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# Equity in protection: bridging global data gaps for an EBV vaccine—a systematic review and meta-analysis

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## ABSTRACT

**Introduction** Epstein–Barr virus (EBV) is linked to multiple malignancies and autoimmune conditions, with different disease burdens globally. Pharmaceutical companies and researchers are placing substantial investment in the development of EBV vaccines. To ensure optimal vaccine roll-out, particularly in resource-limited settings, it is essential to have data on the age at acquisition of EBV. This study aimed to systematically review and meta-analyse seroprevalence by age and country, WHO region and country income level, identify knowledge gaps, and determine an approach to bridge these gaps.

**Methods** MEDLINE, Embase and Web of Science were searched on 22 March 2022 for studies that measured EBV seroprevalence by age. An updated search was conducted on 22 October 2022. There were no language restrictions. Papers were assessed for quality using an adapted version of the Downs and Black checklist. Seroprevalence by age was estimated using a fixed-effect (country) or random-effects (WHO region and income) meta-analysis. This review has been registered on PROSPERO (CRD42022349900).

**Results** Only one country (USA) had enough data for a country meta-analysis. WHO regional analyses revealed the Western Pacific region to have a higher seroprevalence in younger age groups than other WHO regions. Country income level better explained seroprevalence trends per age. Middle-income countries displayed a quicker rise to balance seroprevalence than high-income countries, with a 30% absolute increase in 0- to 4-year-olds in middle-income than in high-income countries (59% [95% CI 28 to 91%, $I^2$=99%] vs 29% [95% CI 16 to 41%, $I^2$=99%]).

**Conclusion** This first meta-analysis producing estimates of EBV seroprevalence by age provides crucial information to guide governments when using a vaccine for EBV. However, data variability and limited consistency of methodologies and EBV seroprevalence measurements hindered comprehensive meta-analyses across all WHO regions and countries. This study provides an interim framework for the extrapolation of seroprevalence using country-specific income levels to aid vaccine roll-out decisions.

**PROSPERO registration number** CRD42022349900

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ This study built on a previous systematic review evaluating the global literature to identify risk factors associated with Epstein–Barr virus (EBV) acquisition. The review searched MEDLINE, Embase and Web of Science for studies investigating EBV risk factors (including age) on 16 March 2017. No meta-analysis was performed, limiting the conclusions that could be drawn, but when data were grouped by country and WHO region, the results revealed that EBV seroconversion tended to occur at younger ages in Asia vs Europe and North America. A substantial data gap was identified for countries in Africa and South America.

### WHAT THIS STUDY ADDS

⇒ This study documents more than double the number of publications on EBV seroprevalence by age globally and provides the first meta-analysis on the topic, which will be vital for governments seeking to deploy an EBV vaccine in their country. Given the dearth of data for many countries (particularly low- and middle-income countries, such as China, where EBV-associated nasopharyngeal carcinoma is endemic), this study demonstrates how country income can be used to group studies and thus extrapolate to fill data gaps.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The deployment strategy and cost-effectiveness case for an EBV vaccine will vary substantially among countries due to geographic variability in a) the burden of EBV-associated diseases and b) when infection is acquired. To inform deployment, it is critical to either have country-by-country data on the age at acquisition or a means to extrapolate from another appropriate setting. This study informs policymakers on both points by providing both meta-analysis estimates, where possible, and an interim framework for the extrapolation of data among countries before new seroprevalence studies arise. This is particularly critical for low- and middle-income countries where data are sparse.

## INTRODUCTION

Epstein–Barr virus (EBV) is known to be associated with the development of several malignancies, including nasopharyngeal carcinoma (NPC), Hodgkin's lymphoma (HL) and Burkitt's lymphoma (BL), as well as autoimmune conditions such as multiple

sclerosis (MS).[1 2] The incidence of these illnesses varies among countries. NPC, a cancer of the neck and throat, shows a distinct geographic distribution and is endemic to areas in Southeast Asia, such as southern China, Taiwan and Hong Kong.[3] BL also shows a geographic distribution, with high incidence in Equatorial Africa.[4] Endemic BL is the most common childhood EBV-associated cancer in countries where malaria is also endemic.[4] The burden of MS is much greater in high-income countries, particularly in the Northern Hemisphere, such as Sweden.[5] These illnesses carry a high economic burden, not least by the costs associated with diagnosis and treatment where healthcare resources may be limited. Because these diseases usually affect individuals in their productive years, it has a subsequent negative effect on the economic output of the country. Moreover, the effect of these diseases extends beyond their economic burden. These illnesses contribute to a decreased quality of life and fatality. Therefore, the prevention of EBV is imperative and of great interest to global health.

Efforts to develop an EBV vaccine have spanned decades, focusing initially on the gp350 antigen, which showed promise in animal models by eliciting neutralising antibodies but failed to prevent infection in humans.[6] Subsequent attempts included subunit vaccines targeting multiple viral glycoproteins, yet these too were only modestly effective. The complexity of EBV's life cycle, involving distinct entry mechanisms into B cells and epithelial cells, has posed significant challenges.[6] Recent advances, including virus-like particles and mRNA-based vaccines, offer renewed hope. Three vaccine candidates aiming to prevent the incidence of infectious mononucleosis are currently in phase I clinical trials at the time of writing, offering new hope to the quest to produce an implementable candidate.[7–9]

Due to the high number of EBV-associated illnesses and their profound effect on countries across the globe, the implementation of preventative measures through vaccination may mitigate their effect on health. If indeed a prophylactic vaccine candidate for EBV was developed and rolled out globally, understanding how best to deploy the vaccine is imperative to improve public health, particularly where resources are limited.

Understanding EBV seroprevalence across different age groups per country plays a critical role in informing policymakers which age groups to target with a future vaccine. In 2017, Winter et al published a systematic review of the global literature on risk factors for EBV acquisition, within which age was one of the risk factors of interest.[10] EBV is known to have an equilibrium seroprevalence of 95% worldwide; however, the age of acquisition varies among populations. Although this review did not include a meta-analysis, EBV seroconversion was found to occur in younger age groups in Asia and older age groups in Europe and North America. A large data gap was uncovered for countries in Africa and South America. Data for these regions were reported only from specific populations, such as HIV-exposed infants,[11] and thus had limited generalisability and were for very specific ages.

As the possibility of a prophylactic EBV vaccine becomes greater,[12–14] recommending bodies must understand EBV seroprevalence by age geographically, including the evidence gaps that need to be filled before vaccine licensing and implementation. Together with the country-specific burden of EBV-associated disease data, the findings will inform decision-making for vaccine deployment. In this study, globally available data were systematically reviewed and, building on the work by Winter et al,[10] presented seroprevalence estimates by age, country and WHO region. Further, to better explain how countries are grouped by their seroprevalence as a function of age, estimates by country income level will be additionally presented.

## METHODS

This systematic review was reported in accordance with the PRISMA guidelines.

### Search strategy and study selection

The search strategy for this review was adapted from the study by Winter et al[10] The search terms included EBV, infectious mononucleosis, glandular fever, seroprevalence and study design terms such as 'case control', 'cohort', 'intervention study', 'cross sectional' and 'clinical trial'. Additional terms related to public health surveillance and monitoring were also included (online supplemental table 1). Unlike the previous review, age was our sole risk factor of interest. Studies were included if they reported seroprevalence for specific age groups and excluded if they reported seroprevalence estimates for broad age ranges or only contained people with EBV-associated disease. Studies measuring all EBV antibody–antigen combinations were included. The full inclusion and exclusion criteria are presented in online supplemental table 2.

MEDLINE, Embase and Web of Science were searched from 7 March 2017 to 22 March 2022 for relevant studies. Those published prior to this time point were taken from the study by Winter et al.[10]An updated search was conducted on 22 October 2022, with a 2-week overlap with the search conducted in March 2022.

### Screening

The studies identified by the search were uploaded to the systematic review management software, Covidence, where title, abstract and full-text screening was conducted in duplicate by MM and either VQ or SK. Conflicts were flagged by Covidence and resolved by consensus. Cohen's kappa statistic for measuring agreement between reviewers was calculated.[15] The full texts of studies from the review by Winter et al[10] were also screened for suitability. Foreign-language papers were screened by speakers fluent in the language together with MM.

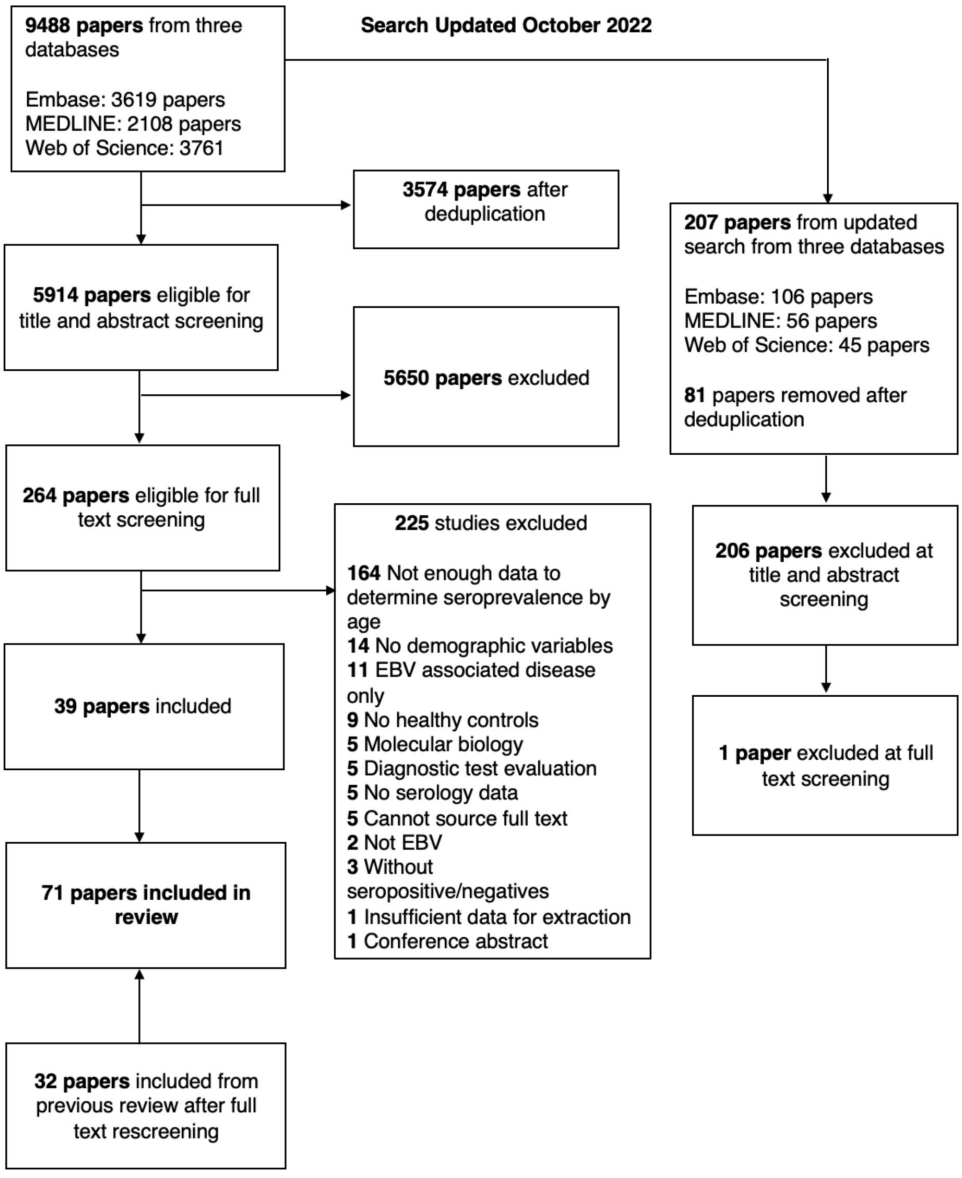


**Figure 1** PRISMA diagram of included studies. EBV, Epstein-Barr virus.

### Data extraction, synthesis and quality assessment

Data were extracted to a predesigned Microsoft Excel spreadsheet by MM and TM, who recorded relevant information, such as study design, study population, years of study, country, EBV test type, antibody used, antigen measured, overall seroprevalence and age-specific seroprevalence. Disagreements were resolved through consensus, and foreign-language papers were extracted by speakers fluent of the respective language along with MM.

Age categories were created for the analysis owing to the impracticality of measuring and meta-analysing seroprevalence per year of age. The predetermined age groups were 0–4, 5–9, 10–14, 15–19, 20–29, 30–39 and ≥40 years, as studies were not expected to report single age years. If the age groups described in a study did not precisely match these categories, it was placed into a category if it included an age range of 2 years on either side of the upper and lower age groups studied. Studies were grouped by WHO region and country income level according to the World Bank designation.[16 17]

Quality assessment was conducted using the Downs and Black[18] checklist, which was adapted as per the guidance by Deeks et al[19] (online supplemental table 3). This included questions surrounding information bias, misclassification and measurement of the exposure and the outcome. The assessment included whether the primary aim of the study was to assess seroprevalence per age and whether the age groups analysed were drawn from the same populations. Detecting seroprevalence using manufacturers' kits was deemed less susceptible to information bias for the outcome compared with in-house tests.

All data were descriptively analysed, including generating seroprevalence plots by country, WHO region and country income level. Only studies measuring anti-viral capsid antigen IgG (VCA IgG), as this antibody–antigen

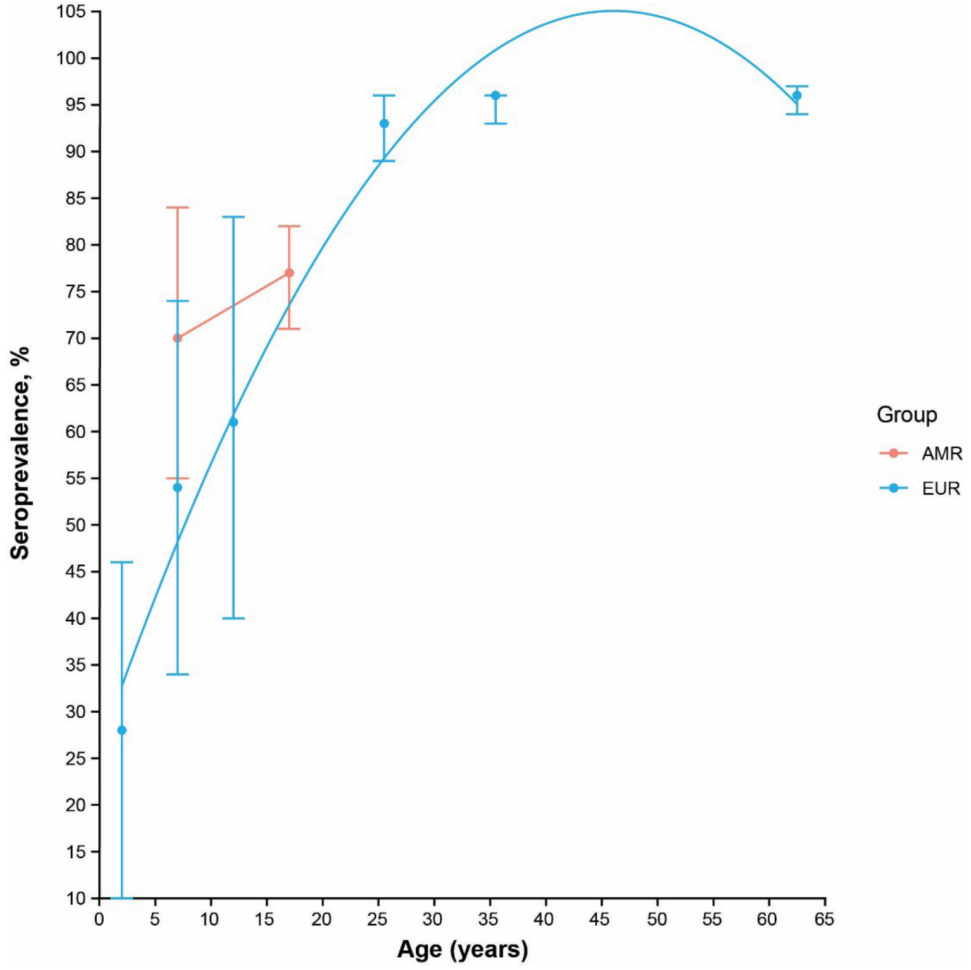


**Figure 2** Seroprevalence meta-analysis estimates for the European and Americas regions. Countries were grouped by WHO region. Seroprevalence data was generated from pooled estimates by a series of meta-analyses for each age group. Data was available across all but one age groups in the EUR region (0-4, 5-9, 10-14, 20-29, 30-30, ≤40) and three in the Americas region (0–4, 5–9, 10–14). Dots represent the centre of each age group. Curves are of best fit from linear regression, and vertical bars represent the 95% confidence intervals for the estimates. WHO, World Health Organization.

combination is most indicative of previous infection, were included from this point. Where possible, meta-analyses of proportions were conducted using metaprop in STATA version 17. The metaprop command automatically applies a logit transformation to the seroprevalence proportions before pooling, which stabilises variances and accounts for proportions near 0 or 1. The pooled estimates are then back-transformed to the original proportion scale for interpretation and presentation. Metaprop also provides $I^2$ estimates to estimate heterogeneity between studies. Meta-analyses were conducted globally per age group and then by WHO region, country and country income level to determine potential sources of heterogeneity. A minimum of three studies were required for each age group for meta-analysis. Fixed-effect meta-analysis was deemed appropriate for analyses per country owing to the presence of a single underlying effect estimate and random effects for the WHO region and income analyses, because this expectation was not anticipated to be fulfilled.

If multiple papers/data points from the same study and age group were present, a sensitivity analysis was performed that restricted the analysis to one data point per study to ensure that no individual study was influencing the overall seroprevalence estimate. The effect of the calendar years in which the study was conducted on seroprevalence estimates was also examined using the midpoint of the years in which the participants were recruited to the study.

Meta-regression analyses were performed using Stata version 17 to determine the percentage of between-study heterogeneity explained by the predictors income level (high vs middle) and region (Europe vs Americas) on EBV seroprevalence. Random-effects meta-regressions were conducted for each age group if data were sufficient to do so; the dependent variable was the logit-transformed proportion of EBV seroprevalence.

### Publication bias

Although publication bias was unlikely to have been an issue for the studies included in this paper, owing to their

descriptive nature (across different age groups), for the global meta-analyses, funnel plots were plotted for each age group. For subgroups with ≥10 studies, Egger's regression test was employed to assess funnel plot asymmetry. Analyses were conducted in Stata using the metafunnel and metabias commands.

### Registration

This review has been registered on PROSPERO (CRD42022349900).

## RESULTS

### Search results

After deduplication, the literature search returned 5 914 papers. 39 studies[20–58] met the inclusion criteria at the full-text stage (figure 1, online supplemental table 4). An additional 32 studies[11 31 59–88] were included from the previous review (figure 1, online supplemental table 4), bringing the total to 71. Cohen's kappa statistic between MM and SK and MM and VQ were 0.76 and 0.61, respectively, indicating substantial agreement among reviewers.

Papers from all WHO regions and across 25 different countries were presented. After full-text extraction, the results showed that these 71 papers represented 68 studies. Three studies appeared in multiple papers.[33 34 36 37 44 45 71] In this instance, seroprevalence data were usually taken from the most recent publication. Most of these studies measured seroprevalence using VCA IgG, with the next most common antigen–antibody combination being EBNA1 IgG. A small number of studies measured VCA or EBNA1 IgM/IgA (online supplemental table 4).

### Overall quality assessment

Studies were assessed against 12 domains of quality (online supplemental table 5). Of the 71 papers, 30 (42.3%)[11 23 24 26–28 30 31 37 38 43–48 50 51 53 55 57 62 64 65 74 75 77 81 84 86] aimed to examine seroprevalence by age and were assessed accordingly. All studies drew all age groups from the same populations and time points. 11 studies (11/71, 15.4%)[33 35–37 39 41 54 60 68 71 78] used tests for seroprevalence that may have introduced information bias, per investigator assessment. Of these 11, only one set out to measure seroprevalence by age.

### Meta-analysis

First, a meta-analysis of proportions was performed across all the studies where three studies were available for each age group. This analysis revealed substantial heterogeneity (online supplemental figure 1), particularly within the younger age groups. To explore potential sources of this heterogeneity, subgroup analyses and meta-regression were conducted, stratifying by WHO region and World Bank income level.

Potential publication bias was also analysed. Funnel plots for all age groups are presented in online supplemental figure 2A–G and Egger's test results in online supplemental table 6. The group aged 20–29 years was the only age group demonstrating potential publication bias; however, it is unlikely that such a phenomenon could have played out for this age group independently of the others.

### WHO region analyses

Then, descriptive analyses and meta-analyses of the studies included in our review were presented. Studies were initially grouped by country and WHO region as per Winter et al.[10]

#### African region

Five papers[11 22 49 74 82] were included from the African region (AFR), including studies from Ghana, Kenya, Malawi and Zambia (online supplemental figure 3). Four of these studies focused on young children aged 0–11 years. Only one study was conducted out in adults (aged 18–65 years). No meta-analyses were possible for this WHO region.

#### European region

A total of 19 studies[21 23 24 35 37–40 45 52 54 55 57–59 70 75 79 85] were from the European region (EUR) in populations spanning aged 0–85 years old (online supplemental figure 4). Overall, seroprevalence was estimated to rapidly increase until the age of 15 years and more slowly thereafter. Barring a single study in the UK that showed a decrease in the seroprevalence after the age of 70, which may have suffered from survival bias,[79] data were relatively consistent.

Meta-analyses were performed for the EUR as one per age category, except for age group 15–19 (0–4, 5–9, 10–14, 20–29, 30–39, ≥40), using data from 14 separate studies[16 17 28 30–32 38 45 47 48 50–52 63 72] (figure 2, online supplemental figure 5). Seroprevalence per age category increased rapidly until age 7 before gradually increasing to 96% at age 35. $I^2$ values varied between 79% and 99% across the meta-analyses, indicating that the percentage of total variability due to between-study heterogeneity was high.

Removing instances of duplicate data points from a single study within a sensitivity analysis did not affect seroprevalence estimates (online supplemental figure 6).

#### Americas region

A total of nine studies were from the Americas region (AMR), encompassing ages from 0-85 years old (online supplemental figure 5).[27 30 53 56 60–62 65 66] Studies were mostly from the USA (n=6/9, 66.7%), with three from Brazil (33.3%). Patients' ages ranged from 0 to 85 years. The two nations provided very distinct estimates of seroprevalence (online supplemental figure 7). Country-specific trends for the USA and Brazil are discussed in the country analyses section of the results.

Four studies were included in the meta-analysis for the AMR (online supplemental figure 8); ≥3 studies examined age categories 0–4, 5–9 and 16–19 only. Seroprevalence was higher than in the EUR for these age groups because the higher seroprevalence in Brazil influenced this estimate.

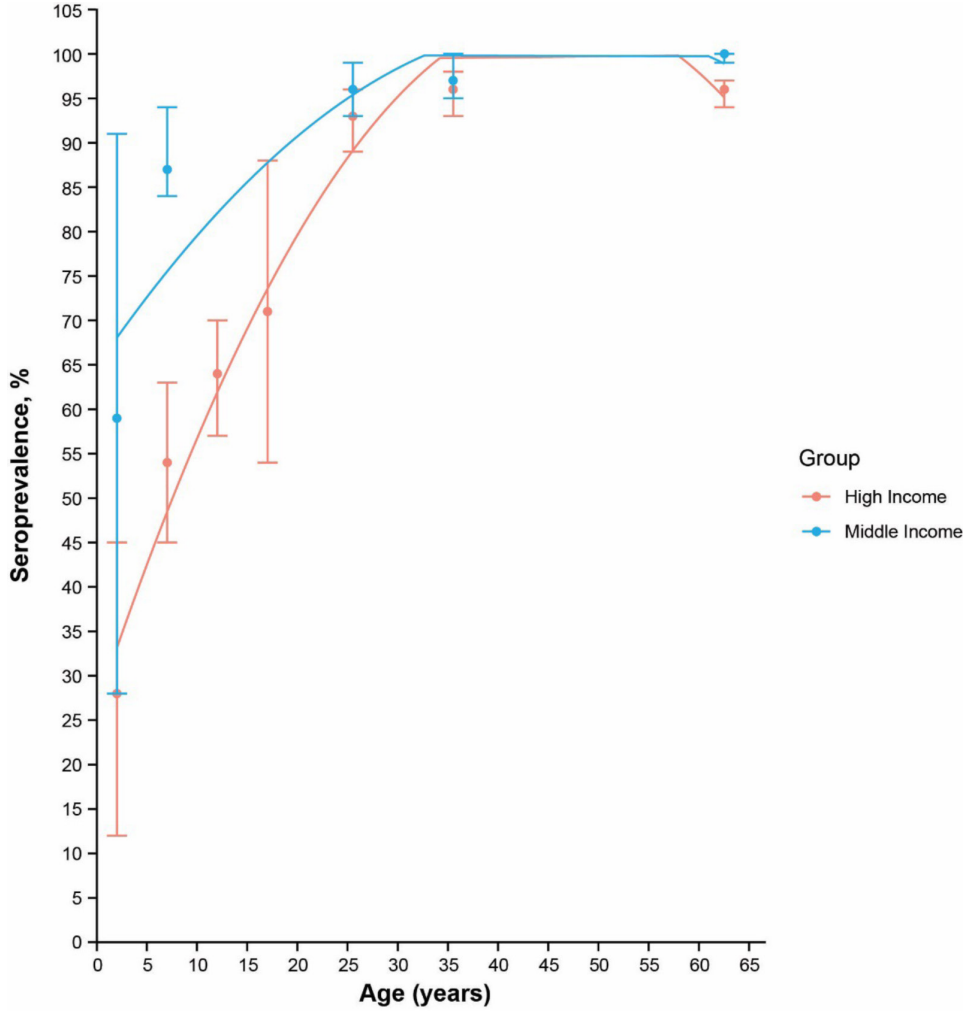


**Figure 3** Seroprevalence meta-analysis estimates for high- and middle-income countries. Countries were grouped by World Bank income classification at the year of study. Seroprevalence data was generated from pooled estimates by a series of meta-analysis for each age group. Data was available across all age groups (0–4, 5–9, 10–14, 15–19, 20–29, 30–39, >40 years old) for high-income countries, and four age categories for middle-income countries (0–4, 5–9, 20–29, ≥40). Dots represent the centre of each age group. Curves are of best fit from linear regression, and vertical bars represent the 95% confidence intervals for the estimates.

$I^2$ values varied between 90% and 99% across the meta-analyses, indicating that the percentage of total variability due to between-study heterogeneity was high.

Removing instances of duplicate data points from a single study within a sensitivity analysis did not influence seroprevalence estimates (online supplemental figure 9).

### Southeast Asia region

One paper from the Southeast Asia region (SEA), specifically from Thailand,[84] was included (online supplemental figure 10). This study covered many age groups, from age 0 to 6 months until >40 years. Seroprevalence increased to 100% at ages 6–8 years and stayed consistently >96% into the older age categories (≥40). Meta-analyses were not possible.

### Eastern Mediterranean region

Only one study was from the Eastern Mediterranean region (EMR), specifically from Iran[47] (online supplemental figure 11). The total age range in this study was 0-≥85 (maximum age not stated). The seroprevalence in Iran increased gradually with age from 50.5% at ages 1–3 years and reached 92% by 20–29 years. Meta-analyses were not possible.

### Western Pacific region

Five of the included studies were from the Western Pacific region (WPR), specifically from China/Taiwan (n=4),[28 48 64 87] and Singapore (n=1)[46] (online supplemental figure 12). In these papers, the age ranged from 0-85 years. Seroprevalence was approximately 66% between ages 0 and 5 years and rapidly increased to 99%–100% by age 30. Likely due to the prevalence of NPC in this region (particularly in specific geographic regions of China), contrary to previous regions, most studies measured either IgA or IgM antibodies. Data were consistent within China. Meta-analyses were not possible.

### WHO region meta-regression

The region explained a portion of the variation in seroprevalence for two younger (aged 0–4 and 5–9 years; $R^2$=3.1% and 25.1%, respectively) and two older (20–29, >40s; 25.3% and 28.5%, respectively) age categories (online supplemental table 7).

## Country income-level analyses

As grouping studies by WHO region did not result in consistent seroprevalence curves across the countries, the included papers were then grouped into different country income levels based on where they were conducted. The total number of papers found for high-, medium- and low-income levels during the study period was 47/71 (63·4%),[23–27 31–46 52 54–59 61 62 65 66 68–73 75 77–79 81 83 85 86] 21/71 (28·2%),[20 21 28–30 47 48 50 51 53 60 63 64 67 76 80 84 87 88] and 4/71 (6·6%),[11 22 74 82] respectively. One study (from Kenya)[49] did not report the study period; therefore, the income level was not determined.

### High income

Across the 47 high-income studies, data were available from 0 to 85 years of age. Broadly, seroprevalence increased gradually between ages 0 and 25, peaking at 90%–100% by around age 25 (online supplemental figure 13A). One study showed a decrease in seroprevalence after age 70; this may be due to survivor bias.[79]

In the meta-analysis, seroprevalence steadily increased until the age of 30 years (figure 3, online supplemental figure 14). $I^2$ values varied between 79% and 99% across the meta-analyses, indicating that the percentage of the total variability due to between-study heterogeneity was very high (with the lowest levels in people aged >40 years).

Removing instances of duplicate data points from a single study within a sensitivity analysis did not affect seroprevalence estimates (online supplemental figure 15).

### Middle-income

Across the 21 studies focusing on middle-income countries, seroprevalence data were available for ages ranging from 0 to 85 years. Two main groupings of studies appeared, one with a more rapid approach to maintain seroprevalence and one with a shallower approach (online supplemental figure 13B); however, both had steeper trajectories than the studies on high income.

Six of the papers were included in the meta-analysis,[28 30 47 53 60 84] across five of the seven age categories (figure 2, online supplemental figure 16). Meta-analysis was not available for groups aged 10–14 and 15–19 years. Data showed a steep increase in seroprevalence up to the middle teenage years, followed by a slower increase. $I^2$ values varied between 46% and 99% across the meta-analyses, indicating that the percentage of the total variability due to between-study heterogeneity was high. Again, data were less variable for individuals aged >40.

Removing instances of duplicate data points from a single study within a sensitivity analysis did not influence seroprevalence estimates (online supplemental figure 17).

Compared with the high-income countries, seroprevalence in middle-income countries had a much sharper increase between the ages of 0 and 10 years, with 10-year-olds reaching nearly 90% seroprevalence (figure 3).

### Low-income

Finally, four papers included populations from low-income countries at the time of the study (online supplemental figure 13C).[11 22 74 82] The age ranged from 0 to 65 years across these papers. The seroprevalence in low-income countries was much higher in younger age groups than those in both high- and middle-income countries, with one study reporting that approximately 90% seroprevalence was reached by age 5.[22] A further study from Ghana was an outlier.[11] Meta-analyses were not feasible for studies on low-income countries.

### Country income-level meta-regression

Meta-regression was possible for all age groups apart from 15 to 19 years (online supplemental table 8). For the groups aged 0–4, 5–9 and 10–14 years, more variations were explained by the income level than by the WHO region, which is in line with the greater degree of difference in seroprevalence between settings for these age groups.

## Country analyses

The papers included in this review covered 25 countries, with 17 reporting seroprevalence data using VCA IgG (online supplemental table 9). SEA and EMR only had one study each; thus, their studies are described above.

In AFR, both Kenya and Malawi demonstrated sharp increases in seropositivity at very young ages (online supplemental figure 3C, D). Only Ghana (online supplemental figure 3B) had data for adults, with substantially lower seroprevalence, even for younger adult age groups than the other African studies.

Data from eight EUR nations could be analysed: UK (n=6),[35 38 45 57 75 79] Sweden (n=3),[24 39 70] Netherlands (n=3),[40 54 59 85] Croatia (n=2),[23 55] Germany, Finland, Turkey and Greece (n=1 each)[21 37 52 58]; however, a meta-analysis could not be performed in any of them (online supplemental figure 4B–I). Only Croatia, Finland, Turkey and the UK had data across the lifespan. Within nations, data were reasonably consistent.

A total of three studies were from Brazil (online supplemental figure 7A).[30 53 60] The seroprevalence across age groups ranged from 80% to 90% by age 10 years. In contrast, the six studies from the USA[27 56 61 62 65 66] showed a much slower increase in seroprevalence (online supplemental figure 7B). A meta-analysis of each US study was possible (online supplemental figure 18). Three studies[62 65 66] were included in the meta-analysis, for age

groups 5–9, 10–14 and 15–19 only. Seroprevalence was similar across each group.

Removing instances of duplicate data points from a single study within a sensitivity analysis did not affect seroprevalence estimates (online supplemental figure 19). At the country level, we further sought to examine whether the calendar years in which the study was conducted influenced the seroprevalence estimates. This was possible only in the study conducted in the USA (online supplemental figure 20). For the groups aged10–14 and 15–19 years, no obvious trend was observed. Estimates for the group aged 5–9 years showed some indication of lower seroprevalence in later studies, although across limited datapoints, with overlapping CIs, and with two different estimates from Delaney *et al*.[66].

## DISCUSSION

This systematic review and meta-analysis provides critical insights into EBV seroprevalence across different countries, income levels and age groups. One of the key findings from this study is the clear distinction in EBV seroprevalence trends between high- and middle-income countries. Middle-income countries demonstrate a faster rise to balance seroprevalence, particularly among children aged 0–4 years, compared with high-income countries where infection tends to occur later. Specifically, a 30% higher seroprevalence was noted in middle-income countries (59% vs 29% in high-income countries) for this age group.

This review is the first to synthesise and conduct a meta-analysis of the global EBV seroprevalence by age, including presenting data grouped by country, WHO region and country income level. It provides recommending bodies with critical information that will be informative when governments are considering implementing targeted vaccine strategies. The number of eligible papers from the original review by Winter et al was doubled.[10] Despite this, substantial gaps in the literature for low- and middle-income countries were identified; however, this review provides evidence of a sharper rise in EBV seroprevalence among younger children in middle- and low-income countries. This highlights the role of a complex array of social and economic factors, including childcare practices and living conditions, in facilitating early transmission.[89] The meta-regression results suggest that income level explains more of the variation in EBV seroprevalence, particularly in the groups aged 5–9 years. Income also explained variations in seroprevalence among 10- to 14-year-olds, where regional analysis showed no explanatory power. This suggests that economic factors may play a larger role in shaping early-life transmission patterns.

The lack of data in AFR, EMR and SEA makes it difficult for policymakers to obtain a reliable estimate of EBV seroprevalence per age group. Studies from South America fall into the WHO AMR; while this review included two studies from South America, both from Brazil, extrapolating the AMR findings to other South American countries should be done cautiously. Future research must include a broader range of countries in South America. However, the present review provides a way to extrapolate data to countries with missing data, based on their income level.

Although this systematic review synthesised a large body of global data on EBV seroprevalence, its limitations must be acknowledged. The meta-analyses displayed substantial heterogeneity across studies with $I^2$ values (up to 99%). This review was also limited by data variability due to different methodologies employed, and not all studies used VCA IgG antibodies to determine seroprevalence. VCA IgG is the only antigen–antibody combination that has persistent titres detected in both acute and past infection.[90] These issues limited our ability to conduct meta-analyses for most WHO regions and countries. Underlying studies were often restricted to specific populations; for example, in the AFR, studies were limited to women and infants, with no data available for men or middle-aged categories. The limited number of data points for the meta-analyses also meant that sensitivity analyses could not be performed to examine the effect of study quality on our estimates.

To address the identified limitations, future research should focus on filling the substantial data gaps in low- and middle-income countries. These regions currently lack sufficient age-stratified seroprevalence data, which is essential for guiding vaccine deployment strategies. EBV seroprevalence estimates, particularly for younger age groups in high-income settings, are possibly changing over time; however, we lacked the data to explore this fully. Ideally, such analyses would be taken from a single data source over a series of calendar years. Future studies should use gold-standard serological assays in measuring VCA IgG to ensure the accuracy and reliability of the measured seroprevalence and avoid non-differential misclassification. Studies must also maximise their generalisability within a setting (ie, with a representative sample to the general population and with a large-enough sample size per age group).

The findings of this review highlight that age is a critical factor to consider when deciding how to deploy a vaccine to prevent EBV infections. Preventing EBV and its associated illnesses is crucial, and the age of acquisition of infection, duration of protection from a vaccine and the burden of EBV-associated disease in a country will affect vaccine roll-out.[91] Approximately half of China's population is EBV-seropositive by the age of 5; thus, it would be critical to vaccinate children under this age. A vaccine could potentially be delivered at the same time as other infant vaccinations. Given that China has NPC-endemic areas, cost-effectiveness is more likely than in a country with a lower burden of EBV-associated disease. As the onset of NPC is commonly many decades after EBV infection,[92] a lengthy duration of protection is likely to be required from a vaccine, although booster doses could also be used. In Uganda, where BL is highly prevalent, the

age of vaccination will be similar to that of China. As BL predominantly affects children in that country, the duration of protection is not as critical.[93] In contrast, in high-income countries, such as Sweden (where HL and MS, which are both associated with IM, are of concern),[94 95] infection is often acquired in the teenage years; thus, deployment could wait until later in life than in China and Uganda. A vaccine that provides a lower duration of protection may be less problematic in such countries if delayed infection takes individuals outside of the highest risk period for IM and thus disease.

## CONCLUSION

This study provides the most current global analysis and meta-analyses of EBV seroprevalence by age across the globe. Knowledge of EBV acquisition per age is useful for future EBV vaccine campaigns to ensure they are as beneficial and cost-effective as possible. An unfortunate data gap was noted in this study, which means that seroprevalence as a function of age cannot be parameterised for low and middle income countries (LMIC); however, we provide an interim framework for extrapolation, which would allow for informed decision-making about vaccine roll-out in these countries before additional studies are performed.

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