

Recent epidemiology of sexually transmissible enteric infections in men who have sex with men

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ABSTRACT (195 words)

Purpose of review

Sexual transmission of enteric pathogens in men who have sex with men (MSM) has been described since the 1970s. Recently, an increasing number of enteric infection outbreaks have been reported in MSM. This article summarises recent outbreaks and discusses the key issues for prevention and control.

Recent findings

Sexually transmissible enteric infections (STEIs) can spread rapidly and internationally within highly connected MSM populations and are often associated with antimicrobial resistance (AMR). The infections often cluster in high-risk groups of HIV-positive MSM who are more likely to engage in diverse sexual practices and chemsex, and to have multiple other sexually transmitted infections (STIs).

Summary

The roles of asymptomatic and/or persistent infection and other contextual factors in STEI transmission are not well described. STEI-associated AMR is increasing and has potential to spread rapidly in MSM warranting further public health attention. A better understanding of the factors associated with sexual transmission will enable the development of more effective control measures. A holistic approach that promotes health and wellbeing as well as infection prevention and management is needed.

Key words

enteric infections; men who have sex with men; infectious disease outbreaks; sexually transmitted infections; antimicrobial resistance

INTRODUCTION

Enteric pathogens can cause serious ill-health and cause gastroenteritis that is characterised by the sudden onset of diarrhoea and/or dysentery, and also abdominal pain, fever and/or vomiting. In severe cases, significant morbidity and mortality may be associated with bloody diarrhoea, severe dehydration, bacteraemia, haemolytic uraemic syndrome and Guillain-Barre Syndrome [1-3]. Transmission occurs via the faecal-oral route and is usually caused by the consumption of contaminated food or water, which is often associated with travel to low income countries with poor food and water hygiene. Sexual transmission is well described and can occur through direct oro-anal practices, indirectly through oral sex after sex or via fingers or fomites.

The importance of sexual transmission in the spread of enteric pathogens was widely recognised in the 1970's. 'Gay bowel syndrome', now an outdated term, was used to refer to a range of anorectal and colon conditions, including traditional sexually transmitted infections (STIs), enteric infections and anorectal disorders found at an unusually high frequency in populations of men who have sex with men (MSM) [4]. At the time, there were reports of enteric infections including *Shigella spp.*, *Salmonella spp.*, *Entamoeba histolytica*, *Giardia lamblia* and Hepatitis A virus among MSM communities, particularly in large urban areas of the USA [4-10].

The environment and context in which the first sexually transmissible enteric infection (STEI) outbreaks were described has changed substantially. In the 1970's, there were major social changes taking place leading to greater sexual freedom and acceptance [5, 11]. However, the onset of HIV/AIDS shortly after this and the subsequent modifications in sexual behaviour led to a reduction in the incidence of HIV transmission and other STIs, including enteric infections [11-13]. These modifications in sexual behaviour were likely sustained until the mid-1990s, after which reported high-risk sexual behaviours, STIs and shigellosis re-emerged among MSM in western industrialised countries, coinciding with the introduction of Highly Active Antiretroviral Therapy (HAART) [13-19].

In recent years, the growing number of STEI outbreaks worldwide among MSM has been a public health concern, particularly due to the emergence of resistance to front-line antimicrobials [20-22]. In this article, we review the distribution and characteristics of recent STEI outbreaks and discuss the key issues for prevention and control.

FACTORS ASSOCIATED WITH SEXUAL TRANSMISSION IN MSM

Sexual transmission of STEIs is caused by direct or indirect oral-anal contact. The specific behavioural characteristics associated with outbreaks in MSM are broadly similar; men frequently report multiple sexual partners [13, 21, 23, 24], attending on-site sex venues [18, 25] or private sex parties [21, 24], and/or the use of the internet [13] or geospatial networking applications [23, 24] to meet casual partners. Networking websites and applications may have increased opportunities for sexual mixing, and to explore and experiment without emotional risks or attachments [26]. HIV-positive men may use these applications to seek partners with the same HIV status for condomless sex (i.e. HIV serosorting) [21, 23].

For some MSM, recreational drug use including chemsex (the specific use of Crystal methamphetamine (crystal meth), GHB/GBL and/or mephedrone immediately before or during sex [27]) may facilitate higher risk behaviours including condomless anal intercourse (CAI) with casual partners [28-31], group sex [27, 30], fisting [27, 32], the use of sex toys [21, 27] and scat play [23]. In particular, social media and networking applications have increased the profile of drug use and chemsex parties [33], which have been linked to outbreaks of enteric infections in the UK including *Shigella flexneri* and verocytotoxin-producing *Escherichia coli* (VTEC) 0117:H7 [23, 24].

STEIs in MSM are often associated with HIV-positive status and STI co-infection and/or previous infection, suggesting overlapping epidemics [23, 24, 34-36]. The interaction between STEIs and HIV infection is likely complex; HIV-related immunosuppression may result in longer carriage, increased shedding and/or more severe disease including chronic or relapsing infection, but increased HIV-

serosorting and high-risk behaviours can create dense sexual networks of HIV-positive MSM thereby facilitating STEI transmission [36-43].

RECENT OUTBREAKS OF STEIS

Hepatitis A

Hepatitis A is an acute and usually self-limiting infection caused by the Hepatitis A virus (HAV). Symptoms are more common in adults and can include fever, malaise, nausea, anorexia and abdominal pain followed by jaundice. Some individuals may experience relapsing hepatitis and in rare cases, acute liver failure [44]. Outbreaks associated with sexual transmission in MSM are well described [45].

In December 2016, the European Centre for Disease Prevention and Control (ECDC) reported an increase of hepatitis A cases predominantly affecting MSM in Europe. Germany, the Netherlands and the UK were among the first EU countries to report an increase in cases [46]. In October 2016 an indistinguishable strain (RIVM_HAV16_090) of genotype 1A was identified in two MSM in the Netherlands associated with sexual contact at the 2016 EuroPride festival in Amsterdam [47]. The infecting strain had not been seen in the Netherlands since 2010, and was related to strains from Japan and most likely originated in Asia; it was found to be genetically identical to the strain associated with a large outbreak in MSM in Taiwan that began in 2015 [47]. In December 2016, the UK reported an increase in cases, mostly in MSM, with an identical strain (VRD_521_2016) of genotype 1A which had not been previously reported in the UK and was related to strains from Latin America [46]. Subsequent phylogenetic and epidemiological analyses revealed likely importation from Spain, followed by secondary sexual transmission among MSM in the UK [48]. In January 2017, Germany reported three distinct clusters of genotype 1A in Berlin primarily among MSM: two involved strains RIVM_HAV16_090 and VRD_521_2016 described above, while the third involved a new strain (V16_25801) identified in Berlin and other German cities [49, 50].

The MSM population in Europe is highly interconnected, and the three distinct clusters quickly spread across Europe (16 EU countries) and beyond [50]. Two of the three strains associated with the European outbreaks were also likely imported to Israel by men who had travelled abroad. Israel introduced universal vaccination for toddlers in 1999 which has led to a low incidence of infection in the general population but most adult men remain susceptible [51]. Increases in the number of HAV cases among MSM were also recently reported in Chile and New York City [52, 53]. In Chile, 706 cases of HAV were reported during the first half of 2017, an increase of 53% compared to the same period in 2016, with the Santiago Metropolitan Region seeing the largest increase in cases [52]. Limited phylogenetic analysis suggested some of the men were infected with a strain of genotype 1A (not specified) associated with the European outbreaks [52].

The characteristics of the cases involved in these international outbreaks have been broadly similar. In the Chilean and Taiwanese outbreaks, the majority were MSM and a high proportion were HIV positive with a history and/or coinfection with STIs or shigellosis [52, 54]. Cases in the UK outbreak reported multiple sexual contacts, the use of apps, websites and/or use of sex venues to meet partners; the majority were MSM living in London although household transmission was also reported, highlighting the potential for spread within the wider community [48, 55].

Control measures have focussed on vaccination of at-risk MSM as well as implementing enhanced surveillance and raising awareness among health professionals and the MSM community of the potential for sexual transmission of HAV [47, 48]. In Taiwan, the provision of free vaccination to HIV positive individuals or individuals under 40 years of age recently diagnosed with syphilis or gonorrhoea coincided with reductions in cases at the end of 2016 [54]. Vaccination of MSM living in outbreak areas or attending Pride events where riskier sexual contact was considered likely was recommended during the European outbreaks in 2017, but implementation was hampered by the current worldwide shortage of vaccine [50].

The HAV outbreaks highlight the importance of global travel in fuelling the spread sexually transmissible infections and further outbreaks are likely given the shortage of vaccine. Sustained transmission could, however, be prevented if the level of immunity in the MSM population exceeds 70% [56].

Shigella spp.

Shigellosis is characterised by severe bacillary dysentery caused by four species of the gram negative bacterium *Shigella*. In high-income countries, shigellosis is typically diagnosed in travellers returning from regions with a high risk for contracting diarrhoeal disease such as Africa, Asia and Latin America [57], but sporadic outbreaks of *S. sonnei* and *S. flexneri* have occurred among MSM in large cities around the world [13, 18, 23, 58-60].

Sexually transmitted shigellosis has been associated with various specific behaviours including douching [18], fisting [21, 23], recreational drug-use [21, 23] and attending sex venues [18]. HIV infection has been described as an independent risk factor [37, 41]. In England, approximately 20% of all *Shigella* cases among men without a reported travel history may be HIV-positive [61]. The burden of illness in MSM can be substantial, particularly with *S. flexneri* which is more virulent and pathogenic [62], resulting in hospital admissions and significant complications such as bacteraemia or acute kidney injury, even among HIV-positive patients with high CD4 counts [59, 63].

In North America and the UK, there have been shifts in the dominant serotype of *Shigella spp.* responsible for outbreaks among MSM, which may reflect levels of herd immunity [9, 59, 62]. Immunity to *Shigella spp.* is thought to be serotype specific allowing new serotypes to enter and spread within a population under the right conditions [64], however, evidence of rapid reinfection with a diverse isolate of the same serotype in a recent phylogenetic study challenges this theory [20].

The primary treatment for uncomplicated *Shigella* spp. infection, where indicated, is ciprofloxacin with alternative therapies including azithromycin and ceftriaxone [65]. Antimicrobial resistance (AMR) to front-line treatments is well reported in *Shigella* spp. and can vary by country of acquisition and route of transmission [20, 22, 66-68]. In 2015, whole genome sequencing of clinical isolates of *S. flexneri* 3a identified a new AMR strain which had spread rapidly through Europe, North America, and Australia via sexual transmission in MSM, and was distinct from the African and Asian-associated lineages [20]. The pathogen had acquired resistance to multiple antimicrobials, including high-level resistance to azithromycin, which may have been an evolutionary response to antibiotic exposure for the treatment of STI coinfections [20]. Reduced susceptibility to azithromycin and/or ciprofloxacin in clusters of MSM isolates has been reported widely across North America, Australia, Europe and Taiwan [20, 21, 60, 67, 69-73] and a recent cluster of multi-drug resistant, extended-spectrum-beta-lactamase (ESBL)-producing *S. sonnei* was reported in England [21]. The resistant phenotype of the latter was conferred by the acquisition of a known plasmid (reported in *Shigella flexneri* 3a), but with an additional mobile genetic element. Although these isolates were sensitive to quinolones, the potential for spread of this plasmid to other enteric pathogens is unknown and it raises concerns about the treatment of *Shigella* and the need for susceptibility testing [21].

Entamoeba histolytica

Entamoeba histolytica is a protozoan parasite endemic in areas with poor water and sanitation infrastructure [74]. In the vast majority of cases, self-limiting and asymptomatic infection occurs but infection can lead to invasive disease with amoebic dysentery or liver abscess [74]. There has been renewed interest in the transmission of *E. histolytica* as a sexually transmissible infection in non-endemic countries following reports of symptomatic amoebiasis among MSM in Japan, Taiwan, the Republic of Korea and Australia, mostly among HIV-positive individuals [38, 40, 75, 76]. The geographical distribution of this re-emerging infection in MSM is thought to reflect the higher background prevalence of infection in Asia [40].

Two small clusters of invasive amoebiasis among MSM were reported in Barcelona, Spain in October 2016 and January 2017 [77]. All cases reported oral-anal sex and some reported multiple sexual partners and attendance at sex parties. Half of the men were HIV-positive and all but one had a concurrent or recent STI and/or tested positive for *Shigella flexneri* [77]. Of note, at least one asymptomatic contact tested positive for *Entamoeba histolytica* while another was previously diagnosed with amoebiasis after travel to Brazil, highlighting the spectrum of clinical illness and potential for international spread.

***Campylobacter* spp.**

Campylobacter infections are one of the most common causes of bacterial gastroenteritis globally [78]. Extragastrintestinal infection is rare but can result in complications including bacteraemia, lung infection, meningitis or reactive arthritis, particularly in those who are immunocompromised [78, 79].

Several clusters of *Campylobacter* spp. including *C. coli* [34, 80], *C. jejuni* [35, 81] and *C. fetus* [82] have been reported among MSM in Canada over the past decade with most exhibiting AMR to at least two of erythromycin, ciprofloxacin or tetracycline [34, 35, 80, 81]. Sexual transmission of a multi-drug resistant strain of *C. jejuni* resulted in a persistent outbreak in MSM lasting over 10 years [35]. As with other STEI clusters, the majority of cases were HIV-positive with a history of STIs and/or enteric infection including *Shigella* spp. and *Giardia lamblia* [34, 35, 80-82]. MSM infected with *C. fetus*, a less characterised species of *Campylobacter*, reported attending sex venues and the use of the internet to meet casual partners [82].

Other STEIs

Other causes of sexually transmissible enteritis include *Giardia lamblia*, *Salmonella* spp. and *Escherichia coli* [83, 84], although there have been few reports in recent years. In 2014, a small cluster of VTEC 0117:H7 was detected MSM in the UK [24]; most were HIV-positive with multiple

sexual partners and engaged in chemsex. *Cryptosporidium* spp. and *Microsporidium* spp. are protozoan parasites commonly seen in HIV-positive MSM, but outbreaks associated with sexual transmission are not commonly reported; infections are usually opportunistic given immunosuppression rather than a function of behaviour [84]. Cytomegalovirus was an important diarrhoeal agent in the pre-HAART era but is now rarely observed [84, 85].

FUTURE IMPLICATIONS

The number and size of STEI outbreaks is likely to represent only a fraction of infections since many symptomatic individuals will not seek care or provide stool specimens for clinical diagnosis [13, 61]; asymptomatic and/or persistent infections may also play a role in transmission [13, 86, 87]. Rectal swabs may provide a cheap and practical method of detecting STEIs in MSM in a sexual health clinic setting even in asymptomatic patients, but further research is required to validate the test and to establish the clinical and public health benefits of such an approach [87].

The syndemics of STEIs, STIs (such as gonorrhoea and syphilis) and HIV in MSM appear to be associated with engagement in more experimental sexual and drug-use behaviours in dense sexual networks [88]. Controlling transmission is challenging and will require improved understanding of the social and psychological motivations for engaging in higher-risk behaviours and a holistic approach that promotes the broader health and wellbeing of MSM, as well as HIV/STI and enteric infection prevention and management [32].

CONCLUSION

The frequency and widespread distribution of STEI outbreaks in MSM warrants public health attention, particularly as the spread of AMR could have implications for the treatment of these and other pathogens. The outbreaks described here show how rapidly global travel can facilitate transmission and introduce new strains into susceptible populations. A better understanding of the contextual factors facilitating sexual transmission, the association with HIV, the role of

asymptomatic infection in transmission and maintenance in a population, and the drivers of AMR will help to inform the development and implementation of better control measures.

KEY POINTS

- Sexually transmissible enteric infections (STeIs) in men who have sex with men (MSM) are reported globally with increasing frequency and are often associated with widespread antimicrobial resistance (AMR).
- Syndemics of STeIs and other sexually transmitted infections including HIV in MSM appear to be associated with engagement in more experimental sexual and drug-use behaviours in dense sexual networks.
- Further understanding and recognition of the contextual factors facilitating sexual transmission and the drivers of AMR will enable the development of more effective control measures and improved patient care.

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CONFLICTS OF INTEREST

None

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