heterogeneity in measured outcomes among studies was explained by meta-regression analyses as being related to epidemiological rather than study methodological factors (Tables 3 and 5).

One-tenth of adults are HSV-2 seropositive in Canada and 15% of adults are seropositive in Australia and New Zealand. Yet, there is no evidence of declining seroprevalence in recent decades, unlike other countries and global regions. Two-thirds of genital herpes cases are caused by HSV-2 infection in these countries, but HSV-2's contribution appears to be declining by 2% per year, possibly because of concurrent growth of HSV-1 infection in genital herpes, particularly among young persons. These findings support the relevance of HSV-2 prophylactic and therapeutic

TABLE 3. Univariable and Multivariable Meta-Regression Analyses for HSV-2 Seroprevalence in Canada, Australia, and New Zealand

			Outcome Measures	Sample Size	Univariable Analysis				Multivariable Analysis*			
							LR Test	Adjusted	Model 1†		Model 2‡	
			Total, n	Total, N	RR (95% CI)	*P*	*P*	R^2 (%)	ARR (95% CI)	*P*	ARR (95% CI)	*P*
Population characteristics	Population type	General populations	70	21,795	1.00	—	<0.001	45.69	1.00	—	1.00	—
		Intermediate-risk populations§	2	747	3.21 (1.20–8.61)	0.021			3.78 (1.53–9.34)	0.004	3.11 (1.28–7.54)	0.013
		Higher-risk populations	6	1515	2.44 (1.34–4.42)	0.004			2.32 (1.29–4.18)	0.006	2.51 (1.39–4.54)	0.003
		STI clinic attendees and symptomatic populations	13	9829	3.28 (2.15–5.01)	<0.001			4.63 (2.67–8.06)	<0.001	4.00 (2.33–6.88)	<0.001
		HIV-positive individuals and individuals in HIV-discordant couples	7	1522	5.44 (3.15–9.40)	<0.001			5.50 (3.20–9.46)	<0.001	5.57 (3.20–9.69)	<0.001
	Age group, y	<20	12	1287	1.00	—	<0.001	35.41	1.00	—	1.00	—
		20–29	16	4583	1.58 (0.81–3.08)	0.175			1.42 (0.81–2.49)	0.216	1.49 (0.84–2.62)	0.164
		30–39	14	3448	3.04 (1.56–5.92)	0.001			2.73 (1.56–7.79)	0.001	3.03 (1.73–5.31)	<0.001
		40–49	8	865	3.24 (1.52–6.92)	0.003			3.29 (1.76–6.14)	<0.001	3.58 (1.84–6.95)	<0.001
		≥50	3	1140	5.88 (2.18–15.89)	0.001			3.61 (1.48–8.82)	0.005	4.61 (1.97–10.81)	0.001
		Mixed	45	24,085	5.33 (3.01–9.43)	<0.001			2.11 (1.16–3.85)	0.016	2.61 (1.52–4.50)	0.001
	Sex	Women	57	16,996	1.00	—	0.087	3.38	1.00	—	1.00	—
		Men	34	9449	1.13 (0.75–1.70)	0.566			0.64 (0.47–0.86)	0.004	0.64 (0.47–0.87)	0.005
		Mixed sexes	7	8963	2.28 (1.10–4.73)	0.028			0.44 (0.24–0.80)	0.008	0.48 (0.26–0.88)	0.018
	Countries¶	Canada	63	21,454	1.00	—	0.284	0.00	—	—	—	—
		Australia	31	12,776	1.35 (0.89–2.05)	0.158			—	—	—	—
		New Zealand	4	1178	1.57 (0.60–4.07)	0.353			—	—	—	—
Study methodology characteristics	Assay type	Western blot	15	7155	1.00	—	0.447	0.51	—	—	—	—
		ELISA	77	27,303	1.28 (0.75–2.19)	0.367			—	—	—	—
		Other‖	6	950	0.85 (0.34–2.15)	0.733			—	—	—	—
	Sample size**	<200	3	443	1.00	—	0.174	0.89	—	—	—	—
		≥200	95	34,965	0.47 (0.16–1.40)	0.174			—	—	—	—
	Sampling method	Probability based	25	10,879	1.00	—	0.779	0.00	—	—	—	—
		Nonprobability based	73	24,529	1.06 (0.69–1.65)	0.779			—	—	—	—
	Response rate	≥80%	11	3489	1.00	—	0.255	0.80	—	—	—	—
		<80%	21	16,598	0.56 (0.28–1.12)	0.099			—	—	—	—
		Unclear	66	15,321	0.68 (0.37–1.25)	0.208			—	—	—	—
Temporal variables	Year of publication category	≤2005	62	17,717	1.00	—	0.001	9.57	1.00	—	—	—
		>2005	36	17,691	1.92 (1.32–2.80)	0.001			1.42 (0.96–2.10)	0.077	—	—
	Year of publication		98	35,408	1.02 (0.99–1.04)	0.170	0.170	1.09	—	—	1.01 (0.99–1.03)	0.407

*Two multivariable models were conducted, one for year of publication as a categorical variable and one for year of publication as a linear term.

†Variance explained by multivariable model 1 (adjusted R^2) = 60.09%.

‡Variance explained by multivariable model 2 (adjusted R^2) = 59.29%.

§Intermediate-risk populations included prisoners from correctional centers.

¶The only one available study from the Pacific Islands nations was excluded from this analysis.

‖Other assay type includes radioimmunoassay.

**Sample size denotes the sample size of each study population found in the original publication.

LR, likelihood ratio; RR, risk ratio.

TABLE 4. Pooled Mean Proportions of HSV-2 Isolation in Clinically Diagnosed GUD and in Laboratory-Confirmed Genital Herpes in Canada and in Australia and New Zealand

	Outcome Measures	Samples	Proportion of HSV-2 Isolation (%)		Pooled Proportion of HSV-2 Isolation (%)	Heterogeneity Measures		
Population Type	Total, n	Total, N	Range	Median	Mean (95% CI)	Q* (*P*)	$I^{2\dagger}$ (%) (95% CI)	Prediction Interval‡ (%)
Patients with GUD in Canada and Australia	5	13,314	1.6–53.3	22.1	17.4 (4.0–37.1)	120.3 (< 0.001)	96.7 (94.4–98.0)	0.0–93.4
Sex								
Men	2§	213	—	—	20.2 (0.0–83.1)	—	—	—
Mixed sexes	3	13,101	5.5–23.1	22.1	17.0 (7.6–29.2)	15.1 (0.001)	86.7 (61.9–95.4)	0.0–100.0
Patients with genital herpes in Canada	27	33,651	24.2–99.0	64.6	62.1 (53.8–70.1)	1185.0 (< 0.001)	97.8 (97.4–98.2)	19.2–96.0
Sex								
Women	11	2425	24.2–95.5	55.8	56.1 (40.7–71.0)	272.1 (< 0.001)	96.3 (94.8–97.4)	5.4–99.0
Men	10	597	45.0–85.7	71.0	63.7 (54.8–71.2)	40.6 (< 0.001)	77.8 (59.4–87.9)	33.2–89.3
Mixed	6	30,629	52.7–99.0	61.7	67.0 (50.1–85.4)	446.6 (< 0.001)	98.9 (98.4–99.2)	7.3–100.0
Age group, y								
<20	2§	458	—	—	34.5 (16.6–54.8)	—	—	—
20–29	4	865	24.2–66.3	41.5	42.6 (25.3–60.9)	51.7 (< 0.001)	94.2 (88.3–97.1)	0.0–100.0
30–39	4	524	50.3–85.7	61.8	56.8 (50.3–63.3)	6.0 (0.113)	49.7 (0.0–83.4)	32.3–79.8
≥40	9	411	64.6–95.5	77.8	78.0 (70.5–84.8)	23.7 (0.003)	66.3 (31.6–83.4)	53.2–95.6
Mixed	8	31,939	36.2–99.0	56.6	62.5 (45.6–78.0)	628.3 (< 0.001)	98.9 (98.5–99.2)	7.5–100.0
Year of publication category¶								
≤2005	20	2458	24.2–99.0	68.6	65.0 (54.2–75.1)	736.1 (< 0.001)	97.4 (96.8–97.9)	16.1–99.3
>2005	7	31,193	36.2–66.2	59.4	54.8 (46.3–63.1)	375.1 (< 0.001)	98.4 (97.8–98.9)	25.5–82.3
Year of data collection category								
≤2000	20	2458	24.2–99.0	68.6	65.0 (54.2–75.1)	736.1 (< 0.001)	97.4 (96.8–97.9)	16.1–99.3
>2000	7	31,193	36.2–66.2	59.4	54.8 (46.3–63.1)	375.1 (< 0.001)	98.4 (97.8–98.9)	25.5–82.3
Patients with genital herpes in Australia and New Zealand	19	34,764	33.9–94.4	70.0	71.9 (64.2–78.9)	2401.5 (< 0.001)	99.3 (99.1–99.4)	34.6–97.1
Sex								
Women	8	16,381	33.9–81.0	67.5	65.8 (54.7–76.1)	221.0 (< 0.001)	96.8 (95.3–97.9)	25.4–95.9
Men	8	11,325	59.8–94.4	79.1	79.2 (68.9–87.9)	386.7 (< 0.001)	98.2 (97.5–98.7)	39.8–100.0
Mixed	3	7058	50.3–89.9	62.8	69.2 (43.1–90.0)	327.1 (< 0.001)	99.4 (99.1–99.6)	0.0–100.0
Age group, y								
<30	1§	165	—	—	33.9 (26.9–41.4)	—	—	—
30–40	2§	865	—	—	56.9 (47.3–66.3)	—	—	—
≥40	6	1048	61.2–94.4	79.5	80.9 (71.0–89.3)	46.8 (< 0.001)	89.3 (79.4–94.5)	42.6–100.0
Mixed	10	33,402	50.3–89.9	67.5	72.3 (63.3–80.5)	2177.6 (< 0.001)	99.6 (99.5–99.7)	36.1–96.8
Year of publication category¶								
≤2005	8	25,722	62.8–89.9	80.6	80.7 (73.6–86.9)	934.8 (< 0.001)	99.3 (99.0–99.4)	51.6–98.0
>2005	11	9042	33.9–94.4	63.6	63.9 (53.6–73.6)	259.1 (< 0.001)	96.1 (94.5–97.3)	25.2–94.4
Year of data collection category								
≤2000	2§	2541	—	—	77.8 (47.0–97.3)	—	—	—
>2000	17	32,223	33.9–94.4	70.0	71.1 (63.0–78.6)	2241.3 (< 0.001)	99.3 (99.2–99.4)	33.4–97.0

*Q: The Cochran's Q statistic is a measure assessing the existence of heterogeneity in pooled outcome measures, here proportions of HSV-2 virus isolation in GUD and in genital herpes.

†I^2: A measure assessing the magnitude of between-study variation that is due to true differences in proportions of HSV-2 virus isolation across studies rather than sampling variation.

‡Prediction interval: A measure quantifying the distribution (95% interval) of true proportions of HSV-2 virus isolation around the estimated pooled mean.

§No meta-analysis was done due to the small number of studies (n < 3).

¶The categories were set based on the observed median time between the year of publication and year of data collection of 5 years.

TABLE 5. Univariable and Multivariable Meta-Regression Models for HSV-2 Isolation in Laboratory-Confirmed Genital Herpes in Canada, Australia, and New Zealand

		Outcome Measures	Samples	Univariable Analysis				Multivariable Analysis*			
								Model 1†		Model 2‡	
		Total, n	Total, N	RR (95% CI)	*P*	LR Test *P*	Adjusted R^2 (%)	ARR (95% CI)	*P*	ARR (95% CI)	*P*
Age group, y	<20	2	458	1.00	—	<0.001	53.07	1.00	—	1.00	—
	20–29	5	1030	1.20 (0.79–1.81)	0.384			1.26 (0.88–1.80)	0.195	1.27 (0.91–1.76)	0.156
	30–39	6	673	1.75 (1.17–2.61)	0.008			1.86 (1.31–2.63)	0.001	1.88 (1.34–2.56)	<0.001
	40–49	6	343	2.14 (1.43–3.21)	<0.001			2.28 (1.61–3.24)	<0.001	2.28 (1.65–3.15)	<0.001
	≥50	9	1116	2.53 (1.72–3.72)	<0.001			2.67 (1.91–3.72)	<0.001	2.69 (1.97–3.66)	<0.001
	Mixed	18	64,795	1.96 (1.35–2.84)	0.001			2.13 (1.52–2.98)	<0.001	2.12 (1.56–2.89)	<0.001
Sex	Women	19	18,806	1.00	—	0.130	4.99	1.00	—	1.00	—
	Men	18	11,922	1.23 (1.00–1.52)	0.051			1.21 (1.06–1.38)	0.005	1.21 (1.08–1.36)	0.002
	Mixed	9	37,687	1.17 (0.91–1.50)	0.223			1.16 (0.97–1.40)	0.106	1.13 (0.96–1.34)	0.134
Country	Canada	27	33,651	1.00	—	0.200	3.35	—	—	—	—
	Australia	17	30,831	1.19 (0.98–1.46)	0.075			—	—	—	—
	New Zealand	2	3,933	1.06 (0.67–1.68)	0.783			—	—	—	—
Sample size§	<200	2	57	1.00	—	0.941	0.00	—	—	—	—
	≥200	44	68,358	1.02 (0.61–1.69)	0.941			—	—	—	—
Year of publication category	≤2005	28	28,180	1.00	—	0.253	1.28	1.00	—	—	—
	>2005	18	40,235	0.89 (0.74–1.09)	0.253			0.82 (0.72–0.93)	0.002	—	—
Year of publication		46	68,415	0.98 (0.97–1.00)	0.069	0.069	6.54	—	—	0.98 (0.97–0.99)	<0.001

*Two multivariable models were conducted, one for year of publication as a categorical variable and one for year of publication as a linear term.

†Variance explained by the final multivariable model 1 (adjusted R^2) = 68.74%.

‡Variance explained by the final multivariable model 2 (adjusted R^2) = 75.94%.

§Sample size denotes the sample size of the study population found in the original publication.

vaccine development, as well as surveillance and further epidemiological research on HSV-2 infection, particularly in Pacific Island nations where data remains limited.

REFERENCES

1. World Health Organization. Massive proportion of world's population are living with herpes infection [internet]. 2020. Available at: https://www.who.int/news/item/01-05-2020-massive-proportion-world-population-living-with-herpes-infection. Accessed May 10, 2021.
2. James C, Harfouche M, Welton NJ, et al. Herpes simplex virus: Global infection prevalence and incidence estimates, 2016. Bull World Health Organ 2020; 98:315–329.
3. Garland SM, Steben M. Genital herpes. Best Pract Res Clin Obstet Gynaecol 2014; 28:1098–1110.
4. Gupta R, Warren T, Wald A. Genital herpes. Lancet 2007; 370: 2127–2137.
5. Wald A, Zeh J, Selke S, et al. Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. N Engl J Med 2000; 342:844–850.
6. Abu-Raddad LJ, Magaret AS, Celum C, et al. Genital herpes has played a more important role than any other sexually transmitted infection in driving HIV prevalence in Africa. PloS One 2008; 3:e2230.
7. Wald A, Langenberg AG, Link K, et al. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. JAMA 2001; 285:3100–3106.
8. Looker KJ, Magaret AS, May MT, et al. First estimates of the global and regional incidence of neonatal herpes infection. Lancet Glob Health 2017; 5:e300–e309.
9. Pinninti SG, Kimberlin DW. Neonatal herpes simplex virus infections. Semin Perinatol 2018; 42:168–175.
10. Corey L, Wald A, Celum CL, et al. The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: A review of two overlapping epidemics. J Acquir Immune Defic Syndr 2004; 35:435–445.
11. Freeman EE, Weiss HA, Glynn JR, et al. Herpes simplex virus 2 infection increases HIV acquisition in men and women: Systematic review and meta-analysis of longitudinal studies. AIDS 2006; 20:73–83.
12. Looker KJ, Elmes JAR, Gottlieb SL, et al. Effect of HSV-2 infection on subsequent HIV acquisition: An updated systematic review and meta-analysis. Lancet Infect Dis 2017; 17:1303–1316.
13. Looker KJ, Welton NJ, Sabin KM, et al. Global and regional estimates of the contribution of herpes simplex virus type 2 infection to HIV incidence: A population attributable fraction analysis using published epidemiological data. Lancet Infect Dis 2020; 20:240–249.
14. Omori R, Nagelkerke N, Abu-Raddad LJ. HIV and herpes simplex virus type 2 epidemiological synergy: Misguided observational evidence? A modelling study. Sex Transm Infect 2018; 94:372–376.
15. World Health Organization. Global health sector strategy on sexually transmitted infections 2016–2021 [internet]. 2016. Available at: https://www.who.int/reproductivehealth/publications/rtis/ghss-stis/en/. Accessed May 10, 2021.
16. Gottlieb SL, Deal CD, Giersing B, et al. The global roadmap for advancing development of vaccines against sexually transmitted infections: Update and next steps. Vaccine 2016; 34:2939–2947.
17. Gottlieb SL, Giersing B, Boily MC, et al. Modelling efforts needed to advance herpes simplex virus (HSV) vaccine development: Key findings from the World Health Organization consultation on HSV vaccine impact modelling. Vaccine 2019; 37:7336–7345.
18. Statistics Canada. Focus on geography series, 2016 census [internet]. 2017. Available at: https://www12.statcan.gc.ca/census-recensement/2016/as-sa/fogs-spg/Facts-can-eng.cfm?Lang=Eng&GK=CAN&GC=01&TOPIC=7. Accessed September 5, 2021.
19. United Nations—Department of Public Information. Oceania: Regional Fact Sheet [Internet]. 2006. Available at: https://www.un.org/migration/presskit/factsheet_oceania.pdf. Accessed May 21, 2021.
20. AlMukdad S, Harfouche M, Wettstein A, et al. Epidemiology of herpes simplex virus type 2 in Asia: A systematic review, meta-analysis, and meta-regression. Lancet Reg Health West Pac 2021; 12:100176.
21. Harfouche M, Abu-Hijleh FM, James C, et al. Epidemiology of herpes simplex virus type 2 in sub-Saharan Africa: Systematic review, meta-analyses, and meta-regressions. EClinicalMedicine 2021; 35:100876.
22. Harfouche M, Maalmi H, Abu-Raddad LJ. Epidemiology of herpes simplex virus type 2 in Latin America and the Caribbean: Systematic review, meta-analyses and metaregressions. Sex Transm Infect 2021; 97:490–500.
23. Higgins JPGS. Cochrane Handbook for Systematic Reviews of Interventions. Chichester, UK: John Wiley & Sons, 2011.
24. Moher D, Liberati A, Tetzlaff J, et al, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. J Clin Epidemiol 2009; 62:1006–1012.
25. United Nations—Department of Economic and Social Affairs. Standard country or area codes for statistical use [internet]. 2006. Available at: https://unstats.un.org/unsd/methodology/m49/. Accessed May 21, 2021.
26. World Health Organization. WHO regional offices [internet]. 2017. Available at: http://www.who.int/about/regions/en/. Accessed May 10, 2021.
27. Ashley RL. Performance and use of HSV type-specific serology test kits. Herpes 2002; 9:38–45.
28. Ashley-Morrow R, Nollkamper J, Robinson NJ, et al. Performance of focus ELISA tests for herpes simplex virus type 1 (HSV-1) and HSV-2 antibodies among women in ten diverse geographical locations. Clin Microbiol Infect 2004; 10:530–536.
29. Borenstein MHL, Higgins J, Rothstein H. Introduction to Meta-analysis. Chichester, UK: John Wiley & Sons, Ltd, 2009.
30. Freeman MF, Tukey JW. Transformations related to the angular and the square root. Ann Math Stat 1950; 21:607–611, 5.

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