

Epidemiology or biology? A systematic review untangling the relationship between Shigella and HIV

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Abstract

Background

Shigella is a genus of Gram-negative bacteria that cause bacillary dysentery, also known as shigellosis. Transmission occurs through the faecal-oral route, and disease burden is concentrated in LMICs due to suboptimal sanitation and lack of clean water. Recent surveillance data from HICs have demonstrated increasing incidence of domestically acquired shigellosis, particularly among men who have sex with men (MSM), many of whom are also people living with HIV (PLWHIV). The overlap of these pathogens is largely assumed to arise from overlap in sexual transmission networks, specifically through practices involving oral-anal contact and condomless sex. However, the exact relationship between HIV status and *Shigella* has not been well characterised, particularly whether the association exists in LMICs and what role HIV-mediated immunological susceptibility may play.

Methods

A systematic search of peer-reviewed literature was conducted in PubMed and Embase to identify epidemiological and biological drivers of HIV-*Shigella* coinfection across both HIC and LMIC settings. Records were imported into Covidence and selected through title/abstract screening followed by full-text assessment by one author according to predefined inclusion and exclusion criteria. Full-text assessment was independently confirmed by a second reader. Using the included studies, citation searching was conducted to identify additional studies not captured by the initial search. All evidence was critically appraised following Critical Appraisal Skills Programme (CASP) or Joanna Briggs Institute (JBI) guidelines by one author and synthesised using a narrative approach informed by study quality and reported statistical measures.

Results

The systematic review search returned 700 unique records, of which 26 were included. Two additional studies were identified through backward citation searching, resulting in 28 studies included overall. Studies were organised into broad epidemiological or biological themes and country income setting. Epidemiological factors associated with HIV-*Shigella* coinfection included MSM-associated sexual transmission, specific sexual behaviours facilitating faecal-oral exposure, and sociodemographic characteristics. Limited biological evidence suggested that HIV-related immune activation and alterations in the gut microbiota may increase susceptibility to *Shigella* infection, although temporality remains undefined.

Conclusion

HIV-*Shigella* coinfection results from a complex interplay of both population epidemiology and possible biological susceptibility rather than a single mechanism. Current evidence supports the further exploration of links between HIV and *Shigella*, with implications for both sexual transmission in HICs and endemic transmission in LMIC settings.

Background

Shigella is a genus of bacteria and the causative agent of the enteric infection, shigellosis [1]. Clinical manifestations range from asymptomatic infection to fever, abdominal cramps, bloody or mucoid diarrhoea, with rarer complications including haemolytic uraemia, toxic megacolon, sepsis, reactive arthritis, and death. Transmission occurs via the faecal-oral route, most commonly through direct person-to-person contact or indirectly through contaminated food, water, flies, or fomites [2, 3]. Globally, shigellosis causes approximately 269 million cases and 212,438 related deaths annually, accounting for 13.2% of all diarrhoeal deaths [4, 5]. Disease burden is disproportionately concentrated in low- and middle-income countries (LMICs), particularly among children under five years old in Africa and South Asia, where inadequate hygiene and sanitation facilitate transmission [3, 6, 7]. In high-income countries (HICs), shigellosis has historically been linked to travel in endemic regions or self-limited outbreaks in close-contact environments (e.g., schools and day-care centres) [3, 4]. Sexual transmission has also been recognised since the 1970s, with risk factors including oral-anal contact and condomless anal intercourse [8, 9].

Shigella epidemiology has changed markedly since the 2000s, with many HICs reporting substantial increases in domestically acquired shigellosis associated with sexual transmission among men who have sex with men (MSM) [2, 3, 8]. Surveillance data from England illustrate this epidemiological shift, with more than half of *Shigella* infections in adults aged 16–60 years between 2004 and 2015 not attributable to foreign travel [10]. More recently, annual diagnoses among MSM rose from 2,318 in 2024 to 2,560 in 2025, with several large clusters known to be sexually transmitted [11].

Notably, outbreak investigations indicate that many of these domestically acquired *Shigella* cases in HICs occur among individuals diagnosed with human immunodeficiency virus (HIV) [12–15]. In England, HIV coinfection was identified in 21% of men with domestically acquired shigellosis between 2004 and 2015 ($n = 720/3,481$, of whom 91% [$n = 657/720$] were MSM). This is in stark contrast to only 2% of coinfecting women ($n = 31/1,946$) [15]. Comparable patterns have been reported in epidemiological investigations across HICs [16, 17]. Furthermore, genomic epidemiology of early documented sexually transmissible *Shigella* outbreaks demonstrates that the emergence of these lineages coincided with the implementation of antiretroviral therapy (ART) for HIV treatment, underscoring the association between the two pathogens [18, 19].

Overlap between HIV and *Shigella* epidemics in HICs is largely attributed to shared sexual exposure [15, 20]. However, genomic epidemiology in South Africa also revealed an expansion of shigellosis coincident with increasing HIV prevalence among an HIV-endemic population [21]. Despite this evidence, few

studies have queried the biological links between *Shigella* infection and HIV-associated pathology as an epidemiologically independent risk factor. Previous literature has established that people living with HIV (PLWHIV) are at risk for opportunistic gastrointestinal (GI) infections [22]. The GI tract is particularly vulnerable during HIV pathogenesis, undergoing rapid CD4 depletion, chronic immune activation, and mucosal integrity loss [23]. These pathological changes are not fully restored following antiretroviral treatment [24], potentially leaving individuals with well-controlled HIV susceptible to opportunistic GI infections. This lack of recovery is particularly relevant in HICs, where most PLWHIV receive ART and achieve virological suppression [25].

Clarifying the relationship between *Shigella* and HIV is important for determining whether coinfection reflects overlapping sexual behaviour risks alone or whether HIV-related pathology also independently contributes to *Shigella* susceptibility. This distinction holds direct implications for *Shigella* prevention and control, as a predominantly behavioural relationship would support targeted efforts focused on sexual practices associated with *Shigella* exposure. Evidence of HIV as an independent biological risk would necessitate broader prevention strategies incorporating PLWHIV as a critical target population. To explore the available evidence base surrounding these questions, this review synthesises the epidemiological and biological factors associated with HIV-*Shigella* coinfection across high- and low-income settings, identifies key research gaps, and provides a comprehensive understanding of the recently observed trend linking these two pathogens.

Methods

This study employed a systematic and iterative search strategy to synthesise evidence on epidemiological and biological associations of HIV-*Shigella* coinfection to understand how they may contribute to recent shifts in shigellosis epidemiology and to explore their relevance in LMICs.

Study design

The methodology integrated diverse evidence sources and narratively evaluated the relevance and strength of reported associations between HIV and *Shigella*. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to minimise bias and increase reproducibility [26]. A preliminary literature search indicated a limited evidence base to support a narrow question or inclusion criteria typically required by systematic reviews, thereby introducing the need for an iterative search strategy. The topic also required engagement with literature from multiple disciplines, such as epidemiology or microbiology. Thus, this review adopted a broad database search with an iterative component. Due to timing constraints, the protocol was not registered with the International Prospective Register of Systematic Reviews (PROSPERO).

Search strategy

The search strategy employed a two-step approach. PubMed and Embase (Ovid) were searched using predefined strings following a systematic, reproducible methodology. Searches combined controlled vocabulary and free-text terms related to “HIV” and “*Shigella*.” Boolean operators (AND/OR), truncation, and database-specific syntax maximised search sensitivity. Multiple databases were employed to improve literature coverage. Complete search strings for each database are provided in Supplementary Table S1.

An iterative search was subsequently conducted, using emerging concepts and backward citation searching from studies included during the systematic search to extend capture. This iterative search concluded at conceptual saturation, assessed by reviewing findings from each search and determining whether new studies identified novel subthemes or research gaps.

Study selection

Following the database search, records from PubMed and Embase were imported into Covidence [27], an online systematic review management platform. Duplicate records were automatically and manually removed. Remaining records underwent a systematic screening process according to PRISMA guidelines to provide a structured approach to study selection. Title and abstract screening was completed by one reviewer (ER) against predefined eligibility criteria (Table 1). Potentially relevant records underwent full-text screening by two reviewers (ER and AU). Throughout screening, each excluded study was assigned a primary reason for exclusion, documented using a PRISMA 2020 flow diagram to ensure transparency [26].

The SPIDER framework (Sample, Phenomenon of Interest, Design, Evaluation, Research Type), developed by Cooke et al. (2012), was used to structure eligibility criteria (Table 1) [28]. The phenomenon of interest was confirmed HIV-*Shigella* coinfection among study participants. An exception was applied to studies investigating the microbiome of PLWHIV. Common molecular diagnostics report the combined taxonomic group *Escherichia-Shigella*, which cannot always be reliably distinguished using these methods [29]. Detection of this genus was accepted as the indirect presence of *Shigella* relevant to this review, though these findings were interpreted cautiously and not treated as confirmation of species-specific infection. Studies investigating multiple enteric pathogens were excluded if the pathogens were evaluated collectively (e.g. without presenting specific analyses for *Shigella* in relation to HIV infection). These analyses could not isolate specific associations for HIV and *Shigella*. Studies investigating systemic/invasive shigellosis were also excluded when there was no discussion of broader coinfection incidence beyond shigellosis severity. Regarding study design, case reports and case series were excluded due to their small sample sizes, which increase the risk of selection bias and confounding [30].

Table 1
Pre-defined inclusion and exclusion criteria based on the SPIDER framework.

SPIDER framework	Inclusion criteria	Exclusion criteria
Sample	HIV or <i>Shigella</i> -positive individuals Individuals in HICs and LMICs All time frames	Non-human participants
Phenomenon of Interest	HIV and <i>Shigella</i> coinfection	Isolated HIV or <i>Shigella</i> cases
Design	Cohort studies Case-control studies Cross-sectional studies Surveillance-based studies Randomised controlled trials	Case reports Case-series Meta-analyses Systematic reviews
Evaluation	Epidemiological associations of coinfection (e.g., demographics, behaviours) Biological associations of coinfection (e.g., immunity markers)	Simple reporting of coinfection prevalence Systemic/invasive disease with no application towards the broader coinfection relationship
Research type	Quantitative Mixed-method	Qualitative Narrative

Data extraction

Data extraction was conducted by ER in Covidence using a standardised template for consistency. Extracted information included study authors, publication year, design, population, setting, main comparator groups when applicable, key findings (including reported statistical measures), and the appropriate epidemiological and biological theme (Supplementary Table S2).

Quality and risk of bias assessment

Included studies were appraised by ER to assess methodological quality and support evidence interpretation. Ratings were based on reviewer judgement of the extent to which each study met appraisal criteria. Appraisal was not used to determine study exclusion. Most observational studies were appraised using the Critical Appraisal Skills Programme (CASP) which is widely used and recommended for health researchers [31] and available for diverse designs, important for a literature review

incorporating heterogeneous texts. CASP does not provide specific guidelines for surveillance-based studies reporting incidence or prevalence data, and these studies do not conform neatly to standard appraisal criteria [32]. As such, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Prevalence Studies was also utilised. This checklist was developed for systematic reviews of observational epidemiological studies that report prevalence and cumulative incidence [33].

Data synthesis

Data were analysed narratively and structured around overarching thematic categories depending on whether the studies' findings were epidemiological or biological in nature. Within each theme, studies were described and compared according to reported odds ratios and/or precision to identify patterns across the evidence base.

When studies reported conflicting findings, the evidence was interpreted in the context of their analytical outputs and critical appraisal rating. Findings derived from higher-quality studies or those with stronger quantitative support were emphasised more and those from studies of lower quality in the context of relevant limitations. This analytical approach allowed the review to transparently report all collected evidence, while informing conclusions by study strengths and weaknesses.

Data visualisation

Data processing and visualisation for Fig. 2 (which shows data reported in the included studies) were conducted in R version 4.5.1 [34] using the ggplot2 [35] and patchwork packages [36].

Results

Literature search and study selection

The systematic database search identified 987 records across PubMed and Embase (Fig. 1). Following automated duplicate removal in Covidence ($n = 236$) and manual deduplication ($n = 51$), 700 unique records remained for title and abstract screening. Following this screening stage, 60 full-text articles were assessed for eligibility. Of these, 11 were excluded because the full text was inaccessible, and 26 met the predefined SPIDER inclusion and exclusion criteria (Table 1). The iterative search identified 2 additional studies meeting the required criteria, resulting in a final sample of 28 studies (Table 2, detailed information provided in Supplementary Table S3).

Publication dates ranged from 1999 to 2025, although most studies were published after 2015. The evidence base comprised 14 surveillance-based studies, 10 cross-sectional studies, 3 case-control studies, and 1 cohort study. Most studies were conducted in HICs, primarily in the UK ($n = 5$) and USA ($n = 5$). Research and thematic focus differed according to country income setting. Studies conducted in HICs predominantly addressed coinfection epidemiology, such as sexual transmission and outbreak

characteristics, while studies from LMICs more frequently covered biological mechanisms linking the two pathogens, such as alterations in the immune system or gut microbiota.

Study critical appraisal

Following detailed appraisal (Supplementary Table S4), included studies were found to be of mixed methodological quality. Using the appropriate CASP or JBI checklist, 5 studies were judged to be of high quality, 17 were of moderate quality, and 6 were of low quality, highlighting the need for more robust evidence. Among studies appraised using CASP checklists, the most frequent limitation was single healthcare centre recruitment. This recruitment method increased the risk of selection bias, as participants from such settings may not be representative of the broader population. Additionally, epidemiological studies commonly collected behavioural data through self-administered questionnaires or participant interviews, possibly introducing information bias.

Across the classified surveillance-based studies, a common limitation was incomplete population coverage resulting from missing behavioural or clinical data. Insufficient coverage may have reduced the representativeness of surveillance datasets, introducing selection bias if missing cases systematically differed from those included in final analyses. Several outbreak investigations also involved relatively small numbers of laboratory-confirmed shigellosis cases, limiting generalisability.

Epidemiological patterns of HIV- *Shigella* coinfection

LMIC settings

While several LMIC-based studies reported on coinfection pathology, only two examined coinfection epidemiology, highlighting a limited evidence base. Frickmann et al. (2025) screened both HIV-positive and HIV-negative individuals presenting with diarrhoea using a polymerase chain reaction (PCR)-based diagnostic. *Shigella spp./Enteroinvasive Escherichia coli* (EIEC) were detected slightly more frequently among PLWHIV ($n = 149/651$, 22.9%) than HIV-negative individuals ($n = 15/84$, 17.9%), with this difference not reaching statistical significance ($p = 0.332$) [37]. Although this result suggests no difference in *Shigella* susceptibility associated with HIV, the HIV-negative comparator group was relatively small, and further work using molecular testing to resolve EIEC and *Shigella* would be beneficial.

Keddy et al. (2012) examined laboratory-confirmed systemic shigellosis cases ($n = 429$) in South Africa collected through national surveillance, finding that HIV infection occurred in 67% of available cases ($n = 120$) [38]. However, this result was not compared to background HIV prevalence. Demographic analyses indicated that coinfection was unevenly distributed, with HIV prevalence significantly higher in females ($n = 55/70$, 79%) than in males ($n = 25/48$, 52%) ($p = 0.002$). Authors suggested this may reflect the typically greater caregiving responsibilities of women driving greater exposure to the contaminated stool of young children [38]. Additionally, HIV prevalence among those aged > 15 years reached 98%, which the authors stated aligned with age-related distributions of HIV in South Africa [38]. Notably, this finding was substantially higher than the cited antenatal HIV prevalence of 29.3% among pregnant women aged 15–

49 years in South Africa in 2008 [38]. Thus, although results suggest that HIV rates in systemic shigellosis cases reflect underlying HIV demographics, the high HIV prevalence should be interpreted cautiously. HIV status was only established for 57% of available cases, and there was limited contextualisation of quantitative findings with broader population statistics.

The limited epidemiological evidence from LMIC settings suggests that HIV may not be associated with *Shigella* infection, but that it is associated with shigellosis patients with invasive disease, indicating a potential role in disease progression. However, both studies exhibited methodological limitations and were rated as moderate quality. Thus, more robust research is needed within LMIC settings surrounding HIV-*Shigella* coinfection and its relevant epidemiology.

HIC settings

Most epidemiological studies were conducted across HICs ($n = 18$). Within these settings, the included literature consistently reported a positive association between HIV and *Shigella spp.* infection among domestically acquired cases. In England, surveillance data revealed that non-travel-associated *Shigella* cases were significantly more likely to occur among PLWHIV compared to travel-associated cases, indicating domestic transmission networks of *Shigella* that were enriched with PLWHIV (14% versus 3%, $p < 0.01$) [15]. Comparable findings were observed in Spain, where HIV infection was identified in 85.7% ($n = 12/14$) of domestically acquired shigellosis cases compared with 2.6% ($n = 2/76$) of travel-associated cases ($p < 0.0001$) [39]. Temporal relationships were explicitly reported by the UK study, where HIV diagnosis preceded shigellosis in 86% ($n = 610/720$) of individuals diagnosed with both infections [15]. Notably, more studies using surveillance data linkage or temporal observational designs are needed to confirm this sequential association. Nevertheless, domestically acquired shigellosis in HICs was concentrated among PLWHIV, in whom HIV diagnosis typically preceded *Shigella* infection.

Demographic patterns of HIV- *Shigella* coinfection

Demographic distributions of HIV-associated shigellosis were consistent across HICs, with coinfection primarily occurring in men [40–42]. Within an English sample, 93% ($n = 815/873$) of shigellosis cases among PLWHIV occurred in men. This pattern held within the study's sub-analysis of domestically acquired shigellosis. HIV-positive status was found among 21% ($n = 720/3481$) of men compared to 2% of women ($n = 31/1946$) ($p < 0.01$), and male coinfection rates increased significantly between 2004 and 2015 [15] (Fig. 2A). In Spain, domestically acquired shigellosis similarly predominated in males living with HIV (85.7%, $n = 12/14$) [39].

This male bias is linked to MSM, to whom evidence points to as the primary risk group for domestic infection in many HICs. Letters to the Editor and Dispatches published in the UK, USA, and Canada reported that at least half of surveyed *Shigella* infections occurred among MSM living with HIV [13, 43–45]. These briefs are limited by small samples, describing local outbreaks or antimicrobial-resistant strains [13, 43–45], but they were supported by larger observational studies demonstrating that shigellosis among PLWHIV predominately occurred in MSM [16, 17]. In England, while shigellosis

incidence across men with HIV rose from 2004–2015, this was particularly attributable to MSM, where incidence increased from 59.7 to 314.4 per 100,000 individuals [15] (Fig. 2B).

The role of sexual transmission among MSM living with HIV

Much of the evidence base suggests sexual transmission as the predominant driver of HIV-*Shigella* coinfection in MSM. Epidemiological traceback of an antibiotic-resistant *Shigella* outbreak in Canada reported that all nine men surveyed had sex with men, and seven were HIV-positive [43]. This result was further supported by Mitchell et al. (2021), a molecular epidemiology study linking whole-genome sequencing data of *S. flexneri* isolates with national HIV surveillance data in the UK. This study revealed that most isolates identified from PLWHIV (86.1%) fell within *S. flexneri* phylogenetic clades associated with sexual transmission. The most commonly reported route of HIV exposure was sex between men, thereby confirming MSM status [41]. Hence, epidemiological and genomic evidence converge to indicate coinfection among MSM reflects sexual networks of HIV-positive populations in which *Shigella* is transmitted.

High-risk sexual behaviours and MSM living with HIV

Specific practices within these networks may contribute to *Shigella* acquisition in PLWHIV. Semi-structured interviews with MSM diagnosed with *S. flexneri* in the UK found that insertive anal intercourse with a casual partner (aOR = 15.0, 95% CI 1.66–∞, $p = 0.01$), receptive fisting (aOR = 18.3, 95% CI 1.29–∞, $p = 0.03$), and use of apps that facilitate unprotected sex (aOR = 19.8, 95% CI 1.65–∞, $p = 0.02$) were significantly associated with being HIV-positive (compared to HIV-negative) [9]. Confidence intervals are extremely wide, reflecting a small sample ($n = 34$), so associations should be interpreted cautiously. However, they provide preliminary evidence that HIV-positive MSM may engage in additional sexual behaviours relative to HIV-negative MSM that could exacerbate *Shigella* infection.

High-risk behaviours have also been associated with shigellosis in HIV-positive MSM among Taiwanese populations. Specifically, shigellosis was associated with chemsex (use of crystal methamphetamine or γ -hydroxybutyrate (GHB), γ -butyrolactone (GBL), or mephedrone immediately before or during sex; aOR = 5.6, 95% CI 1.4–22.7), poppers use (aOR = 10.9, 95% CI 1.9–64.2), and oral-to-anal sex (aOR = 15.5, 95% CI 3.6–66.7) [47]. Chiou et al. (2016) found that no HIV outpatient follow-up within 12 months before the end of observation (aOR = 22.3, 95% CI 2.5–201) was also associated with shigellosis [48].

Both Taiwanese studies compared HIV-positive MSM with shigellosis and HIV-positive MSM without shigellosis. Therefore, the reported odds ratios indicate associations between specific behaviours and shigellosis among HIV-positive MSM. These findings suggest that certain behaviours may compound shigellosis risk *within* an HIV-positive population, but they cannot establish whether these behavioural factors account for greater shigellosis burden observed among PLWHIV compared to HIV-negative populations.

MSM status independent of HIV infection

As established, MSM living with HIV bear the greatest burden of shigellosis in HICs. Using active surveillance in California, Baer et al. (1999) compared 1996 annual incidence rates of shigellosis by both sexual orientation and HIV status. HIV-positive MSM had the highest incidence rate of 442, but HIV-negative MSM also experienced a high incidence rate of 60.1, suggesting MSM as an independent risk factor [46] (Fig. 2C). Additionally, surveillance studies in the UK and Netherlands observed *Shigella* infection occurring more often in HIV-negative PrEP-using MSM than in HIV-positive MSM [49, 50]. Hence, part of the increased shigellosis burden among PLWHIV may in fact be driven by MSM-associated sexual transmission.

Biological mechanisms underlying HIV- *Shigella* coinfection

Evidence indicates that much of HIV-*Shigella* coinfection in HICs is explained by sexual transmission. However, several studies suggest behavioural factors may not fully account for the observed pathogenic association. Baer et al. (1999) reported that heterosexual PLWHIV experienced an incidence ratio of 30.6 (95% CI 12.8–63.0) for shigellosis compared to HIV-negative individuals [46] (Fig. 2C), and Aragón et al. (2007) showed that HIV remained independently associated with shigellosis among MSM (OR = 8.59, $p < 0.001$) [20]. Residual confounding from unmeasured behaviours cannot be discounted. Furthermore, Baer et al. (1999) was an early study conducted only at the introduction of ART [18]. However, HIV may still drive shigellosis susceptibility through important biological mechanisms.

Viral load and HIV-infection load

HIV-related plasma viral load (pVL) has previously been investigated as a risk factor for shigellosis susceptibility. Several surveillance-based studies reported a majority of coinfecting individuals had well-controlled viral loads [15, 16, 41, 43]. Wu et al. (2019) found that MSM with HIV-*Shigella* coinfections had significantly higher viral loads than matched controls, with pVL $\geq 100,000$ copies/mL serving as an independent risk factor for shigellosis (aOR = 4.9, 95% CI 1.4–16.9) [47]. Other studies identified coinfecting MSM in whom either the median or majority had uncontrolled viral loads [17, 39]. A second case-control study in Taiwan also observed a higher median viral load among HIV-positive MSM ($n = 9$) with shigellosis than matched controls ($n = 45$), but this difference was not significant ($p = 0.37$) [48]. Comparing the Taiwanese case-control studies, both were of moderate quality. Wu et al. (2019) included a substantially larger sample size ($n = 300$ vs. $n = 54$). However, its reported adjusted odds ratio for viral load still spanned a wide confidence interval (1.4 to 16.9), indicating uncertainty surrounding the estimate. Considering these limitations, further work is needed to explore whether HIV viral load is associated with increased shigellosis susceptibility.

HIV-associated peripheral white blood cell counts

HIV infection may also increase shigellosis risk through immune dysfunction not captured by peripheral CD4 count. Frickmann et al. (2025) found that *Shigella spp.* detection among PLWHIV was associated with an estimated reduction of 96.3 CD4 cells/ μ L ($p = 0.002$) [37]. Detection was also associated with a

lower CD4/CD8 ratio ($p = 0.032$) and increased CD8 + T cell activation ($p = 0.042$). Notably, these results may just represent measurable immune dysregulation associated with *Shigella* infection among PLWHIV, as the study did not compare immune changes to HIV-negative individuals.

Cross-sectional studies of PLWHIV in India did not report significant associations between *Shigella* and peripheral white cell counts [51, 52]. Inferences from these studies are limited by their low appraisal rating, but they are consistent with HIC-based studies reporting no evidence for a relationship between peripheral CD4 count and increased shigellosis risk. Chiou et al. (2016) found that shigellosis cases ($n = 9$) among PLWHIV had a median CD4 count of 348 cells/mm³ (range 178–940) compared to *Shigella*-negative controls ($n = 45$), who had a median of 511 cells/mm³ (range 127–848); this difference did not reach statistical significance ($p = 0.62$) [48]. Surveillance-based studies in the UK, Spain, and Canada also identified a majority of coinfecting cases met the 200 cells/mm³ threshold [16, 39, 41, 43, 44]. However, small samples mean these findings should be interpreted cautiously, as HIV-related susceptibility to *Shigella* infection may be inconsistently marked by peripheral CD4 count.

HIV-associated disruption of the gut microbiota

Gut dysbiosis

Cross-sectional studies demonstrate gut dysbiosis among PLWHIV, offering a non-immune mediated mechanism for shigellosis susceptibility. PLWHIV exhibited significantly lower species diversity (alpha diversity) and differences in community composition (beta diversity) [53–55]. San-Juan-Vergara et al. (2018) found no alpha diversity differences between PLWHIV and controls, but still identified significant changes in microbial network structure [56]. Nkenfou et al. (2019) isolated more bacterial species ($n = 15$) in HIV-positive infants than HIV-negative infants ($n = 11$) [57]; however, this study was assessed as low quality, as gut bacteria were identified using growth media and biochemical testing, and half of all gut bacterial diversity cannot be cultured [58].

Persistence of dysbiosis in controlled HIV

HIV-associated dysbiosis may not resolve following virologic suppression and immune recovery. Previous work has reported no significant differences between dysbiosis measures in PLWHIV when stratified by immunocompetence [55, 59]. Specifically, Xie et al. (2021) found no significant differences in alpha and beta diversity between participants considered immunological responders ($CD4 \geq 500$ cells/ μ L) and non-responders (< 200 cells/ μ L), who were recruited following two years of ART [59]. Li et al. (2023) observed recovery in gut alpha diversity among PLWHIV following 12 weeks of ART; however, beta diversity still showed separation from healthy controls [55]. Hence, effective treatment and CD4 restoration may not correspond to complete microbiome recovery, or full re-equilibrium may take longer to occur.

Changes in Escherichia-Shigella during dysbiosis

HIV-associated dysbiosis was marked by a microbial environment that favoured *Shigella*-related species. Cross-sectional studies identified *Escherichia-Shigella* among the dominant genera in PLWHIV [53–55]. San-Juan-Vergara et al. (2018) did not find an overall increase in *Enterobacteriaceae* abundance, but network-based analyses specifically implicated *Escherichia-Shigella* in dysbiosis [56]. The genus became a central node in the microbial co-occurrence network, forming new strong associations with *Yersinia* and *Coprococcus*, which were absent in HIV-negative controls [56].

Changes in *Escherichia-Shigella* were also inconsistently associated with HIV-related immune dysfunction. Li et al. (2023) found that *Escherichia-Shigella* abundance was significantly higher among PLWHIV with CD4 counts below 200 cells/ μ L compared with those above 200 cells/ μ L ($p = 0.017$). This difference persisted relative to HIV-negative controls ($p = 0.025$) [55]. In contrast, Xie et al. (2021) observed significantly higher *Escherichia-Shigella* abundance among immunological responders than non-responders. However, *Escherichia-Shigella* abundance remained negatively correlated with CD4/CD8 ratios and positively correlated with CD8 + CD57+ T cell count [59]. Hence, *Escherichia-Shigella* enrichment may occur within the context of HIV-associated gut dysbiosis, but similar to previous findings, is not consistently associated with CD4 cell depletion.

Discussion

This review provides a comprehensive synthesis of epidemiological and biological evidence surrounding the relationship between HIV infection and shigellosis across HIC and LMIC settings. Twenty-eight studies were identified following a systematic and iterative search. Here, we synthesise these studies and an extended evidence base to develop a conceptual model for coinfection that captures a complex network of demographic, behavioural, and biological mechanisms. The coinfection model illustrates how epidemiological exposures and HIV-associated pathology (including gut dysbiosis and gut immune changes) may combine to increase susceptibility to shigellosis, rather than either mechanism acting alone (Fig. 3).

Epidemiological evidence from HICs converged strongly on a sexually driven pathway for HIV-*Shigella* coinfection among MSM. The importance of sexual transmission to rapidly spread pathogens is demonstrated by the frequent detection of other STIs. For example, Ridpath et al. (2022) reported that 20% of male shigellosis cases had been diagnosed with a bacterial STI (chlamydia, gonorrhoea, or all stages of syphilis) within 24 months, compared to only 4% of female cases [42]. As shigellosis occurs within MSM networks where STIs are prevalent, MSM sexual transmission alone may substantially increase HIV-*Shigella* coinfection risk. This interpretation is also consistent with HIC-based HIV epidemics concentrated among MSM [60]. This substantial burden is sustained primarily by the biological efficiency of HIV transmission during anal intercourse, highly connected MSM sexual networks with elevated background prevalence, high-risk behaviours during intercourse, and structural barriers to prevention and care [61]. *Shigella* spp. circulating through MSM networks will thus inherently include a substantial proportion of PLWHIV, increasing opportunities for coinfection.

Shigella transmission-facilitating behaviours reported specifically by HIV-positive MSM may further contribute to increased exposure. “Chemsex” refers to the intentional use of disinhibiting drugs before or during sex to increase sexual pleasure/arousal and is associated with condomless anal sex and multiple sexual partners [62, 63]. It is also linked with increased bacterial STI risk [64], and likely similarly facilitate *Shigella* transmission. Consistent with this idea, Wu et al. (2019) found that shigellosis cases among HIV-positive MSM were significantly associated with chemsex [47]. Limited engagement in outpatient care was also associated with shigellosis among HIV-positive MSM [48]. HIV medical care provides opportunities for the identification of coinfections and safe sex counselling to prevent STI transmission [65]. These opportunities are especially important considering the low public awareness of sexually transmitted enteric infections, such as *Shigella* [66]. Among the included studies, Gilbert et al. (2015) found that 88% of interviewed patients had never heard of shigellosis prior to their diagnosis [9]. When PLWHIV experience limited outpatient engagement, they may miss awareness opportunities and continue practices associated with increased *Shigella spp.* exposure without appropriate risk-reduction measures.

The very limited epidemiological evidence from LMICs suggested that HIV was enriched in patients experiencing severe shigellosis, but that HIV-positive individuals were not more likely to contract shigellosis. Frickmann et al. (2025) detected *Shigella spp.* in both HIV-positive and HIV-negative individuals, with no statistical difference [37]. However, further research powered to detect small differences between the groups would be needed to validate this result. Importantly, in these settings, inadequate water, sanitation, and hygiene (WASH) infrastructure sustains a high background risk of faecal-oral transmission. For example, *Shigella spp.* have been detected in up to 60% of wastewater effluent samples in South Africa at colony-forming unit (CFU) concentrations sufficient to establish infection [67]. Under such conditions, HIV epidemiology may exert comparatively little influence over shigellosis incidence, but this relationship between poor WASH and coinfection also remains insufficiently characterised. Frickmann et al. (2025) provided the closest available analysis by modelling *Shigella*/EIEC against a composite SES index, defined by tap water access, electricity, and refrigerator ownership [37]. This index primarily reflects general household socioeconomic position and does not directly measure WASH conditions most relevant to faecal-oral transmission. Further studies are needed to clarify the extent to which WASH shapes shigellosis risk among PLWHIV.

Conflict

ing with HICs once more, evidence from South Africa points towards a possible association between *Shigella* and HIV-positive adult women [38]. This difference is likely shaped by the disproportionate burden of HIV in South Africa, where approximately 64% of PLWHIV are women. High HIV prevalence and incidence can be attributed to violence, gender inequalities, low levels of education, and biological susceptibility during unprotected sex [68, 69]. Adult women aged 15–24 specifically account for the majority of these HIV infections in sub-Saharan Africa [70]. Coinfection may therefore reflect a high overall *Shigella* burden overlaid by local HIV demographics.

Although overlapping transmission epidemiology is clearly a major driver of HIV-*Shigella* infection, there was also evidence indicating that HIV-associated pathology may contribute. Existing evidence has linked high viral load to CD4 + T cell decline, rapid disease progression, and reduced survival [71–73]. As viral load marks impaired immunity, it is plausible for individuals with high pVL to be increasingly susceptible to *Shigella* infection, and this was supported by some studies [47]. However, surveillance across HICs also makes clear that coinfection can occur in individuals with well-controlled pVL [15, 16, 41, 43, 44], as well as normal peripheral CD4 counts [16, 39, 41, 43, 44]. CD4 lymphocytes play a central role in immune protection against a wide range of pathogens [74]. Their progressive depletion is a defining feature of HIV, eventually leading to immune failure and opportunistic infections [75, 76]. Lower counts among PLWHIV would be expected to mark increased *Shigella* susceptibility, though the reviewed evidence was inconsistent, and no studies involving measures of gut-specific immunity were available. Peripheral CD4 count and viral load may overestimate immune recovery relevant to shigellosis.

Importantly, conclusions regarding cell count are constrained by the employed definition of “immunosuppression.” WHO guidelines define advanced HIV by CD4 counts < 200 cells/mm³ [77], a threshold that serves as the clinical cut-off for severe disease and heightened mortality risk [78]. However, CD4 counts in healthy adults typically range from approximately 500 to 1500 cells/mm³ [79]. Adequate immune recovery following ART is therefore generally considered to be CD4 restoration above 500 cells/mm³, at which morbidity and mortality approach that observed in HIV-negative populations [80]. Individuals with CD4 counts above 200 cells/mm³, but below 500 cells/mm³, may therefore exhibit immunosuppression despite not meeting the definition for advanced HIV. Studies applying this conventional threshold may have overlooked residual immunosuppression among PLWHIV, potentially underestimating associations between low CD4 count and *Shigella* susceptibility.

Although the evidence was severely limited, broader markers of immune dysfunction better characterised *Shigella* susceptibility. Frickmann et al. (2025) found that *Shigella*/EIEC detection was associated with lower CD4/CD8 ratios and increased CD8 + T cell activation among HIV-positive participants [37]. Despite virological suppression and CD4 recovery, elevated CD8 counts may persist and prevent normalisation of the ratio. A persistently low ratio is recognised as a marker of immune senescence, immune activation, and chronic inflammation [81]. This marker may be especially relevant to the GI tract. During early infection, CD4 cells are rapidly depleted from the gut and restoration is less complete compared to that in the blood [23]. This loss is followed by structural impairment of the mucosal barrier, leading to increased microbial translocation [82]. Further alterations in intestinal homeostasis occur due to the rapid influx of CD8 cells [83]. Given that the GI tract is the primary site of *Shigella* infection, persistent immune dysfunction at this location may increase susceptibility among PLWHIV defined as immunocompetent according to traditional measures.

Another putative mechanism of gut-associated susceptibility to *Shigella* in PLWHIV is gut dysbiosis. Dysbiosis was characterised by reduced alpha diversity, beta diversity, and microbial network changes. Evidence suggested that this dysbiosis persisted following CD4 immune recovery or treatment [55, 59], indicating that this pathway does not coincide with peripheral CD4 count. The observed dysbiosis may

influence susceptibility to *Shigella* by creating an intestinal environment favouring closely related bacterial taxa, where *Escherichia-Shigella* consistently emerged as one of the dominant bacterial genera among PLWHIV [54, 55, 59]. Enrichment was not consistently associated with peripheral CD4 recovery [47, 55], again reinforcing that this cell marker inadequately captures gut pathology relevant to *Shigella* infection. Instead, PLWHIV experiencing well-controlled or treated infections may still harbour a dysbiotic gut environment favourable to *Shigella*-related bacteria.

Gut enrichment of *Escherichia-Shigella* does not establish that HIV-associated dysbiosis directly leads to shigellosis. None of the included microbial genomic studies demonstrated prospectively that participants experiencing microbiome alterations subsequently acquired clinical *Shigella* infection. However, they introduce a plausible pathway through which dysbiosis may favour *Shigella* spp. expansion and increase susceptibility among PLWHIV. Precedent for such a pathway exists. In healthy individuals, the gut microbiota confers resistance against pathogens through secretion of antimicrobial products, nutrient competition, maintenance of epithelial barrier integrity, and immune stimulation [84, 85], and these mechanisms hold true for *Shigella*. Epidemiologically successful *S. sonnei* lineages perform interbacterial competition through colicin-mediated mechanisms, supporting the importance of competition between *Shigella* and intestinal bacteria in determining establishment within the gut [86]. Alterations in microbiota composition may disrupt these processes, provide colonisation opportunities for bacteria, and facilitate subsequent infection [87]. For example, antibiotic-induced gut dysbiosis is well-established as a contributor to the colonisation and disease initiation of the enteric pathogen, *Clostridioides difficile* [85]. Although the pathogenic mechanisms of *Shigella* spp. and *C. difficile* differ, persistent HIV-associated dysbiosis could similarly create an environment more permissive to *Shigella*. Consequently, it may represent an important biological pathway contributing to increased *Shigella* susceptibility and subsequent HIV-*Shigella* coinfection.

This review has several strengths, including a search strategy, study selection, and critical appraisal guided by PRISMA. These robust methodological processes for identifying and analysing literature reduced the risk of bias by following pre-specified criteria. Furthermore, the provided search strings and written inclusion/exclusion criteria increase reproducibility [88]. We also included an iterative search strategy, strengthening coverage by identifying studies missed during the initial systematic search, but relevant to the question [89].

However, limitations should be considered when interpreting review findings. The use of a single reviewer introduced a risk of bias during the initial study selection and critical appraisal. Attempts were made to mitigate this limitation, and a second reviewer independently confirmed full-text assessments (n = 60). The key limitation of the evidence base was its reliance on case-control or analytical cross-sectional designs, both of which were unable to establish temporality surrounding identified risk factors, HIV infection, and shigellosis. This limitation was partly mitigated by studies confirming HIV-positivity preceded shigellosis infection through database linkage. However, temporal relationships between the proposed biological mechanisms underlying increased susceptibility to shigellosis are less clear. *Shigella* infection itself has been shown to alter peripheral CD4 cell counts [90]. Peripheral cell count

measurements may not accurately reflect individual HIV-related immune status prior to shigellosis. Additionally, disruptions to the gut can contribute to systemic immune activation, including CD8 cell activation [82]. The proposed biological pathway should therefore be interpreted as a hypothesis in need of confirmation (Fig. 3). The mechanism may even be expanded or better conceptualised as a bidirectional process, whereby feedback between the gut microbiome and immune activation creates a self-perpetuating susceptibility cycle within a complex landscape of overlapping epidemiology across demographics.

Gaps remain in understanding HIV-*Shigella* coinfection. Longitudinal studies of PLWHIV are required to establish temporality by measuring various exposures before shigellosis onset. Repeated assessment of CD8 activation, CD4/CD8 ratios, and the gut microbiota are required to help determine the progression of immune dysregulation and dysbiosis preceding shigellosis. Such monitoring would evaluate the proposed model.

Interestingly, several small but recent studies observed greater shigellosis incidence among HIV-negative MSM using PrEP relative to HIV-negative and HIV-positive MSM [49, 50]. Braam et al. (2022) theorised that this result may have been due to the number of sexual partners; however, there was virtually no difference between HIV-negative PrEP users and HIV-positive MSM. [49]. One consideration is that PrEP users may engage in high-risk behaviours while on prophylactic medication [91]. This is consistent with observational studies that have found MSM are more likely to engage in condomless anal sex and report a higher incidence of bacterial STIs following PrEP initiation [91–94]. *Shigella* infection among HIV-negative MSM may similarly be linked to behaviours surrounding PrEP-mediated risk. Future studies investigating shigellosis outbreaks should report both PrEP use and perceptions of the medication to address this gap.

The current evidence base is also heavily concentrated on investigating coinfection epidemiology in HICs (n = 18). LMIC populations remain substantially underrepresented, despite these settings contributing to the highest global burden of both HIV and *Shigella* infections [1, 95]. Future studies conducted in these settings should aim to fully contextualise coinfection burden with coupled data on these pathogens. Patterns identified within HICs could be present within these settings, where MSM also exhibit a high prevalence of HIV infection [96], but they could be masked by the high burden of endemic, non-sexually transmitted disease. Furthermore, the evidence base predominantly focused on adult populations, once again ignoring an important population experiencing substantial shigellosis burden: children under five years old [2]. Future studies should include children to understand coinfection among this population.

Conclusion

This review evaluated epidemiological and biological factors contributing to increased HIV-*Shigella* coinfection across HIC and LMIC settings. Pre-existing evidence has largely simplified *Shigella* incidence among PLWHIV as a consequence of MSM-related sexual transmission. However, the literature base

suggests that HIV-*Shigella* coinfection should not be attributed to a single mechanism. It reflects a complex model of behavioural exposures, background HIV prevalence, and HIV-related biological susceptibility. This model has important implications for clinical practice and public health. Clinicians should consider testing for *Shigella* infection among men presenting with gastrointestinal symptoms, particularly MSM, as well as testing for HIV when shigellosis is suspected [97]. Prevention efforts should address behaviours associated with *Shigella*'s sexual transmission, as well as HIV-related susceptibility. Sexual health clinicians must also raise awareness among these patients about the transmission of enteric pathogens [9]. Risk-reduction strategies include improved hygiene during sexual activities, such as condom use and/or washing hands and genitalia after sex [97]. Additionally, interventions aimed at gut restoration warrant consideration for PLWHIV at risk for shigellosis. Integrating behavioural and biological prevention efforts may ultimately provide a comprehensive approach to reducing the burden of HIV-*Shigella* coinfection.

Abbreviations

AMR
Antimicrobial resistance
aOR
Adjusted odds ratio
ART
Antiretroviral therapy
CASP
Critical Appraisal Skills Programme
CD4
Cluster of differentiation 4
CD8
Cluster of differentiation 8
CI
Confidence interval
EIEC
<i>Enteroinvasive Escherichia coli</i>
GBL
γ -butyrolactone
GHB
γ -hydroxybutyrate
GI
Gastrointestinal
HIC
High-income country
HIV

Human immunodeficiency virus
JBI
Joanna Briggs Institute
LMIC
Low- and middle-income country
MSM
Men who have sex with men
OR
Odds ratio
PLWHIV
People living with HIV
PrEP
Pre-exposure prophylaxis
PRISMA
Preferred Reporting Items for Systematic Reviews
pVL
Plasma viral load
SES
Socioeconomic status
STI
Sexually transmitted infection
UK
United Kingdom
USA
United States of America
WHO
World Health Organisation

Declarations

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Author Contribution

ER developed the methodology and conducted literature searches, text screening, critical appraisal, data extraction, and the main manuscript text. KSB and DJP guided methodology development and supervised the study. KSB also conceptualised the study, contributed to evidence synthesis and interpretation of the findings, as well as provided critical revision. AU assessed full-text eligibility of all studies from the systematic search, and JT provided critical revision. All authors reviewed the manuscript.

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Not applicable

Data Availability

The data used to generate Figure 2 were obtained from the published sources cited in the figure legend and are publicly available in those publications.

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Figures

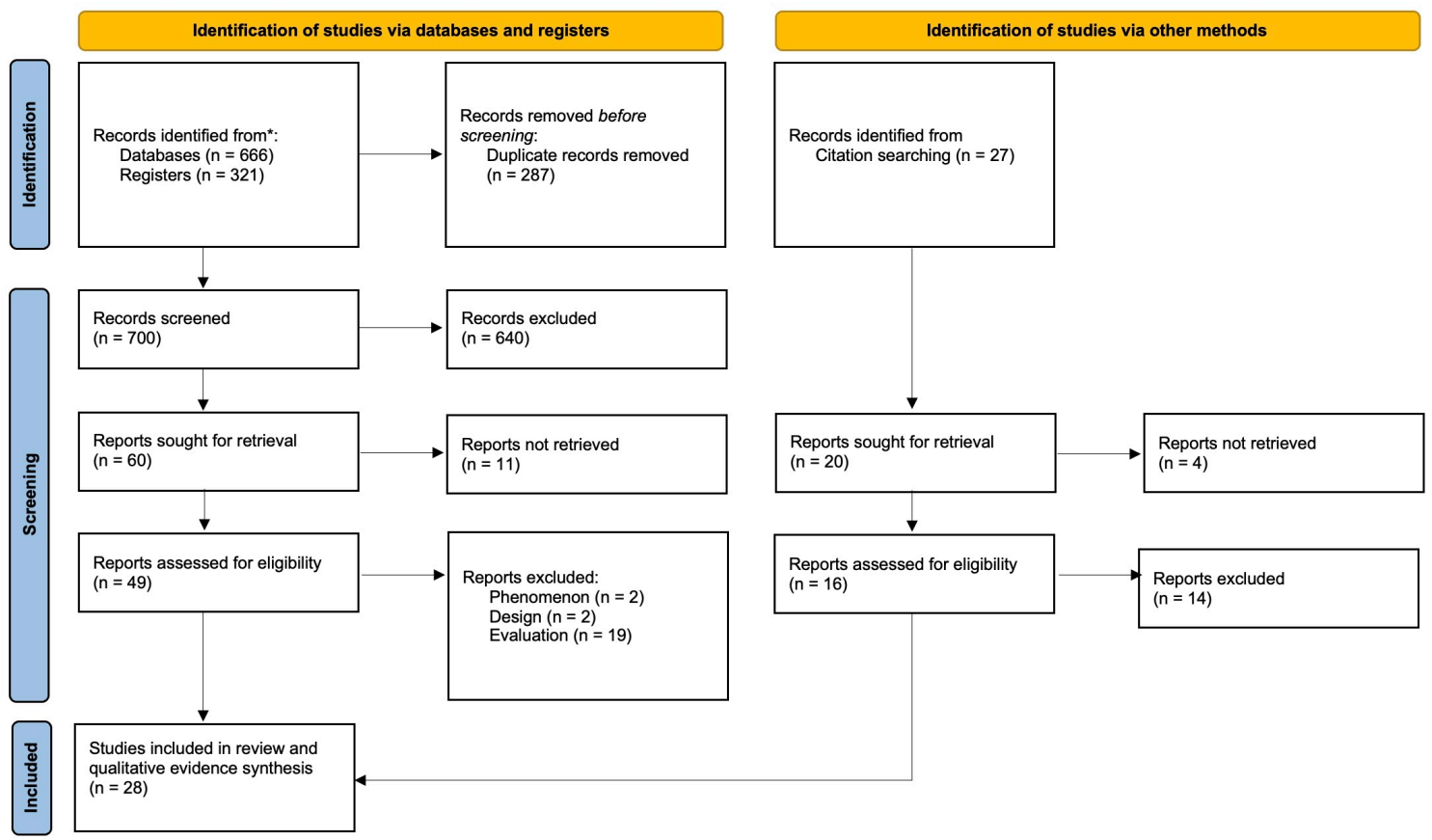
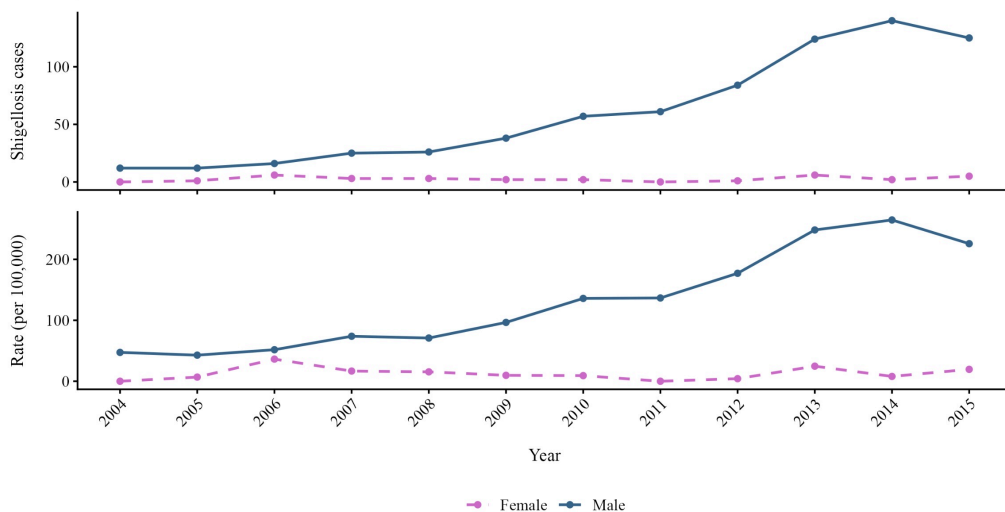


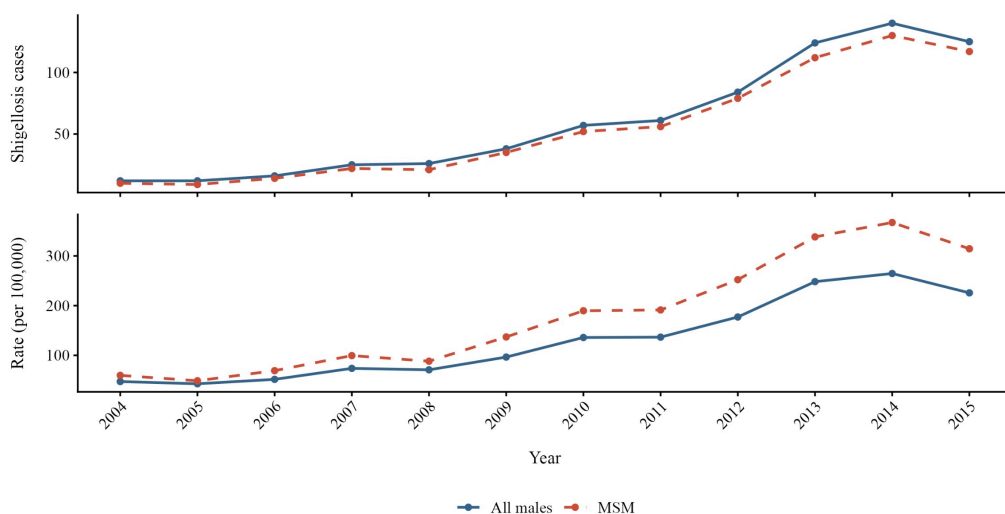
Figure 1

PRISMA flowchart. Of 987 records systematically identified from PubMed and Embase, 26 studies met inclusion criteria for the qualitative synthesis. An additional 2 records were identified from these studies through backward citation searching. Chart adapted from Page et al. (2020) [26].

A. Shigellosis in PLWHIV by gender, UK



B. Shigellosis in men living with HIV by sexual orientation, UK



C. Shigellosis in men by HIV status and sexual orientation, USA

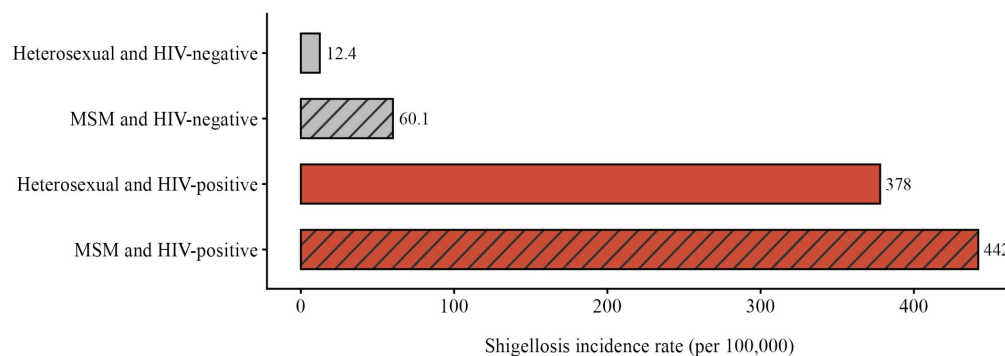


Figure 2

The intersection of HIV, gender, and sexual orientation with shigellosis in HICs. 2A: Domestically acquired shigellosis cases and incidence rates (per 100,000 HIV-positive individuals) among PLWHIV in England (2004–2015), stratified by sex. Data taken from Mohan et al. (2018) [15]. 2B: Domestically acquired shigellosis cases and incidence rates (per 100,000 HIV-positive individuals) among all males and MSM specifically in England (2004–2015). Data taken from Mohan et al. (2018) [15]. 2C: Shigellosis

incidence rates among men in San Francisco (1996), stratified by sexual orientation and HIV status. Data taken from Baer et al. (1999) [46].

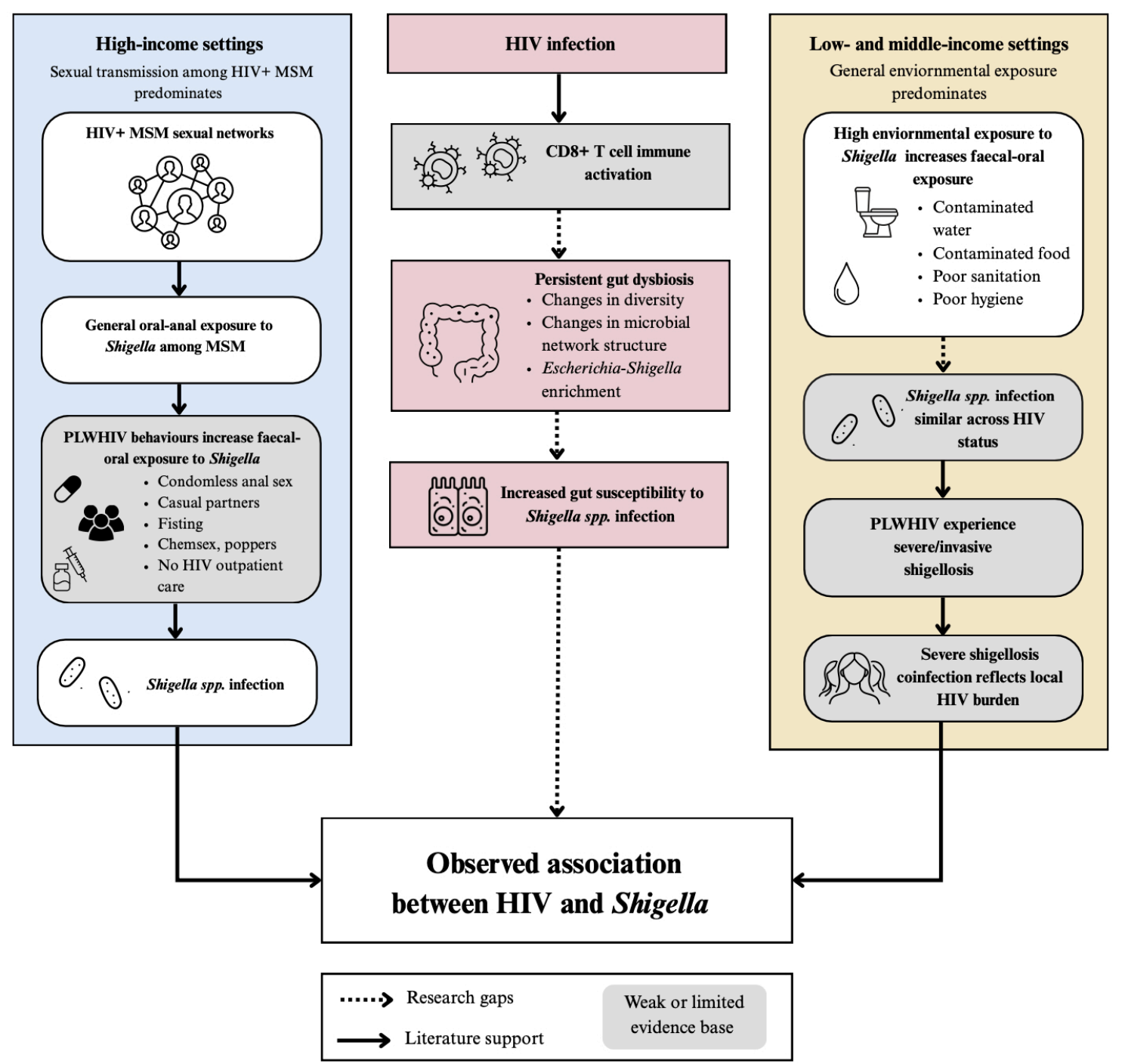


Figure 3

Proposed coinfection model of epidemiological and biological associations linking HIV and *Shigella* infection. In HICs, sexual transmission among HIV-positive MSM and associated behaviours may lead to a high incidence of HIV-*Shigella*coinfection. In LMICs, high background exposure to *Shigella*predominates, with HIV more frequently observed in cases of invasive shigellosis rather than being associated with infection incidence. Centrally, HIV-associated immune activation and subsequent

gut dysbiosis may also provide a favourable environment for *Shigella*. Notably, much of the evidence in this conceptual model requires strengthening and more detailed investigation.

Supplementary Files

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