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Herpes simplex virus type 1 in Europe: systematic review, meta-analyses and meta-regressions

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ABSTRACT

Objective To describe the epidemiology of herpes simplex virus type 1 (HSV-1) in Europe.

Methods We systematically reviewed HSV-1 related publications, conducted various meta-analyses and meta-regressions, assessed pooled mean seroprevalence, and estimated pooled mean proportions of HSV-1 viral detection in clinically diagnosed genital ulcer disease (GUD) and in genital herpes.

Results We extracted, from 142 relevant records, 179 overall (622 stratified) seroprevalence measures, 4 overall proportions of HSV-1 in GUD and 64 overall (162 stratified) proportions of HSV-1 in genital herpes. Pooled mean seroprevalence was 67.4% (95% CI 65.5% to 69.3%) with 32.5% (95% CI 29.4% to 35.7%) of children and 74.4% (95% CI 72.8% to 76.0%) of adults infected. Pooled seroprevalence increased steadily with age, being lowest in those aged <20 years (39.3%, 95% CI 35.9% to 42.7%) and highest in those aged >50 years (82.9%, 95% CI 78.8% to 86.6%). Pooled seroprevalence decreased yearly by 0.99-fold (95% CI 0.99 to 1.00). Pooled mean proportion of HSV-1 detection was 13.6% (95% CI 4.1% to 27.1%) in GUD, 34.1% (95% CI 31.7% to 36.5%) in genital herpes and 49.3% (95% CI 42.2% to 56.4%) in first episode genital herpes. Pooled proportion of HSV-1 detection in genital herpes increased yearly by 1.01-fold (95% CI 1.00 to 1.02), with higher detection in women (42.0%, 95% CI 37.4% to 46.7%) than men (24.1%, 95% CI 19.8% to 28.6%).

Conclusions HSV-1 epidemiology is transitioning away from its historical pattern of oral acquisition in childhood. Every year, seroprevalence is declining by 1% and the proportion of HSV-1 in genital herpes is increasing by 1%. As many as two-thirds of children are reaching sexual debut unexposed, and at risk of HSV-1 genital acquisition in adulthood.

Key questions

What is already known?

- Herpes simplex virus type 1 (HSV-1) infection is typically acquired through oral transmission during childhood.
- Recent data from North America and Europe suggest a decrease in acquisition of HSV-1 in childhood, a decline in seroprevalence in youth and an increase in genital herpes cases that are caused by HSV-1.

What are the new findings?

- Only two-thirds of the population in Europe are HSV-1 seropositive, far lower than the historical level of universal infection in childhood.
- Two-thirds of European children are reaching sexual debut unexposed to this infection, and at risk of genital acquisition in adulthood.
- Half of first episode genital herpes cases in Europe are already due to HSV-1, as opposed to HSV-2 infection.
- Seroprevalence in Europe is declining by 1% per year, and the contribution of HSV-1 to genital herpes is increasing, also by 1% per year.

What do the new findings imply?

- HSV-1 epidemiology in Europe is in transition and shifting away from its historical pattern of oral acquisition in childhood.
- HSV-1 transition in Europe is leading to more heterogeneous and variable transmission by age and geography, and an increasing role for HSV-1 in genital herpes and as a sexually transmitted disease.
- The findings highlight the importance of disease surveillance and monitoring of HSV-1 seroprevalence and genital herpes aetiology, and strengthen the case for an HSV-1 vaccine to limit transmission.

INTRODUCTION

Herpes simplex virus type 1 (HSV-1) causes a latent and mostly asymptomatic infection, and is typically acquired orally during childhood.[1 2] Infection is lifelong, with most viral shedding occurring through subclinical short-duration reactivations on the oral mucosa.[3] When symptomatic, HSV-1 can result in a number of adverse outcomes and sequelae such as mucocutaneous conditions and central nervous system complications.[1 2] The historical pattern of HSV-1 epidemiology appears to be changing, at least in a few regions.[4–12] Studies show a decrease in early acquisition of HSV-1, a decline in seroprevalence among youths and an increase in genital herpes cases

caused by HSV-1.[4 5 11 13–17] The disease burden of this infection, alongside its evolving epidemiology, has drawn the attention of the World Health Organization (WHO) and global partners, who are leading an international multisectorial effort focused on understanding the epidemiology of the virus and developing a HSV vaccine.[18–20]

Under this guise, we conducted a comprehensive systematic review to characterise HSV-1 epidemiology in Europe. We also used meta-analytical methods to provide robust estimates for HSV-1 seroprevalence across different populations, as well as proportions of HSV-1 detection in genital ulcer disease (GUD) and in genital herpes. We further assessed associations and temporal trends for these outcome measures.

METHODS

The methodology of this study was adapted from a previously conducted systematic review investigating the epidemiology of HSV-1 in Asia.[9] Details of the methodology are described in table 1.

Patient and public involvement

Patients were not involved in this study.

Data sources and search strategy

This systematic review followed the Cochrane Collaboration Handbook[21] and reported its findings in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (see online supplementary table s1).[22] We conducted a systematic literature search to identify HSV-1 related publications in Europe. Europe's definition and subregional classification were informed by the WHO and the United Nations Geoscheme, respectively[23 24] (see details in table 1). The search strategies used can be found in online supplementary box s1.

Study selection and inclusion and exclusion criteria

WY and HI conducted the initial screening, and MH conducted the double screening, as detailed in table 1. In this review, the term 'publication' refers to a document reporting one or several overall outcome measures in one or several (different) populations. 'Study' or 'measure' refers to a specific outcome measure and its details.

Data extraction and data synthesis

Extraction and double extraction of relevant data were conducted. Extracted variables are listed in table 1. Overall outcome measures and their strata were extracted based on a preset hierarchy, provided the sample size in each stratum was ≥10 (table 1). Strata of outcome measures were extracted for more statistical power in assessing predictors of heterogeneity in effect size.

Quality assessment

An initial quality assessment of relevant publications was conducted to assess the validity of the diagnostic assay in each study, given documented limitations.[25 26] Professor Rhoda Ashley-Morrow, an expert advisor from the University of Washington, evaluated the validity, sensitivity, and specificity of the assays. Only studies with valid and reliable assays were included in the systematic review. The precision and quality of each study were subsequently evaluated using the Cochrane approach for risk of bias (ROB) assessment[21] (table 1).

Meta-analyses

We conducted meta-analyses in R V.3.4.1[27] using the DerSimonian–Laird random effects models and the Freeman–Tukey double arcsine transformation,[28 29] as listed in the meta package,[30] whenever ≥3 measures were available. This methodology was selected as it accounts for sampling variation and heterogeneity in effect size[28] (see table 1).

A sensitivity analysis was conducted using logit transformation instead of the Freeman–Tukey double arcsine transformation, in view of the recently identified issue for the latter transformation.[31] A second sensitivity analysis was conducted using a multilevel meta-analytic model[32] to account for potential dependence in measures extracted from the same study.

Meta-regressions

We regressed log transformed seroprevalence and log transformed GUD/genital herpes proportions in Stata/SE V.13,[33] using the metareg package.[34] We used log transformation because we needed to estimate the risk ratios and not the odds ratios—HSV-1 seroprevalence is very high and thus the odds ratios may not be as meaningful. Univariable and multivariable random effects meta-regression analyses were conducted to identify sources of between study heterogeneity and predictors of outcomes (table 1). A sensitivity analysis was conducted using a multilevel meta-analytic model[32] to account for potential dependence in measures extracted from the same study.

RESULTS

Search results and scope of evidence

Figure 1 describes the study selection process based on PRISMA guidelines.[22] The search identified 5803 citations (PubMed=1309 and Embase=4494). After performing the first two stages of the screening process, 912 citations were relevant or potentially relevant. The full text screening of these citations identified 135 relevant publications, and a further 7 relevant publications were identified through bibliography screening, including country level reports and articles in non-indexed journal.[35–41]

In total, 142 publications met the inclusion criteria. The extracted outcome measures were: 179 overall and 622 stratified HSV-1 seroprevalence measures; 4 overall proportions of HSV-1 detection in GUD, and 62 overall and 161 stratified proportions of HSV-1 detection in genital herpes.

Table 1 Detailed methodology for this study

Methodology	Detailed description
Data source and search strategy	► Search conducted on 16 September 2019 in PubMed and Embase ► Search strategies included exploded MeSH/Emtree terms and broad terms with no language or time restriction ► The definition of Europe included 53 countries stratified by European subregion/country: – Eastern Europe: Belarus, Bulgaria, Czech Republic, Hungary, Poland, Republic of Moldova, Romania, Russian Federation, Slovakia and Ukraine. – Northern Europe: Denmark, Estonia, Finland, Iceland, Ireland, Latvia, Lithuania, Norway, Sweden and UK – Southern Europe: Albania, Andorra, Bosnia and Herzegovina, Croatia, Greece, Italy, Malta, Montenegro, Portugal, Republic of Macedonia, San Marino, Serbia, Slovenia and Spain – Western Europe: Austria, Belgium, France, Germany, Luxembourg, Monaco, The Netherlands and Switzerland – Intersection of Europe and Asia: Armenia, Azerbaijan, Cyprus, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan and Uzbekistan – Israel – Turkey
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: – Duplicate publications were identified and excluded – Titles and abstracts were screened for relevant and potentially relevant publications – Full texts of relevant and potentially relevant publications were retrieved and screened for relevance – Bibliographies of relevant publications and reviews were checked for additional potentially relevant publications ► Inclusion criteria were any publication, with a minimum sample size of 10, reporting primary data on any of the following outcome measures: – HSV-1 seroprevalence as detected by a type specific diagnostic assay – Proportion of HSV-1 in GUD, as detected by standard viral detection and subtyping methods – Proportion of HSV-1 in genital herpes (as opposed to HSV-2), as detected 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 aged <6 months as their antibodies are maternal in origin
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 (eg, sex and age), sample size, HSV-1 outcome measures and diagnostic assay ► 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 seroprevalence in descending order of preference were population type, age bracket and age group: 1. Population type classified as: – Healthy general populations: healthy populations such as blood donors, pregnant women and outpatients with minor health conditions – Clinical populations: any population with a major clinical condition, or a condition related (potentially) to HSV-1 infection – Other populations: other populations not satisfying above definitions, or populations with an undetermined risk of acquiring HSV-1, such as HIV positive patients, sex workers, men who have sex with men and prisoners 2. Age category classified as: – Children: age ≤15 years – Adults: age >15 years 3. Age group classified as (groups optimised to best fit reported data): – <20 years – 20–30 years – 30–40 years – 40–50 years – >50 years ► 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
Quality assessment	The Cochrane's approach for risk of bias assessment included: ► Study's precision classification into low vs high based on the sample size (<100 vs ≥100) ► Study's appraisal into low vs high risk of bias was determined using two quality domains: – Sampling method: probability based vs non-probability based – Response rate: ≥80% vs <80% or unclear

Continued

Table 1 Continued

Methodology	Detailed description
Meta-analyses	► Meta-analyses were conducted using the DerSimonian–Laird random effects models with inverse variance weighting. The variance of each outcome measure was stabilised using the Freeman–Tukey double arcsine transformation ► Pooled means HSV-1 seroprevalence were estimated by age bracket, age group, European subregion/country, population type, genital herpes episode status, sex and year of publication range. ► Pooled proportions of HSV-1 detection in genital herpes cases were estimated by age group, European subregion/country, sex and year of publication range. ► Overall pooled proportion of HSV-1 detection in GUD cases was estimated ► Heterogeneity assessment was based on three complementary metrics: – Cochran's Q statistic to assess existence of heterogeneity in effect size (p value <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-1 seroprevalence and HSV-1 proportion in genital herpes ► Factors in the univariable model with a p value <0.1 were included in the multivariable analysis ► Factors in the multivariable model with a p value ≤0.05 were deemed to be significant predictors ► Variables included in the meta-regression models for HSV-1 seroprevalence were: – Age bracket – Age group – Sex – Population type – European subregion/country – Country's income: upper middle income countries and high income countries according to the World Bank classification, for countries with available data – Assay type (western blot, ELISA and others) – Sample size – Sampling method – Response rate – Year of publication – Year of publication range (<2000; 2000–2010; >2010) ► Variables included in the meta-regression models for proportion of HSV-1 detection in genital herpes were: – Age group – Sex – Genital herpes episode status – European subregion/country – Sample size – Year of publication – Year of publication range

ELISA, enzyme linked immunosorbent type specific assay; GUD, genital ulcer disease; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2.

HSV-1 seroprevalence overview

Online supplementary tables S2, S3 and S4 list the overall seroprevalence measures (number of measures (n)=179). The earliest publication was published in 1972. Studies were mainly cross sectional (n=117; 65.4%) and based on convenience sampling (n=133; 74.3%).

Stratified seroprevalence measures across all studies (n=622) ranged between 0.0% and 100% with a median of 70.0% (table 2). In healthy general populations, HSV-1 seroprevalence ranged between 0.0% and 82.0% with a median of 31.0% among children (n=101), and between 20.0% and 100% with a median of 73.6% among adults (n=402). In clinical populations, HSV-1 seroprevalence ranged between 31.0% and 52.0% with a median of 36.0% among children (n=3), and between 0.0% and 100% with a median of 73.3% among adults (n=59). A summary of HSV-1 seroprevalence measures across various populations and subpopulations is shown in table 2.

Pooled mean estimates for HSV-1 seroprevalence

Table 2 shows the seroprevalence meta-analyses. Overall pooled mean seroprevalence (across all measures, n=622) was 67.4% (95% CI 65.5% to 69.3%). The pooled mean seroprevalences for healthy (n=101) and for clinical (n=3) children were 32.4% (95% CI 29.2% to 35.6%) and 37.8% (95% CI 28.3% to 47.8%), respectively. The pooled mean for healthy (n=402) and for clinical (n=59) adults was 73.7% (95% CI 71.9% to 75.4%) and 73.8% (95% CI 68.9% to 78.5%), respectively.

Across age groups, pooled mean seroprevalence increased gradually from 39.3% (n=147, 95% CI 35.9% to 42.7%) in those aged <20 years, followed by 66.7% (n=73, 95% CI 62.0% to 71.1%) in 20–30 year olds, 72.9% (n=60, 95% CI 69.3% to 76.3%) in 30–40 year olds, 74.5% (n=25, 95% CI 68.5% to 80.0%) in 40–50 year olds, to 82.9% (n=47, 95% CI 78.8% to 86.6%) in those aged >50 years.

Across European subregions/countries, the pooled mean seroprevalence was lowest at 57.7% (n=161, 95% CI 54.4% to 60.9%) in Northern Europe, followed by 64.8%

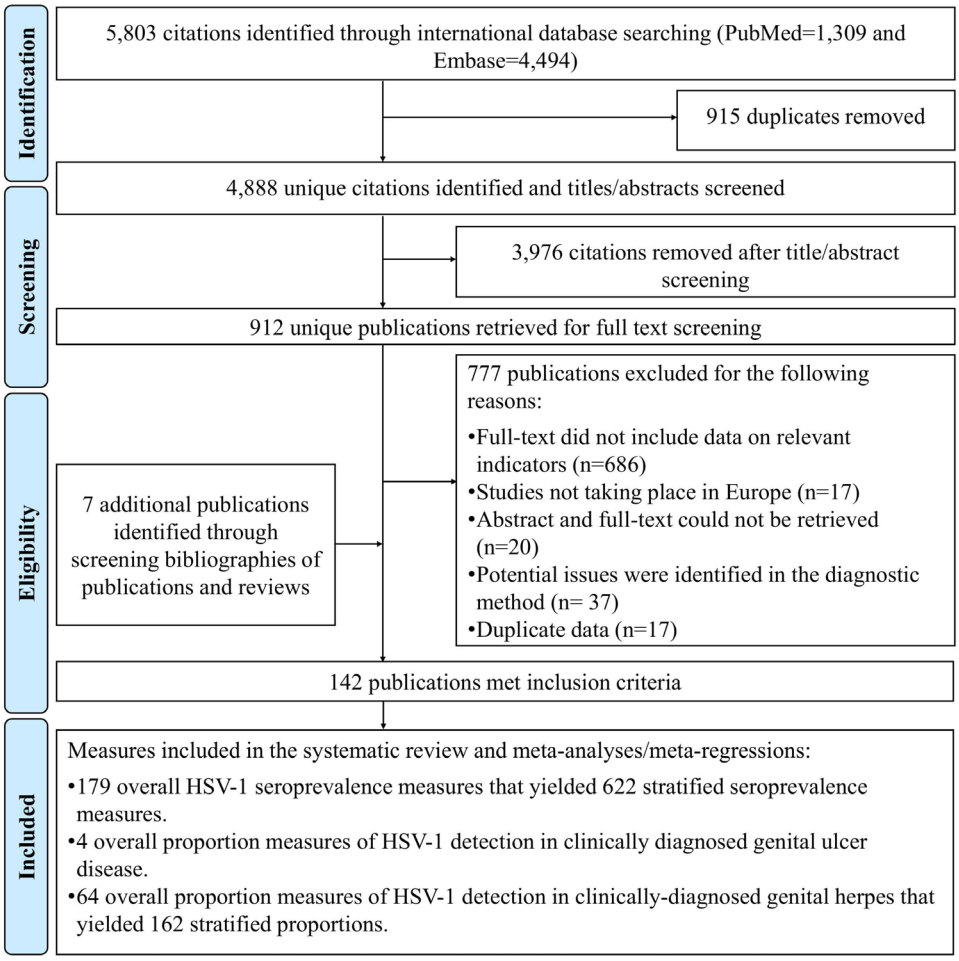

Figure 1 Flowchart of article selection for the systematic review of herpes simplex virus type 1 (HSV-1) infection in Europe, according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[22]

(n=35, 95% CI 58.8% to 70.7%) in Israel, 66.1% (n=264, 95% CI 63.1% to 69.0%) in Western Europe, 77.2% (n=77, 95% CI 71.7% to 82.3%) in Southern Europe, 78.7% (n=64, 95% CI 74.1%–83.0%) in Eastern Europe and 87.9% (n=17, 95% CI 79.6% to 94.2%) in Turkey.

Heterogeneity was evident in the majority of meta-analyses (p value <0.001; table 2), and affirmed by wide prediction intervals. Variation in seroprevalence was due to true variation in seroprevalence as opposed to sampling variation (I^2 >50%). Forest plots for meta-analyses across age groups can be found in online supplementary figure s1. Sensitivity analyses using the logit transformation and the multilevel meta-analytic model generated overall similar results (online supplementary table s5).

Predictors of HSV-1 seroprevalence

Table 3 and online supplementary table s6 show seroprevalence meta-regression analyses. Four multivariable models were conducted due to collinearity between age bracket and age group, as well as between year of publication as a categorical variable and year of publication as a continuous linear term. Each multivariable model included nine eligible variables (yielding a p value <0.1 in the univariable analysis).

The first model in table 3 included age bracket, sex, population type, European subregion/country, country's income, assay type, sample size, response rate and year of publication range. This model explained 63.80% of the seroprevalence variation. HSV-1 seroprevalence was 2.11-fold (95% CI 1.98 to 2.26) higher in adults compared with children, and 0.93-fold (95% CI 0.87 to 0.98) lower in men compared with women. Compared with Northern Europe, HSV-1 seroprevalence was 1.24-fold (95% CI 1.16 to 1.32) higher in Western Europe, 1.29-fold (95% CI 1.16 to 1.44) higher in Israel, 1.36-fold (95% CI 1.25 to 1.49) higher in Southern Europe, 1.37-fold (95% CI 1.12 to 1.67) higher in Turkey and 1.54-fold (95% CI 1.39 to 1.72) higher in Eastern Europe. Evidence of a decline in seroprevalence over time was significant. Compared with the years before 2000, HSV-1 seroprevalence was 0.89-fold (95% CI 0.83 to 0.96) and 0.85-fold (95% CI 0.78 to 0.93) lower between the years 2000–2010 and the years after 2010, respectively.

The second model incorporated age group in proxy of age bracket, explained 63.69% of the seroprevalence variation and yielded similar results (table 3). Compared with those aged <20 years, HSV-1 seroprevalence was

Table 2 Pooled mean estimates for herpes simplex virus type 1 seroprevalence in Europe

	Outcome measure	Sample	HSV-1 seroprevalence		Pooled mean HSV-1 seroprevalence	Heterogeneity measures		
Population	Total N	Total N	Range	Median	Mean (95% CI)	Q* (p value)	I²† (%) (95% CI)	Prediction interval‡ (%)
Healthy general populations								
Children	101	23948	0.0–82.0	31.0	32.4 (29.2 to 35.6)	2689.7 (p<0.001)	96.3 (95.9 to 96.7)	7.0–65.3
Adults	402	105523	20.0–100	73.6	73.7 (71.9 to 75.4)	13302.3 (p<0.001)	97.5 (97.4 to 97.7)	36.0–98.1
Age mixed	13	5985	30.4–68.6	53.7	54.3 (47.4 to 61.0)	301.1 (p<0.001)	96.0 (94.5 to 97.1)	27.4–79.9
All healthy general populations	516	135456	0.0–100	68.0	65.5 (63.3 to 67.6)	35415.7 (p<0.001)	98.5 (98.5 to 98.6)	17.8–98.9
Clinical populations								
Clinical children	3	149	31.0–52.0	36.0	37.8 (28.3 to 47.8)	2.5 (p=0.281)	21.3 (0.0 to 91.8)	0.0–100
Clinical adults	59	11071	0.0–100	73.3	73.8 (68.9 to 78.5)	1770.0 (p<0.001)	96.7 (96.2 to 97.1)	33.3–99.0
All clinical populations	62	11071	0.0–100	72.5	72.4 (67.4 to 77.2)	1847.3 (p<0.001)	96.7 (96.2 to 97.1)	31.3–98.8
Other populations								
HIV positive patients	19	2493	76.0–97.0	90.1	89.0 (86.3 to 91.5)	65.2 (p<0.001)	72.4 (56.4 to 82.6)	77.2–97.1
Female sex workers	6	1062	60.9–99.0	78.3	83.2 (66.9 to 94.8)	171.7 (p<0.001)	97.1 (95.4 to 98.1)	18.5–100
Men who have sex with men	10	6074	52.1–91.0	68.0	67.0 (59.9 to 73.8)	286.9 (p<0.001)	96.9 (95.6 to 97.8)	39.3–89.5
Prisoners	9	357	67.0–86.4	77.0	80.4 (75.8 to 84.6)	5.7 (p=0.680)	0.0 (0.0 to 50.6)	74.9–84.4
European subregion/country								
Northern Europe	161	47202	13.0–100	67.2	57.7 (54.4 to 60.9)	7721.3 (p<0.001)	97.9 (97.8 to 98.1)	19.3–91.4
Eastern Europe	64	12260	0.0–100	85.5	78.7 (74.1 to 83.0)	2153.3 (p<0.001)	97.1 (96.7 to 97.4)	37.8–100
Southern Europe	77	16063	3.6–100	81.4	77.2 (71.7 to 82.3)	4677.4 (p<0.001)	98.4 (98.2 to 98.5)	24.8–100
Western Europe	264	68556	0.0–95.7	67.9	66.1 (63.1 to 69.0)	17258.0 (p<0.001)	98.5 (98.4 to 98.5)	18.8–98.9
Israel	35	7060	22.2–94.9	67.9	64.8 (58.8 to 70.7)	910.9 (p<0.001)	96.3 (95.5 to 96.9)	28.3–93.6
Turkey	17	3076	30.4–99.0	92.3	87.9 (79.8 to 94.2)	557.2 (p<0.001)	97.1 (96.3 to 97.8)	43.4–100
Mixed subregions	4	2295	55.3–76.7	71.7	68.9 (56.9 to 79.8)	101.7 (p<0.001)	97.0 (94.8 to 98.3)	13.5–100
Sex								
Women	258	62162	2.0–100	72.1	69.5 (66.5 to 72.5)	16531.4 (p<0.001)	98.4 (98.4 to 98.5)	20.8–99.8
Men	194	49887	7.5–100	65.5	63.3 (59.7 to 66.7)	12372.9 (p<0.001)	98.4 (98.3 to 98.5)	16.8–97.9
Mixed sexes	170	44463	0.0–100	70.0	68.8 (65.3 to 72.2)	9860.3 (p<0.001)	98.3 (98.2 to 98.4)	23.0–99.1
Age group (years)								
<20	147	32492	0.0–100	36.4	39.3 (35.9 to 42.7)	5530.3 (p<0.001)	97.4 (97.1 to 97.6)	6.8–78.5
20–30	73	13156	32.0–100	66.7	66.7 (62.0 to 71.1)	2204.1 (p<0.001)	96.7 (96.3 to 97.1)	26.8–96.1
30–40	60	9594	40.0–96.9	73.0	72.9 (69.3 to 76.3)	854.6 (p<0.001)	93.1 (91.8 to 94.2)	44.1–94.0
40–50	25	5188	49.0–96.6	76.0	74.5 (68.5 to 80.0)	487.7 (p<0.001)	95.1 (93.7 to 96.1)	42.3–96.4

Continued

Table 2 Continued

Population	Outcome measure: Total N	Sample: Total N	HSV-1 seroprevalence: Range	HSV-1 seroprevalence: Median	Pooled mean HSV-1 seroprevalence: Mean (95% CI)	Heterogeneity measures: Q* (p value)	Heterogeneity measures: I²† (%) (95% CI)	Heterogeneity measures: Prediction interval‡ (%)
>50	47	16363	57.1–100	84.0	82.9 (78.8 to 86.6)	1546.3 (p<0.001)	97.0 (96.5 to 97.4)	52.2–99.6
Mixed	270	79719	0.0–100	78.2	77.1 (75.1 to 79.1)	11355.6 (p<0.001)	97.6 (97.5 to 97.8)	41.1–98.9
Year or publication range								
<2000	127	23076	0.0–100	71.6	70.0 (66.0 to 73.9)	4826.5 (p<0.001)	97.4 (97.2 to 97.6)	25.2–99.2
2000–2010	361	86175	6.0–100	72.0	69.3 (67.0 to 71.5)	1891.5 (p<0.001)	97.1 (98.0 to 98.2)	24.7–98.8
>2010	134	47261	0.0–100	62.7	59.7 (55.1 to 64.3)	13668.2 (p<0.001)	99.0 (99.0 to 99.1)	11.0–98.2
Age bracket								
All children	104	24097	0.0–82.0	31.5	32.5 (29.4 to 35.7)	2698.1 (p<0.001)	96.2 (95.7 to 96.6)	7.1–65.4
All adults	505	126430	0.0–100	76.0	74.4 (72.8 to 76.0)	19321.3 (p<0.001)	97.4 (97.3 to 97.5)	37.1–98.3
All age mixed	13	5985	30.4–68.6	53.7	54.3 (47.4 to 61.0)	301.1 (p<0.001)	96.0 (94.5 to 97.1)	27.4–79.9
All studies	622	156512	0.0–100	70.0	67.4 (65.5 to 69.3)	39384.9 (p<0.001)	98.4 (98.4 to 98.5)	20.2–99.1

*The Cochran's Q statistic is a measure assessing the existence of heterogeneity in pooled outcome measures (here, HSV-1 seroprevalence).
†I^2 is a measure assessing the magnitude of between study variation that is due to true differences in HSV-1 seroprevalence across studies rather than sampling variation.
‡Prediction interval is a measure quantifying the 95% interval of the distribution of true HSV-1 seroprevalence around the estimated pooled mean.
HSV-1, herpes simplex virus type 1.

Table 3 Univariable and multivariable meta-regression models for herpes simplex virus type 1 seroprevalence in Europe, with time trend assessed categorically by decade

	Outcome measure	Sample	Univariable analysis				Multivariable analysis*			
							Model 1*		Model 2†	
	Total n	Total N	RR (95% CI)	P value	LR test p value	Adjusted R^2 (%)	ARR (95% CI)	P value	ARR (95% CI)	P value
Population characteristics										
Age bracket										
Children	104	24 097	1.00	–	<0.001	50.16	1.00	–	–	–
Adults	505	126 430	2.23 (2.07 to 2.4)	<0.001			2.11 (1.98 to 2.26)	<0.001	–	–
Age mixed	13	5985	1.67 (1.38 to 2.02)	<0.001			1.43 (1.21 to 1.69)	<0.001	–	–
Age group (years)										
<20	147	32 492	1.00	–	<0.001	48.69	–	–	1.00	–
20–30	73	13 156	1.70 (1.54 to 1.87)	<0.001			–	–	1.62 (1.49 to 1.76)	<0.001
30–40	60	9594	1.91 (1.73 to 2.11)	<0.001			–	–	1.82 (1.67 to 1.99)	<0.001
40–50	25	5188	1.95 (1.70 to 2.24)	<0.001			–	–	1.93 (1.70 to 2.18)	<0.001
>50	47	16 363	2.17 (1.94 to 2.42)	<0.001			–	–	2.29 (2.06 to 2.53)	<0.001
Mixed	270	79 719	1.99 (1.86 to 2.13)	<0.001			–	–	1.91 (1.79 to 2.04)	<0.001
Sex										
Women	258	62 162	1.00	–	0.027	1.27	1.00	–	1.00	–
Men	194	49 887	0.91 (0.83 to 0.98)	0.020			0.93 (0.87 to 0.98)	0.006	0.91 (0.86 to 0.96)	0.001
Mixed	170	44 463	1.01 (0.93 to 1.10)	0.773			0.98 (0.92 to 1.05)	0.633	0.93 (0.87 to 1.00)	0.039
Population type										
Healthy	516	135 456	1.00	–	<0.001	3.71	1.00	–	1.00	–
Clinical	62	11 071	1.16 (1.03 to 1.30)	0.014			1.05 (0.96 to 1.15)	0.256	1.06 (0.97 to 1.16)	0.179
Other	44	9985	1.33 (1.16 to 1.52)	<0.001			1.24 (1.13 to 1.36)	<0.001	1.22 (1.11 to 1.34)	<0.001
European subregion/country										
Northern Europe	161	47 202	1.00	–	<0.001	8.78	1.00	–	1.00	–
Eastern Europe	64	12 260	1.42 (1.26 to 1.61)	<0.001			1.54 (1.39 to 1.72)	<0.001	1.54 (1.39 to 1.72)	<0.001
Southern Europe	77	16 063	1.34 (1.19 to 1.51)	<0.001			1.37 (1.25 to 1.49)	<0.001	1.36 (1.25 to 1.49)	<0.001
Western Europe	264	68 556	1.16 (1.06 to 1.26)	0.001			1.24 (1.16 to 1.32)	<0.001	1.20 (1.12 to 1.28)	<0.001
Israel	35	7060	1.17 (0.99 to 1.37)	0.053			1.29 (1.16 to 1.44)	<0.001	1.22 (1.09 to 1.37)	0.001
Turkey	17	3076	1.56 (1.26 to 1.93)	<0.001			1.37 (1.12 to 1.67)	0.002	1.38 (1.15 to 1.72)	0.001
Mixed subregions	4	2295	1.28 (0.84 to 1.95)	0.239			1.14 (0.86 to 1.51)	0.339	1.13 (0.85 to 1.50)	0.386
Country's income										
UMIC	46	8893	1.00	–	<0.001	3.68	1.00	–	1.00	–
HIC‡	576	147 619	0.74 (0.65 to 0.84)	<0.001			0.92 (0.80 to 1.05)	0.245	0.92 (0.81 to 1.06)	0.274
Study methodology characteristics										

Continued

Table 3 Continued

	Outcome measure	Sample	Univariable analysis				Multivariable analysis*			
							Model 1*		Model 2†	
	Total n	Total N	RR (95% CI)	P value	LR test p value	Adjusted R^2 (%)	ARR (95% CI)	P value	ARR (95% CI)	P value
Assay type										
Western blot	52	6551	1.00	–	0.021	0.92	1.00	–	1.00	–
ELISA	518	137 318	0.84 (0.74 to 0.96)	0.011			0.94 (0.86 to 1.03)	0.258	1.00 (0.91 to 1.10)	0.977
Others	52	12 643	0.80 (0.67 to 0.95)	0.013			0.85 (0.73 to 0.98)	0.031	0.89 (0.77 to 1.03)	0.131
Sample size§										
<100	46	1795	1.00	–	0.016	1.19	1.00	–	1.00	–
≥100	576	154 717	0.84 (0.73 to 0.96)	0.016			0.91 (0.82 to 1.01)	0.090	0.94 (0.84 to 1.04)	0.240
Sampling method										
Probability based	267	67 601	1.00	–	0.395	0.00	–	–	–	–
Non- probability based	355	88 911	1.03 (0.96 to 1.11)	0.395			–	–	–	–
Response rate										
≥80	37	11 985	1.00	–	0.083	0.42	1.00	–	1.00	–
<80	94	29 203	0.84 (0.71 to 0.99)	0.049			0.96 (0.84 to 1.10)	0.606	0.90 (0.79 to 1.02)	0.123
Unclear	491	115 324	0.93 (0.80 to 1.08)	0.326			0.98 (0.89 to 1.09)	0.768	0.96 (0.86 to 1.06)	0.387
Year of publication range										
<2000	127	23 076	1.00	–	0.001	2.22	1.00	–	1.00	–
2000–2010	361	86 175	0.97 (0.88 to 1.06)	0.482			0.89 (0.83 to 0.96)	0.003	0.91 (0.84 to 0.98)	0.010
>2010	134	47 261	0.83 (0.74 to 0.93)	0.001			0.85 (0.78 to 0.93)	<0.001	0.87 (0.80 to 0.95)	0.002

*Variance explained by the final multivariable model 1 (adjusted R^2)=63.80%.
†Variance explained by the final multivariable model 2 (adjusted R^2)=63.69%.
‡High income country category includes one measure representing 12 European countries.
§Sample size denotes the sample size of the study population found in the original publication.
ARR, adjusted risk ratio; ELISA, enzyme linked immunosorbent type specific assay; HIC, high income country; HSV-1, herpes simplex virus type 1; RR, risk ratio; UMIC, upper middle income country.

1.62-fold (95% CI 1.49 to 1.76) higher in 20–30 year olds, 1.82-fold (95% CI 1.67 to 1.99) higher in 30–40 year olds, 1.93-fold (95% CI 1.70 to 2.18) higher in 40–50 year olds and 2.29-fold (95% CI 2.06 to 2.53) higher in those aged >50 years.

Online supplementary table s6 includes the univariable and multivariable analyses using year of publication as a continuous variable. The results were similar to those observed in the two models listed above. The models showed evidence of a decline in HSV-1 seroprevalence of 0.99-fold (95% CI 0.99 to 1.00) per year.

These analyses were conducted using year of publication instead of year of data collection for completeness—13% of studies had no specified year of data collection. With imputation using year of publication adjusted for median difference with year of data collection, the declining trend did not reach statistical significance. Sensitivity analyses using the multilevel meta-analytic model supported the findings of the baseline analysis results, but some of the effects had wider CI (online supplementary table s7).

HSV-1 isolation in genital ulcer disease and in genital herpes: overview and meta-analyses

Online supplementary table s8 and table 4 summarise the extracted proportion measures of HSV-1 detection in GUD and in genital herpes; table 4 also includes the results of the meta-analyses.

In GUD cases (n=4), proportion measures ranged between 4.7% and 39.8% with a median of 8.5% and a pooled proportion of 13.6% (95% CI 4.1% to 27.1%). In genital herpes cases (n=162), proportion measures ranged between 0.0% and 89.7% with a median of 34.7% and a pooled proportion of 34.1% (95% CI 31.7% to 36.5%) (table 4).

Among women, proportions of HSV-1 detection in genital herpes ranged between 6.0% and 89.6% with a median of 43.5% and a pooled mean of 42.0% (n=62, 95% CI 37.4% to 46.7%), and among men, between 0.0% and 75.0% with a median of 26.6% and a pooled mean of 24.1% (n=56, 95% CI 19.8% to 28.6%).

In first episode genital herpes cases, proportions of HSV-1 detection ranged between 31.0% and 75.0% with a median of 49.0% and a pooled mean of 49.3% (n=13, 95% CI 42.2% to 56.4%). In recurrent genital herpes cases, proportions ranged between 1.0% and 77.3% with a median of 10.0% and a pooled mean of 13.7% (n=11, 95% CI 5.8% to 24.1%)

Table 4 lists summaries for other population classifications. The majority of meta-analyses showed evidence of heterogeneity with I^2 >50%, and large prediction intervals. The two key forest plots (all GUD and all genital herpes) are available in online supplementary figure s2. Sensitivity analyses using the logit transformation and the multilevel meta-analytic model generated overall similar results (online supplementary table s9).

Predictors of HSV-1 detection in genital herpes

Table 5 shows meta-regression analyses for proportion measures of HSV-1 virus isolation in genital herpes. In the univariable analyses, sex, genital herpes episode status, year of publication and year of publication range had a p value<0.1 and thus were included in the multivariable analyses. Two multivariable models were constructed due to collinearity between year of publication range (categorical variable) and year of publication (continuous variable).

The first model, including year of publication range, explained 26.10% of the proportion variation. Compared with women, the proportion of HSV-1 virus isolation in genital herpes was 0.62-fold (95% CI 0.50 to 0.79) lower in men. Genital herpes episode status showed a 0.29-fold (95% CI 0.49 to 0.93) lower proportion of HSV-1 detection in recurrent genital herpes compared with first episode genital herpes. Compared with the years before 2000, evidence of a 1.28-fold (95% CI 1.02 to 1.66) increase in HSV-1 detection in genital herpes was observed in the years after 2010. Similar results were observed when using imputed year of data collection as a categorical term in the model.

The second model, including year of publication as a linear term, had similar results and explained 14.99% of the proportion variation. Evidence of a 1.01-fold (95% CI 1.00 to 1.02) yearly increase in the proportion of HSV-1 detection in genital herpes was observed. Similar results were observed when using imputed year of data collection as a linear term in the model. Sensitivity analyses using the multilevel meta-analytic model supported the findings of the baseline analysis results, but some of the effects had wider CI (online supplementary table s10).

Quality assessment

Online supplementary table s11 summarises the quality assessment of seroprevalence studies (n=179). A total of 149 studies (83.2%) had high precision, 45 studies (25.1%) had low ROB in the sampling methodology domain and 12 studies (6.7%) had low ROB in the response rate domain. Only five studies (2.8%) had low ROB in both quality domains. Despite this, the meta-regression analyses (table 3) did not demonstrate an association between these study quality variables and HSV-1 seroprevalence, suggesting a minimal impact on the findings of this study.

DISCUSSION

This comprehensive systematic review presented a detailed assessment of the epidemiology of HSV-1 in Europe. The results demonstrated that the epidemiology is in transition, with seroprevalence declining by 1% per year (online supplementary table s6), and HSV-1 detection in genital herpes increasing concurrently by 1% per year (table 5). With only two-thirds of the population being seropositive (table 2), HSV-1 seroprevalence in Europe is lower than that in most other regions,[6–10 12] and

Table 4 Pooled proportions of herpes simplex virus type 1 virus isolation in clinically diagnosed genital ulcer disease and in clinically diagnosed genital herpes in Europe

	Outcome measure	Sample	Proportion of HSV-1 detection		Pooled proportion of HSV-1 detection	Heterogeneity measures		
Population	Total N	Total N	Range	Median	Mean (95% CI)	Q* (p-value)	I^2† (%) (95% CI)	Prediction interval‡ (%)
Patients with clinically diagnosed GUD								
All patients with GUD	4	800	4.7–39.8	8.5	13.6 (4.1 to 27.1)	58.1 (p<0.001)	94.8 (89.0 to 97.4)	0.0–85.5
Patients with clinically diagnosed genital herpes								
Sex								
Women	62	4933	6.0–89.6	43.5	42.0 (37.4 to 46.7)	615.3 (p<0.001)	90.2 (88.0 to 91.8)	11.6–76.0
Men	56	3578	0.0–75.0	26.6	24.1 (19.8 to 28.6)	461.1 (p<0.001)	88.1 (85.3 to 90.3)	1.8–58.4
Mixed	44	32570	4.6–81.8	45.0	35.8 (32.1 to 39.6)	1778.5 (p<0.001)	97.6 (97.2 to 97.9)	14.7–60.3
Age group (years)								
<20	3	157	45.4–66.6	53.3	52.1 (39.1 to 64.9)	3.2 (p=0.197)	38.5 (0.0 to 80.8)	0.0–100
20–30	6	643	27.3–54.9	38.5	39.9 (32.2 to 47.8)	18.3 (p=0.003)	72.7 (37.1 to 88.1)	17.1–65.2
30–40	2§	102	34.0–51.8	43.3	43.5 (27.4 to 60.3)§	–	–	–
Mixed	151	40179	0.0–89.6	33.3	33.4 (30.9 to 39.6)	3497.8 (p<0.001)	95.7 (95.3 to 96.1)	9.5–62.8
Genital herpes episode status								
First episode genital herpes	13	1366	31.0–75.0	49.0	49.3 (42.2 to 56.4)	66.1 (p<0.001)	81.8 (70.1 to 89.0)	24.5–74.2
Recurrent genital herpes	11	893	1.0–77.3	10.0	13.7 (5.8 to 24.1)	152.7 (p<0.001)	92.5 (90.2 to 95.6)	0.060.5
Unspecified status	138	38822	0.0–89.6	34.7	34.7 (32.3 to 37.1)	2730.0 (p<0.001)	95.0 (94.4 to 95.5)	12.3–61.2
European subregion/country								
Northern Europe	131	38843	1.0–89.6	34.8	35.0 (32.5 to 37.6)	2854.7 (p<0.001)	95.4 (95.0 to 95.9)	12.1–62.2
Eastern Europe	2§	100	34.9–63.1	49.0	49.3 (22.7 to 76.0)§	–	–	–
Southern Europe	8	286	0.0–50.0	15.4	18.2 (7.3 to 23.1)	39.1 (p<0.001)	82.1 (66.0 to 90.6)	0.0–68.9
Western Europe	5	462	7.5–37.1	25.0	21.8 (11.7 to 33.8)	33.2 (p<0.001)	88.0 (74.4 to 94.3)	0.0–70.2
Israel	4	605	21.0–72.7	54.0	50.3 (20.8 to 79.7)	142.4 (p<0.001)	97.9 (96.5 to 98.7)	0.0–100
Mixed subregions	12	785	6.0–57.5	37.9	30.8 (19.5 to 43.4)	140.4 (p<0.001)	92.2 (88.2 to 94.8)	0.0–79.5
Year or publication range								
<2000	74	5072	0.0–81.8	34.8	33.4 (28.3 to 38.8)	1099.7 (p<0.001)	93.4 (92.3 to 94.3)	1.7–78.1
2000–2010	53	8727	4.0–77.3	25.0	29.4 (24.6 to 34.5)	1196.4 (p<0.001)	95.7 (94.9 to 96.3)	3.0–67.1
>2010	35	27282	18.7–89.6	42.8	46.0 (43.6 to 48.3)	280.0 (p<0.001)	87.9 (84.1 to 90.7)	35.6–56.5
All patients with genital herpes	162	41081	0.0–89.7	34.7	34.1 (31.7 to 36.5)	3529.8 (p<0.001)	95.4 (95.0 to 95.8)	10.1–63.2

*The Cochran's Q statistic is a measure assessing the existence of heterogeneity in pooled outcome measures (here, proportions of HSV-1 virus isolation).
†I^2 is a measure assessing the magnitude of between study variation that is due to true differences in proportions of HSV-1 virus isolation across studies rather than sampling variation.
‡Prediction interval is a measure quantifying the 95% interval of the distribution of true proportions of HSV-1 virus isolation around the estimated pooled mean.
§No meta-analysis was done as number of studies was <3. The two study samples were merged to yield one sample size, for which the 95% CI was calculated.
GUD, genital ulcer disease; HSV-1, herpes simplex virus type 1.

Table 5 Univariable and multivariable meta-regression models for proportion measures of herpes simplex virus type 1 virus isolation in clinically diagnosed genital herpes in Europe

	Outcome measure	Sample	Univariable analysis				Multivariable analysis			
							Model 1*		Model 2†	
	Total n	Total N	RR (95% CI)	P value	LR test p value	Adjusted R^2 (%)	ARR (95% CI)	P value	ARR (95% CI)	P value
Age group (years)										
<20	3	157	1.00	–	0.394	0.00	–	–	–	–
20–30	6	643	0.71 (0.29 to 1.71)	0.447			–	–	–	–
30–40	2	102	0.78 (0.25 to 2.44)	0.675			–	–	–	–
Mixed	151	40 179	0.58 (0.28 to 1.21)	0.147			–	–	–	–
Sex										
Women	62	4933	1.00	–	0.001	11.27	1.00	–	1.00	–
Men	56	3578	0.63 (0.50 to 0.80)	<0.001			0.62 (0.50 to 0.76)	<0.001	0.61 (0.49 to 0.75)	<0.001
Mixed	44	32 570	0.63 (0.65 to 1.02)	0.074			0.81 (0.65 to 1.00)	0.061	0.81 (0.66 to 1.01)	0.067
Genital herpes episode status										
First episode genital herpes	13	1366	1.00	–	<0.001	12.19	1.00	–	1.00	–
Recurrent genital herpes	11	893	0.27 (0.17 to 0.47)	<0.001			0.29 (0.49 to 0.93)	0.016	0.27 (0.17 to 0.44)	<0.001
Unspecified status	138	38 822	0.68 (0.49 to 0.95)	0.026			0.67 (0.49 to 0.92)	0.016	0.66 (0.48 to 0.89)	0.008
European subregion/country										
Northern Europe	131	38 843	1.00	–	0.397	0.61	–	–	–	–
Eastern Europe	2	100	1.44 (0.59 to 3.46)	0.417			–	–	–	–
Southern Europe	8	286	0.79 (0.44 to 1.40)	0.424			–	–	–	–
Western Europe	5	462	0.63 (0.34 to 1.13)	0.119			–	–	–	–
Israel	4	605	1.38 (0.74 to 2.60)	0.304			–	–	–	–
Mixed subregions	12	785	0.89 (0.60 to 1.34)	0.600			–	–	–	–
Sample size‡										
<100	56	3905	1.00	–	0.591	0.00	–	–	–	–
≥100	106	37 176	1.06 (0.85 to 1.32)	0.591			–	–	–	–
Year of publication range										
<2000	74	5072	1.00	–	0.021	3.95	1.00	–	–	–
2000–2010	53	8727	0.86 (0.68 to 1.08)	0.193			0.94 (0.76 to 1.16)	0.555	–	–
>2010	35	27 282	1.26 (0.98 to 1.63)	0.070			1.26 (1.00 to 1.58)	0.049	–	–
Year of publication	162	41 081	1.01 (1.00 to 1.02)	0.043	0.043	2.57	–	–	1.01 (1.00 to 1.02)	0.014

*Variance explained by the final multivariable model 1 (adjusted R^2)=26.10%.
†Variance explained by the final multivariable model 2 (adjusted R^2)=28.38%.
‡Sample size denotes the sample size of the study population found in the original publication.
ARR, adjusted risk ratio; HSV-1, herpes simplex virus type 1; RR, risk ratio.

far lower than its historical level of nearly universal childhood infection still seen in other parts of the world,[6 9 12] notably Africa.[7]

The epidemiology of HSV-1 in Europe appears to be traversing a path seen already in North America,[17 42] with the declining seroprevalence possibly attributable to the general decrease in both family size and school crowding, as well as improved hygiene.[43 44] Although a seroprevalence decline is a positive development, there is cause for concern as a larger proportion of youth (as much as two-thirds) are reaching sexual debut uninfected (table 2), and are thus at risk of acquiring the infection genitally, through (mostly) oral–genital sex or genital–genital sex (genital herpes),[4] with a range of psychosexual adverse outcomes, such as effects on sexual relations and quality of life, depression, anxiety and shame.[45–48] This outcome is affirmed by the concurrency of seroprevalence decline with HSV-1 genital herpes increase (table 3 and online supplementary table s6 vs table 5).

HSV-1 seroprevalence increased with age, reflecting cumulative exposure, with age alone explaining about 50% of the seroprevalence variation (table 3). This confirms the general global age pattern seen in other regions,[6 7 9 12 42] where age typically explained half of the seroprevalence variation,[6 9 12] with the notable exception of Africa where age explained 80% of the variation.[7] There was also substantial difference in seroprevalence among those aged <20 years and >20 years (Tables 2 and 3), suggesting that older cohorts had higher exposure in their youth, compared with the current young cohort, and affirming the decreasing trend in seroprevalence in recent decades.

Seroprevalence also varied by geographical location, with Eastern and Southern Europe as well as Turkey exhibiting higher seroprevalence rates compared with Northern and Western Europe (tables 2 and 3), possibly mirroring the individual level association between HSV-1 infection and lower socioeconomic status.[43 49] This within region variation has also been observed in other regions,[6 9 12 17 42 49] with the exception of Africa[7] where the infection is homogenous and universal. Seroprevalence in Europe was also lower in men than women, in contrast with all other regions,[6 9 12] a finding that remains to be explained. Remarkably, clinical condition and country's income (after adjustment for European subregion) as well as study characteristics, did not appear to affect seroprevalence (table 3), probably highlighting that HSV-1 is a truly general population infection.

HSV-1 (vs HSV-2) detection in genital herpes was high at 34% and increasing (table 4), similar to that observed in North America,[5 11 50] but substantially higher than that observed in other regions.[7 9 12] This affirms that Europe has progressed in its epidemiological transition towards less oral acquisition and more genital acquisition, and that HSV-1 infection plays an increasing role as a sexually transmitted disease. Our results also demonstrated that women are more affected by HSV-1 genital herpes than men, possibly reflecting the age gap in sexual mixing, with younger women partnering with older men, or possibly reflecting biological susceptibility differences by sex.[51 52] Our results also demonstrated a much higher detection of HSV-1 in first episode genital herpes (at 49%) than in recurrent herpes (at only 10%) (tables 4 and 5), supporting the fact that HSV-2 reactivates (in the genital tract) for a longer duration than HSV-1.[47]

This systematic review had limitations, primarily the unavailability of data for 25 of 53 European countries, and comparatively less data for GUD and genital herpes than for seroprevalence. For example, we expected to observe variation in HSV-1 detection in genital herpes by age or subregion, but no significant effect was found (table 5), possibly because of an insufficient number of studies. Included studies exhibited heterogeneity (table 2), but most seroprevalence variation (64%) was subsequently explained through meta-regressions (table 3 and online supplementary table s6). Studies differed by assay type, sample size, sampling method and response rate, but none of these study characteristics appeared to affect seroprevalence (table 3 and online supplementary table s6). Thus while these remain theoretical limitations, they do not appear to pose a barrier to the interpretation of the results of the study. It is also important to note that even though this study identified an increasing role for HSV-1 in genital herpes, this possibly could have been caused by a decreasing seroprevalence of the other competing cause, that is HSV-2 infection.

CONCLUSIONS

The epidemiology of HSV-1 in Europe is in transition and shifting away from its historical pattern of oral acquisition in childhood. As many as two-thirds of children are reaching sexual debut unexposed to this infection, and at risk of genital acquisition in adulthood. The transition is leading to more heterogeneous and variable transmission by age and geography, and an increasing role for HSV-1 in genital herpes. Seroprevalence is declining by 1% per year, and the contribution of HSV-1 to genital herpes is increasing, also by 1% per year. At present, half of first episode genital herpes is due to HSV-1 as opposed to HSV-2 infection. These findings highlight the importance of disease surveillance and monitoring of HSV-1 seroprevalence and genital herpes aetiology, and strengthen the case for a HSV-1 vaccine to limit transmission.

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Contributors WY, HI, and MH conducted the systematic search, data extraction, data analysis and wrote the first draft of the paper. FAH conducted the double extraction. LA-R conceived the study and led the data analysis and interpretation of

the results. All authors contributed to drafting and revision of the article, and read and approved the final manuscript.

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