Estimated prevalence and associations of sexually transmissible bacterial enteric pathogens in asymptomatic men who have sex with men: a systematic review and meta-analysis

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ABSTRACT

Objective The reservoir of sexually transmissible bacterial enteric pathogens in asymptomatic men who have sex with men (MSM) may impact future outbreaks, and the evolution of antimicrobial resistance. We aimed to estimate the pooled prevalence and explore any factors associated with *Shigella* spp, *Campylobacter* spp, diarrhoeagenic *Escherichia coli* and *Salmonella* spp in asymptomatic MSM using the random effects model.

Methods We searched Embase, MEDLINE, CINAHL and Web of Science Core Collections for manuscripts published up to February 2024. One author screened citations and abstracts; two authors independently conducted a full-text review. We included manuscripts which measured the prevalence of *Shigella* spp, *Campylobacter* spp, diarrhoeagenic *E. coli* and *Salmonella* spp in asymptomatic MSM. Quality and risk of bias was assessed independently by two authors using the Joanna Briggs Institute critical appraisal tools. We calculated pooled prevalence and CIs using the random effects model.

Results Six manuscripts were included in the final review. The manuscripts were from Australia (n=2), the UK (n=2), the Netherlands (n=1) and the USA (n=1) and included data from 3766 asymptomatic MSM tested for bacterial enteric pathogens. The prevalence of *Shigella* spp was 1.1% (95% CI 0.7% to 1.7%), *Campylobacter* spp 1.9% (95% CI 1.5% to 2.5%), diarrhoeagenic *E. coli* 3.8% (95% CI 2.1% to 6.7%) and *Salmonella* spp 0.3% (95% CI 0.1% to 0.6%). Two manuscripts demonstrated that the detection of bacterial enteric pathogen was more frequent in asymptomatic MSM using HIV-pre-exposure prophylaxis (PrEP), living with HIV, reporting <5 new sexual partners in the past 3 months, reporting insertive oral-anal sex and group sex compared with MSM testing negative.

Conclusion Despite a small number of manuscripts, this review has estimated the pooled prevalence, and highlighted some possible associations with sexually transmissible bacterial enteric pathogens in asymptomatic MSM, which can inform future clinical guidelines, public health control strategies and research to increase our understanding of transmission and the evolution of antimicrobial resistance.

PROSPERO registration number CRD42024518700.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Bacterial enteric pathogens (eg, *Shigella* spp, *Campylobacter* spp, *Escherichia coli, Salmonella* spp) are sexually transmissible in men who have sex with men.

WHAT THIS STUDY ADDS

⇒ We have estimated the pooled prevalence of *Shigella* spp, *Campylobacter* spp, *E. coli*, *Salmonella* spp in asymptomatic men who have sex with men.

⇒ In two studies, we highlighted that bacterial enteric pathogen detection was more frequent in MSM using HIV-pre-exposure prophylaxis, living with HIV, having <5 new sexual partners in the past 3 months, reporting insertive oral-anal sex (past month) and group sex (past 12 months) compared with MSM testing negative for bacterial enteric pathogens.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Understanding the asymptomatic reservoir of sexually transmissible enteric pathogens in asymptomatic MSM may provide insight into outbreaks, the evolution of antimicrobial resistance and inform future clinical guidelines.

BACKGROUND

Notifications of bacterial sexually transmitted infections (STIs) in men who have sex with men are at an all-time high, however, there are few mechanisms for surveillance of bacterial sexually transmitted enteric infections.[1] Bacterial enteric infections can cause significant morbidity and mortality globally and are sexually transmissible in sexual networks of men who have sex with men (MSM).[2] *Shigella* spp, *Campylobacter* spp, diarrhoeagenic *Escherichia coli* and Salmonella spp are transmitted via the faeco-oral route and some sexual behaviours among MSM can lead to faecal contamination and sexual transmission.[2] Since the 1970s, there have been outbreaks of *Shigella* spp. in MSM reported from high-income settings including the transmission of extensively resistant *Shigella*.[3 4] The sexual transmission dynamics of bacterial sexually transmissible enteric infections are poorly understood but the

FIGURE 1: Prisma flowchart of manuscript reviewing process

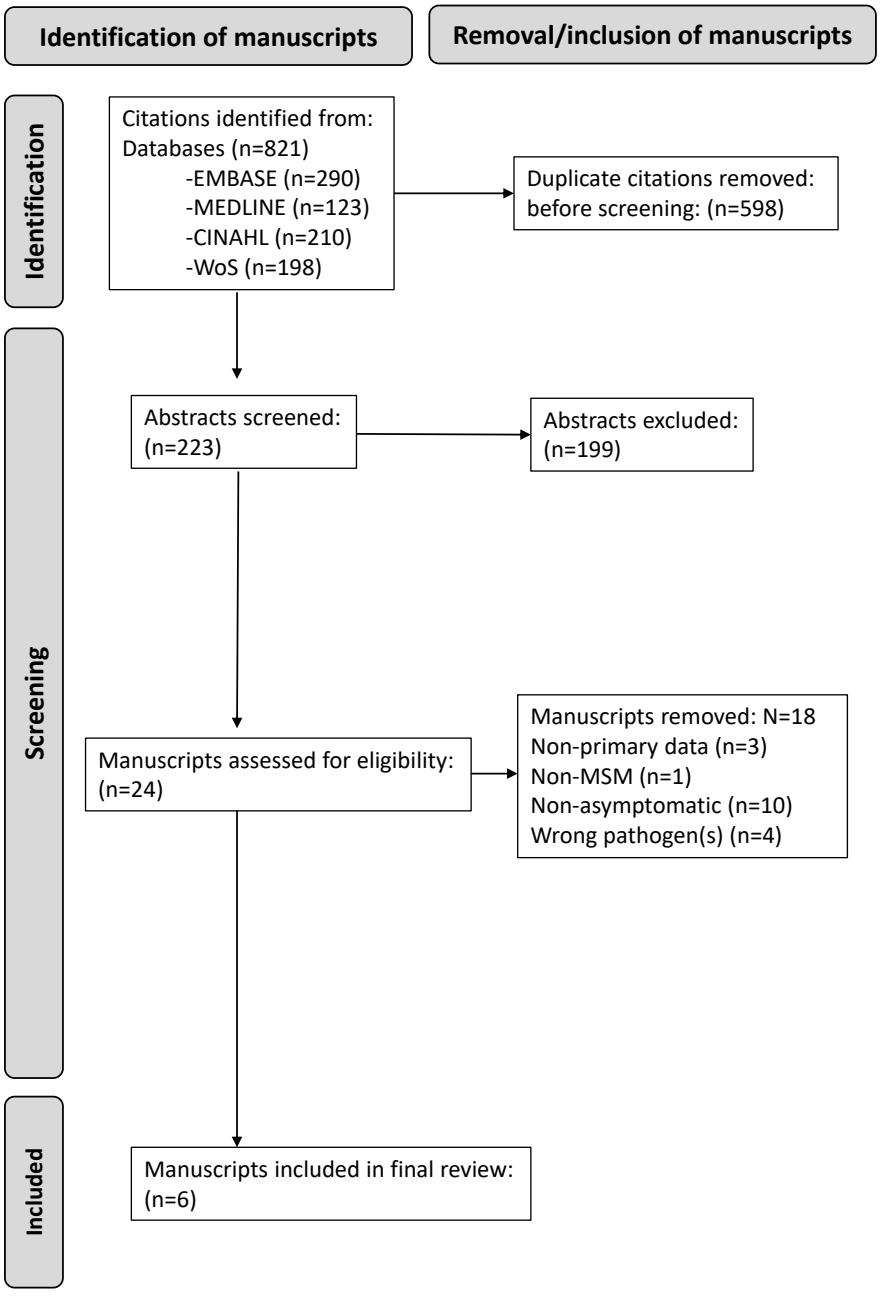

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram. WoS, Web of Science.

asymptomatic carriage in MSM is likely to drive outbreaks.[5 6] The introduction of highly sensitive molecular testing for enteric infections has improved the diagnostic yields and ability to screen asymptomatic patients.[7] A study of bacterial enteric pathogens in an asymptomatic general adult population of 1195 individuals in the Netherlands estimated the prevalence of *Shigella* spp (0%), *Salmonella* spp (0.3%), *Campylobacter* spp (2.8%) and diarrhoeagenic *E. coli* (6.3%).[8] Understanding the reservoir of asymptomatic bacterial enteric pathogens may provide some insight into the transmission dynamics including transmission of antimicrobial resistance. We aimed to review the published literature of prevalence studies of sexually transmissible bacterial enteric infections in asymptomatic MSM to estimate a pooled prevalence and any factors associated with pathogen detection.

METHODS

Search strategy

A systematic review of the literature was conducted in September 2023 using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to estimate the prevalence and explore factors associated with sexually transmissible enteric infections in asymptomatic MSM. We searched Embase, MEDLINE, CINAHL and Web of Science Core Collections for manuscripts published up to March 2024 to identify manuscripts

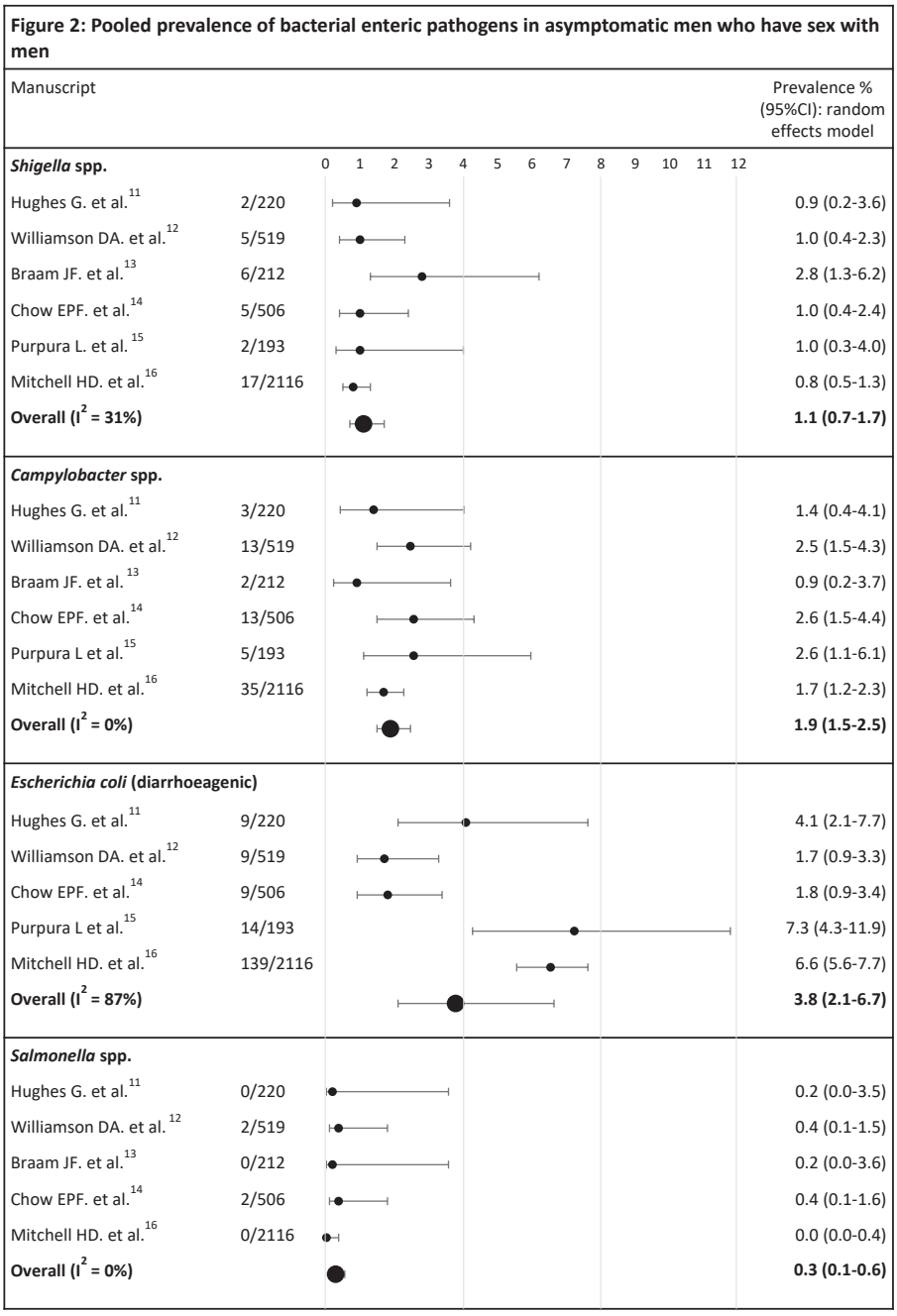

Figure 2 Pooled prevalence of bacterial enteric pathogens in asymptomatic MSM

using the following search terms: (Escherichia coli OR E. coli) AND (Campylobacter OR Campylobacteriosis) AND (Shigella OR Shigellosis) AND (Salmonella OR Salmonellosis OR Typhoid) AND (Proctitis OR Colitis OR Gastrointestinal OR proctocolitis OR (GI infection) AND (men who have sex with men OR queer OR homosexual OR gay) AND (asymptomatic). Manuscripts meeting the following criteria were included in our review: written in English, exploring the prevalence of enteric infections in asymptomatic MSM using PCR (or other molecular test) and the publication date was not restricted. The primary author conducted an initial screen of abstracts and full-text eligibility. Where manuscripts included a mix of symptomatic and asymptomatic MSM, we only extracted and analysed data from asymptomatic MSM. A staged process was used for screening and selection of manuscripts for the final review. Each record from the initial search of citations was reviewed and duplicate citations were removed. Manuscript abstracts were screened by the primary researcher (DR) and then full-text manuscripts were then assessed for eligibility independently by the primary researcher (DR) and an associate researcher (AS-T or CF). Any discrepancies were discussed (DR, AS-T and CF) for a final decision regarding eligibility.

Risk of bias and data synthesis

The quality and risk of bias of each manuscript was assessed independently by two authors using the Joanna Briggs Institute critical appraisal tools.[9] We calculated the random effects

Table 1 Manuscripts and factors associated with enteric pathogen detection in asymptomatic men who have sex with men (MSM)

Study	Population	Factors associated with positive enteric pathogen PCR test
Hughes *et al*,[11] UK	220 asymptomatic MSM attending 12 sexual health clinics in the UK	NA
Williamson *et al*,[12] Australia	519 asymptomatic MSM attending a Melbourne sexual health clinic	Insertive oral-anal sex (past month) (aOR 3.32; 95% CI 1.38 to 7.97) Group sex (past 12 months) (aOR 2.00; 95% CI 1.11 to 3.60)
Braam *et al*,[13] The Netherlands	212 asymptomatic MSM attending an Amsterdam sexual health clinic	NA
Chow *et al*,[14] Australia	506 asymptomatic MSM attending a Melbourne sexual health clinic	NA
Purpura *et al*,[15] USA	193 asymptomatic MSM attending a New York sexual health clinic	NA
Mitchell *et al*,[16] UK	2116 asymptomatic MSM attending a London sexual health clinic	Having 5–9 (aPR 2.02, 95% CI 1.29 to 3.16, p<0.001) or >10 (aPR 2.40, 95% CI 1.51 to 3.80, p<0.001) new sexual partners in past 3 months Having a bacterial STI in past 12 months (p=0.01) HIV-negative MSM using HIV-PrEP (aPR 2.06, 95% CI 1.48 to 2.86, p<0.001) MSM living with HIV (aPR 1.85, 95% CI 1.25 to 2.75, p<0.01)

aOR, adjusted OR; aPR, adjusted prevalence ratio; MSM, men who have sex with men; NA, not available; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

prevalence with 95% CIs and calculated heterogeneity between studies and the I^2 statistic to assess heterogenicity using the Comprehensive Meta-analysis Software (CMA) online meta-analyses tool. We collected any associations with having asymptomatic bacterial enteric infections in MSM using a narrative synthesis using the Synthesis without meta-analysis (SWiM) guidance and toolkit.[10] This review was registered on PROSPERO (CRD42024518700).

RESULTS

We included six prevalence study manuscripts in the final review from Australia (n=2), the UK (n=2), the Netherlands (n=1) and the USA (n=1), which included 3766 individual MSM published between 2018 and 2023[11–16] (figure 1). We assessed the risk of bias as being medium in four manuscripts and low in two manuscripts (online supplemental table 1). All six manuscripts estimated the prevalence of *Shigella* spp and *Campylobacter* spp, however only five manuscripts estimated the prevalence of diarrhoeagenic *E. coli* and *Salmonella* spp. The estimated pooled prevalence (using the random effects model) of *Shigella* spp was 1.1% (95% CI 0.7% to 1.7%), *Campylobacter* spp 1.9% (95% CI 1.5% to 2.5%), diarrhoeagenic *E. coli* 3.8% (95% CI 2.1% to 6.7%) and *Salmonella* spp 0.3% (95% CI 0.1% to 0.6%) (figure 2). Two manuscripts explored risk factors for asymptomatic bacterial pathogens in MSM. The study from Melbourne, Australia of 519 asymptomatic MSM estimated that enteric pathogen detection was independently associated with men who reported insertive oral-anal sex in past month (adjusted OR (aOR) 3.32; 95% CI 1.38 to 7.97) and with men who reported group sex in past 12 months (aOR 2.00; 95% CI 1.11 to 3.60) compared with asymptomatic MSM testing negative for bacterial enteric pathogens.[12] The manuscript from 56-Dean Street clinic, London of 2116 MSM estimated that enteric pathogen detection was associated with having 5–9 (adjusted prevalence ratio (aPR) 2.02, 95% CI 1.29 to 3.16, p<0.001) or >10 (aPR 2.40, 95% CI 1.51 to 3.80, p<0.001) new sexual partners in the past 3 months; a bacterial STI in past 12 months (p=0.01); being an HIV-negative MSM using HIV-pre-exposure prophylaxis (PrEP) (aPR 2.06, 95% CI 1.48 to 2.86, p<0.001) or an MSM living with HIV (aPR 1.85, 95% CI 1.25 to 2.75, p<0.01) compared with asymptomatic MSM testing negative for bacterial enteric pathogens[16] (table 1).

DISCUSSION

We believe that this is the first systematic review and meta-analysis to estimate the pooled prevalence of bacterial sexually transmissible enteric infections in asymptomatic MSM attending sexual health clinics. We have highlighted that *Shigella* spp, *Campylobacter* spp, diarrhoeagenic *E. coli* and *Salmonella* spp in asymptomatic MSM attending sexual health clinics are associated with oral-anal sexual behaviour, group sexual behaviour, in MSM using HIV-PrEP and MSM living with HIV and having 5–9 or >10 new sexual partners in the past 3 months.[12 16] There appears to be significant variation in the prevalence of *Shigella* spp, *Campylobacter* spp, diarrhoeagenic *E. coli* and *Salmonella* spp in asymptomatic MSM, which maybe in part due to the varying transmission dynamics and infective dose required for each pathogen.[11–16] For *Shigella* spp, the inoculum dose for transmission has been estimated be as low as 10 organisms and for *Campylobacter* spp, 300–10 000 organisms.[17–19] In contrast, the infectious dose for *Salmonella* spp may be as high as 1 million organisms and diarrhoeagenic *E. coli* varies significantly depending on the subtype between 2 and 1000 organisms.[20 21] Pathogens with a low inoculum dose are likely to be more transmissible from person to person through sexual contact in particular when the risk of faecal contamination increase such as with oral-anal sex, fisting and the use of sex toys.[22] There are limited data estimating the bacterial enteric pathogen prevalence in the general asymptomatic adult general population. Our meta-data crudely suggest that rates of *Shigella* spp (1.1% vs 0.0%) are higher than in a general adult population study, but rates of *Campylobacter* spp (1.9% vs 2.8%), diarrhoeagenic *E. coli* (3.8% vs 6.3%) and *Salmonella* spp (0.3% vs 1.3%) are similar or lower.[8 11–16] These data support what is currently observed in epidemiological reports in symptomatic MSM. *Shigella flexneri* and *sonnei*, requiring a very low inoculum dose, are endemic in some populations of MSM with prolonged outbreaks reported from the UK, Europe and Australasia.[23–25] However, outbreaks of symptomatic *Campylobacter* spp, diarrhoeagenic *E. coli* or *Salmonella* spp in MSM, which require a higher inoculum dose, are less frequently reported.[26–28]

Extensively antimicrobial-resistant *Shigella* spp in MSM is an emerging public health issue.[3] Recent British Association for Sexual Health and HIV guidelines do not recommend using empirical or susceptibility-driven antimicrobials unless there are signs of severe illness including sepsis.[7] Although the use

of molecular technology has improved the diagnosis of enteric infections, this is limited by the lack of antimicrobial resistance data from currently available molecular tests which limits possibilities for antimicrobial resistance surveillance and control. It is likely that asymptomatic carriage of enteric pathogens increases the evolution of antimicrobial-resistant strains due to the use of antimicrobials for other reasons including treatment of STIs.[29] The transmission of antimicrobial resistance genes in enteric infections and the impact of the microbiome is poorly understood.[30] Several factors have increased the consumption of antimicrobials in MSM including asymptomatic STI screening in MSM using HIV-PrEP and the use of doxycycline postexposure prophylaxis to prevent STIs.[31 32] It is important that we continue to ask MSM with diarrhoea to provide adequate stool samples to enable traditional culture and antimicrobial resistance data for the surveillance of antimicrobial-resistant enteric infections.[7] Sexual networks of MSM where sexual behaviours risking faecal contamination, such as oral-anal sex, combined with increasing number of sexual partners and availability of HIV-PrEP are optimal for the transmission of enteric pathogens such as *Shigella*.[22] What is not well understood is the role of asymptomatic individuals within these networks on the transmission of enteric pathogens.[12 16]

This analysis has several important limitations which will affect the overall interpretation and generalisability of these data. There are a small number of studies providing data for the meta-analysis and the narrative systematic review and an overall small number of enteric pathogens identified. All of the manuscripts were from clinic populations of MSM in high-income settings who were attending sexual health clinics which may not be representative of other groups of MSM at risk of enteric infections. For the pooled prevalence estimates, the heterogenicity was highly variable due to the small and varied number of bacterial enteric infections identified in each study demonstrated by the I^2 ranging from 0% to 87%. The false positive rate of PCR platforms for bacterial enteric pathogens is unknown but believed to be extremely low.[33] MSM in these studies may not have all been able to disclose their sexual behaviours due to the stigma and inequalities experienced by MSM. Some of the enteric pathogens may have been acquired from different routes including food or water contamination and from travel-associated transmission.

Enteric pathogens remain neglected conditions globally, and their transmission is being affected by climate change where the most vulnerable people are affected.[34] More work is needed to understand the transmission dynamics and evolution of antimicrobial resistance in sexually transmissible enteric infections in MSM to develop effective control intervention strategies. In part, understanding the asymptomatic carriage and reservoirs of sexually transmissible enteric pathogens may provide a basis for designing research programmes and intervention strategies. We have estimated the pooled prevalence of *Shigella* spp, *Campylobacter* spp, diarrhoeagenic *E. coli* and Salmonella spp in asymptomatic MSM attending sexual health clinics and highlight some important associations. These data provide some insight into the ongoing transmission and outbreaks of enteric pathogens in MSM.

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Contributors DR developed the study concept, designed the study protocol, DR conducted the data search and initial citation and abstract reviews, DR, AS-T and CF independently reviewed the manuscripts eligibility, DR and CF conducted the risk of bias assessment, DR conducted the data analysis and synthesis, DR produced the first draft and DR, AS-T, CF and DW all contributed to the final manuscript. DR is the study guarantor.

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Supplementary table 1: Risk of bias assessment

Manuscript	Risk of Bias	Comments
Hughes G. et al. 2018, UK	Medium	Residual samples from *Chlamydia trachomatis* study. Bias group: MSM attending sexual health clinic who enrolled in a rectal *Chlamydia* study in central London. Small number of positive bacterial enteric pathogens by PCR
Williamson DA. et al. 2019, Australia	Low	Large study, asymptomatic MSM attending Melbourne sexual health clinic providing a rectal sample for bacterial enteric pathogen PCR analysis. This study also provided clinical data where an adjusted multivariate analysis model was used to explore associations with a positive PCR.
Braam JF. et al. 2021, The Netherlands	Medium	Medium sized study of asymptomatic MSM attending Amsterdam sexual health clinic testing for bacterial enteric pathogen by PCR
Chow EPF. et al. 2021, Australia	Low	Large study, asymptomatic MSM attending Melbourne sexual health centre providing a rectal sample for bacterial enteric pathogen PCR.
Purpura L et al. 2022, USA	Medium	Medium sized study of MSM using HIV-PrEP attending HIV-PrEP clinic in New York enrolled to provide a rectal sample for bacterial enteric pathogen PCR.
Mitchell HD et al. 2023, UK	Medium	Very large study of MSM attending a large sexual health clinic in central London provided a rectal sample for bacterial enteric pathogen PCT, small number of positives, very small proportion of MSM were symptomatic. This study also collected clinical data where an adjusted multivariate analysis model was used to explore associations with having a positive PCR.