REVIEW ARTICLE

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# Emerging and Reemerging Sexually Transmitted Infections

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THE 21ST CENTURY HAS SEEN A GLOBAL RESURGENCE OF SEXUALLY TRANSmitted infections (STIs). From a nadir in the 1990s, the rates of gonorrhea, syphilis, and chlamydia infections have increased substantially in high-income countries, with particular increases among men who have sex with men (MSM). Concurrent with the increase in these established STIs are emerging epidemics and outbreaks of nonclassical sexually transmissible pathogens that cause a wide range of clinical syndromes. These pathogens include enteric pathogens (e.g., shigella and hepatitis A virus), those spread by close contact (e.g., *Neisseria meningitidis*), and recently characterized pathogens that can spread through sexual contact (e.g., Zika virus) (Table 1). Furthermore, increases in antimicrobial resistance have heightened concern about ever more limited treatment options for STIs, particularly gonorrhea and *Mycoplasma genitalium* infection.

The factors contributing to sustained transmission of STIs within populations are multiple, complex, and context specific. In principle, these factors include the probability of transmission, the rate of change in sexual partners, and the duration of infectiousness. Examples of factors that have enhanced STI transmission include unprecedented connectivity between persons, facilitated by global travel and online social networking, and increasing use of preexposure prophylaxis against human immunodeficiency virus (HIV) infection.[1-3] The multitude of socioeconomic and structural variables that impede access to testing and treatment are important in sustaining epidemics of curable STIs. In this review, we provide an overview of major pathogens that have emerged or reemerged as STIs over the past decade. We discuss epidemiologic features of these infections, including insights provided by genomic technologies, diagnostic approaches, and practical issues relating to treatment and control.

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## SEXUALLY TRANSMISSIBLE ENTERIC PATHOGENS

### SHIGELLA

Sexual transmission of shigella species was reported in the 1970s, with regular outbreaks of *Shigella sonnei* and *S. flexneri* in urban centers among MSM.[4-6] Shigellosis ranges from self-limiting gastroenteritis to severe, bloody dysentery. Behavioral factors associated with sexually transmissible shigellosis include direct oral anal contact, chemsex (use of drugs to enhance sexual experiences), condomless sex, multiple sexual partners, use of social networking (apps) to meet sexual partners, and attendance at sex parties.[7-9] Sexually transmitted shigellosis has also been associated with HIV infection.[7] This may reflect biologic factors such as increased susceptibility to or duration of shigella infection, behavioral factors such as assortative mixing of MSM according to HIV status (i.e., men with similar HIV serostatus), possibly facilitated by social networking apps, or both biologic and behavioral factors.[7,10]

**Table 1. Clinical Syndromes Caused by Major Emerging or Reemerging Sexually Transmissible Pathogens.**

| Clinical Syndrome | Pathogens |
|---|---|
| Enteritis or colitis | Shigella species<br>Shiga toxin producing *Escherichia coli*<br>Campylobacter species<br>*Entamoeba histolytica* |
| Urethritis | *Neisseria meningitidis* (unencapsulated)<br>*Mycoplasma genitalium*<br>*N. gonorrhoeae* |
| Proctitis | Lymphogranuloma venereum<br>Enteric pathogens causing colitis |
| Systemic infections | *N. meningitidis* (capsulated)<br>Zika virus<br>Ebola virus<br>*Treponema pallidum* |

One of the major features of sexually transmitted shigellosis is resistance to multiple antimicrobial agents, particularly azithromycin and ciprofloxacin, with outbreaks of antimicrobial-resistant shigellosis reported among MSM in Europe, North America, Australia, and Asia.[4,6,11-13] A study from Australia, reported in 2019, showed high rates of azithromycin-resistant shigellosis among MSM: 93% among those with *S. sonnei* infection and 71% among those with *S. flexneri* infection.[4] Data from the United States show that azithromycin resistance is higher in cases of shigellosis among MSM than in cases that do not involve MSM.[5,6] Since 2013, three major epidemic lineages associated with MSM have been characterized within *S. sonnei* biotype g, *S. flexneri* 2a, and *S. flexneri* 3a, with whole-genome sequencing confirming the global spread of these lineages among MSM.[4,12,13] If antimicrobial treatment is indicated, the choice of agent should be guided by susceptibility testing of the shigella isolate or, if empirical therapy is required, by local susceptibility data.

### HEPATITIS A VIRUS

Hepatitis A virus (HAV) causes an acute, self-limiting hepatitis that is fulminant in less than 0.5% of infections. HAV is transmitted by the fecal oral route through ingestion of contaminated food or water or by direct contact with an infectious person. In countries where the prevalence of HAV infection is low, such as the United States, the low incidence of childhood infection has resulted in a large proportion of nonimmune adults, increasing the potential for large-scale outbreaks, including outbreaks spread by sexual contact among MSM.[14] In 2018, an increase in HAV infections disproportionately affecting MSM was reported in Europe, with approximately 1400 cases occurring across 16 European countries between June 2016 and May 2017.[15] Molecular genotyping of HAV from these cases showed the presence of three cocirculating HAV lineages, all belonging to genotype 1A.[15] Phylogenetic analysis revealed intercontinental dissemination of these three lineages among MSM, with one lineage detected in Southeast Asia,[16] another in Latin America,[17] and all three in the United States.[18] The rapid global spread of these lineages highlights the role of international travel in facilitating the spread of STIs. Coinfection with HIV has been common among HAV-infected MSM,[16] and other characteristics noted in outbreak cases include the use of electronic dating apps,[15] sex with multiple partners,[15] infection with other STIs,[19] and attendance at sex venues.[15]

Efforts to control recent outbreaks of HAV infection among MSM have been multimodal, focusing on awareness raising in the community and among health care professionals, vaccination of MSM, and enhanced health services for all sexual contacts ( partner management ), including through the use of dating apps and websites.[20] Recent data suggest that previous HAV vaccination in persons with HIV infection may not reliably provide protection against the development of HAV infection.[21] Accordingly, provision of postexposure prophylaxis (consisting of immune globulin and monovalent HAV vaccine) may be considered for persons with HIV infection who have had a recent high-risk exposure to HAV, irrespective of status with regard to previous HAV vaccination.[21]

### OTHER ENTERIC PATHOGENS

Sexual transmission of enteric pathogens other than shigella and HAV has also been described. Campylobacter species have been associated with gastrointestinal outbreaks in MSM, including a sustained outbreak, lasting for approximately 10 years, of erythromycin- and ciprofloxacin-resistant

*Campylobacter jejuni* in Quebec, Canada.[22] Furthermore, an outbreak of Shiga toxin producing *Escherichia coli* involving nine MSM occurred in the United Kingdom, with the behavioral profiles of cases similar to those of shigellosis in MSM ó namely, HIV-positive MSM engaging in chemsex with multiple sexual partners.[23] Sexual transmission of the protozoan *Entamoeba histolytica* has also been increasingly reported among MSM, particularly those with HIV infection, in countries where amebiasis is nonendemic, including Australia, Taiwan, Korea, Japan, and Spain.[24,25]

### PATIENTS WITH SEXUALLY TRANSMISSIBLE ENTERIC INFECTIONS

Sexual transmission of enteric pathogens is well recognized and can be direct (e.g., through oral anal contact) or indirect (e.g., through contact with fecally contaminated fingers or objects). Outbreaks of sexually transmissible enteric infections among MSM can be driven by a combination of pathogen, host, and environmental factors (Table 2). A general approach to the investigation, diagnosis, and management of enteric infections in MSM is shown in Table 3. A major challenge with diagnosis of enteric infections is the use of culture-independent diagnostic tests, since bacterial isolates may not be available for additional characterization, including antimicrobial susceptibility testing.[26] Clinicians should contact their local microbiology laboratory or public health agency to ensure that stool cultures from patients are performed when a sexually transmissible enteric infection is suspected.

Patients should also be given advice on how to prevent the spread of infection (Table 4). The role of partner management in preventing the spread of sexually transmissible enteric infections is unknown, and testing of asymptomatic contacts is not generally recommended. Additional investigations should include screening for nonenteric sexually transmitted pathogens, since coinfections with such pathogens, including HIV, are common.[7,27] The consultation should also be used as an opportunity to ensure that relevant vaccinations are up to date and that preexposure prophylaxis against HIV infection is discussed with MSM who report sexual risk or who receive a diagnosis of an STI.

**Table 2. Factors Contributing to the Emergence, Reemergence, and Spread of Sexually Transmissible Infections.***

| Factor | Contributions |
|---|---|
| Pathogen | Antimicrobial resistance<br>Infectiousness<br>Virulence |
| Environment | Access to biomedical interventions (e.g., HIV PrEP)<br>Behavioral aspects (e.g., chemsex , condomless sex)<br>International travel<br>Access to testing and treatment<br>Social media and use of online dating apps |
| Host | Previous immunity (e.g., to hepatitis A, *N. meningitidis*)<br>Coinfection with other sexually transmissible pathogens<br>Coexisting conditions (e.g., HIV infection) |

* HIV denotes human immunodeficiency virus, and PrEP preexposure prophylaxis.
Chemsex is the use of drugs to enhance sexual experiences.

## EMERGING SEXUALLY TRANSMISSIBLE PATHOGENS

### *NEISSERIA MENINGITIDIS*

*N. meningitidis* colonizes the nasopharynx in approximately 10% of healthy persons and, less frequently, also colonizes other mucosal sites, such as the cervix, urethra, and rectum.[28] The pathogen has increasingly been recognized as sexually transmissible, with two distinct clinical contexts emerging: *N. meningitidis* associated urethritis in heterosexual men and invasive meningococcal disease in MSM.[29-36]

Since 2015, there have been increasing reports from U.S. cities of cases of symptomatic urethritis caused by *N. meningitidis*,[29,30] with the largest outbreak involving 75 patients who presented for screening at an STI clinic in Columbus, Ohio.[31] To date, cases have predominantly involved heterosexual men, with most reporting recent insertive oral sex, suggestive of oral genital transmission.[29,31] Cases were initially detected because of discrepancies in diagnostic test results: gram-negative intracellular diplococci suggestive of gonorrhea were seen in urethral swabs, but nucleic acid amplification testing did not reveal gonococcal DNA. Whole-genome sequencing and analysis of *N. meningitidis* isolates from recent U.S. clusters showed the presence of a distinct clade within the hypervirulent sequence type 11 clonal complex (CC11).[30] Unlike *N. meningitidis* associated with invasive meningococcal disease, urethritis-associated isolates lack a bac-

**Table 3. Assessment for and Treatment of Sexually Transmitted Enteric Infections in Men Who Have Sex with Men.***

| |
|---|
| **History taking** |
| Onset and duration of symptoms |
| Symptoms of enteritis or colitis (diarrhea, abdominal pain) or proctitis (anorectal pain or discharge) |
| Assessment of severity (fever, dehydration, weight loss) |
| HIV status |
| Risk of HIV infection, if HIV-negative |
| Sexual risk factors: direct oral–anal contact (rimming), indirect oral–anal contact (e.g., use of sex toys), multiple sexual partners or group sex, chemsex, use of online dating apps or sex-on-premises venues |
| Nonsexual risk factors: contact with person with diarrhea, recent overseas travel (timing, duration, location), relevant food consumption in 2-wk period before illness (e.g., restaurant food, poultry, shellfish, raw eggs), occupational exposure (e.g., employment involving health care or childcare) |
| **Clinical examination** |
| Signs of severe infection (confusion, dehydration, fever) |
| Signs of concurrent proctitis |
| **Diagnostic investigations** |
| Stool culture |
| Antimicrobial susceptibility testing of relevant pathogen |
| Stool PCR test for enteric pathogens (with reflex culture if bacterial pathogen is identified) |
| Testing for HIV and other sexually transmitted pathogens, including rectal pathogens if proctitis is clinically suspected |
| **Treatment** |
| Conservative management with oral rehydration in most cases |
| Antimicrobial treatment guided by susceptibility testing in patients with severe disease or coexisting conditions |
| Consider hospital admission for severe disease |
| Vaccination for HAV in the case of an outbreak |
| Discuss HIV PrEP if patient is HIV-negative and reports high-risk behavior |

* If infection with a sexually transmissible enteric pathogen is diagnosed, the clinician or laboratory should ensure that statutory notification occurs, depending on the causative pathogen and local public health regulations. HAV denotes hepatitis A virus, and PCR polymerase chain reaction.
If symptoms or signs of proctitis are present, rectal swabs for relevant sexually transmitted pathogens should be obtained for nucleic acid amplification testing and culture.
Patients with mild-to-moderate diarrhea generally have a self-limiting infection, which can be managed conservatively with oral rehydration. In cases of severe disease, antibiotic therapy is often warranted and should be guided by the cause of the infection, antibiotic susceptibility testing, or knowledge of local resistance patterns.

terial capsule because of the deletion of capsular genes and display some phenotypic traits similar to those of *N. gonorrhoeae*, suggesting adaptation to the urogenital niche.[37] In the Ohio cluster, most cases were successfully treated according to the treatment for gonorrhea recommended by the Centers for Disease Control and Prevention (CDC): a single 250-mg dose of ceftriaxone (intramuscularly) and a single 1-g dose of azithromycin (orally).[31]

Concurrent with the emergence of *N. meningitidis* associated urethritis have been reports of clusters of invasive meningococcal disease among MSM in urban centers in the United States and Europe.[32-36] Between 2012 and 2015, there were 74 cases of invasive meningococcal disease reported among MSM in the United States, with 46 cases reported as part of clusters from three areas: New York, Los Angeles, and Chicago.[35] In a high proportion of cluster-associated cases, patients reported the use of online dating apps or websites and anonymous or multiple sexual partners, suggesting close-contact transmission in distinct social networks.[35] Similarly, an increase in invasive meningococcal disease among MSM in Italy in 2015 and 2016 was

driven by a series of small clusters, focused on several gay venues.[36] Genomic analyses showed that recent global clusters of invasive meningococcal disease among MSM have been predominantly due to serogroup C isolates from the hypervirulent CC11 lineage, although with different molecular profiles across clusters, suggesting possible international spread of the CC11 lineage with subsequent local evolution. To date, no clear risk factors have been identified for cluster-associated invasive meningococcal disease in MSM, although HIV infection is a recognized risk factor for sporadic cases of invasive meningococcal disease.[38]

Control efforts have focused mainly on vaccination with quadrivalent meningococcal conjugate (MenACWY) vaccine. Although the CDC Advisory Committee on Immunization Practices does not recommend routine MenACWY vaccination of all MSM, routine vaccination of HIV-positive persons 2 months of age or older is recommended.[39]

**Table 4. Advice for Patients with a Sexually Transmissible Enteric Infection on Preventing Transmission.**

| |
|---|
| **Hygiene** |
| Wash hands with soap after using the toilet and before preparing and eating food |
| Clean bathroom and kitchen surfaces with disinfectant regularly |
| Do not share towels and linens |
| Wash soiled linens separately |
| Avoid swimming for 2 wk after cessation of diarrhea |
| **Sexual practices** |
| Abstain from sex (including oral anal sex and sharing of sex toys) while symptomatic and for 7 days after resolution of symptoms |
| Wash hands and body before and after sex |
| Use condoms for sexual intercourse |
| **Occupation** |
| Patients with occupations that pose a high risk of transmission (food handlers, childcare workers, health care workers, workers at residential care facilities) should follow local health department guidance about returning to work |

### LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum (LGV) is caused by *Chlamydia trachomatis* serovar L1, L2, or L3. Unlike infections caused by the more common chlamydial serovars D through K, LGV infections generally spread through the lymphatics to regional lymph nodes, resulting in inguinal lymphadenopathy. Rectal LGV infection can cause proctitis with rectal pain and discharge and in some cases may be clinically severe, with proctocolitis mimicking inflammatory bowel disease. Increased use of *C. trachomatis* genotyping has revealed that approximately half of rectal LGV infections are asymptomatic or clinically mild, like most non-LGV chlamydial infections.[40]

Since 2003, LGV has reemerged among MSM, with a predominance of rectal rather than genital infections.[41] LGV outbreaks have been reported from many high-income countries, with most cases caused by the L2b variant, first described among MSM in San Francisco in the 1980s.[42] Rectal LGV infections in MSM have been associated with high-risk sexual practices such as condomless receptive anal sex and fisting (the use of a fist for insertive sex), and coinfection with HIV has been common.[43] Between 2004 and 2016, a total of 10,105 cases of LGV were reported from 15 European countries, with most from the United Kingdom, France, and the Netherlands.[44] However, this is likely to be an underestimate, since genotyping for LGV is limited, and most countries do not have LGV surveillance systems.[41]

LGV is ideally diagnosed by detection of serovar-specific *C. trachomatis* nucleic acid in clinical samples. A two-step process is recommended, in which *C. trachomatis* is initially detected with the use of nucleic acid amplification testing, with subsequent genotyping (e.g., polymerase-chain-reaction [PCR] genotyping) performed to differentiate between LGV and non-LGV serovars. However, these additional genotyping tests are not widely available.[45] Men presenting with severe proctitis who report having sex with men will require treatment before positive *C. trachomatis* or genotype results are available and should also be tested and treated for other sexually acquired causes of proctitis (Table 1).[46]

The recommended therapy for LGV has been a 21-day regimen of doxycycline, longer than the 7-day course recommended for rectal chlamydia, underscoring the value of genotyping to distinguish between *C. trachomatis* serovars.[47] However, recent evidence suggests that 7 days of doxycycline may be sufficient to cure LGV.[40,48] Patients with clinically severe cases of LGV, such as those involving chronic proctocolitis or bubo formation, should continue to receive at least 21 days of doxycycline treatment.[48] Patients with LGV should be offered testing for other STIs, especially HIV infection.

### *MYCOPLASMA GENITALIUM*

*M. genitalium* was first described as an STI in 1981, when it was isolated from two men with nongonococcal urethritis.[49] Because *M. genitalium* does not grow in routine laboratory culture, molecular testing is used for diagnosis, with the first Food and Drug Administration approved nucleic acid amplification test available in the United States as of 2019 for use on urogenital samples from both symptomatic and asymptomatic persons.[50] The wider use of nucleic acid amplification testing for *M. genitalium* has increased the diagnosis of *M. genitalium* infections, which is an established cause of nongonococcal urethritis in men and pelvic inflammatory disease in women. Further studies are required to determine the morbidity attributable to *M. genitalium* in men and women.[51] Screening of asymptomatic persons for *M. genitalium* is not recommended.[51] European guidelines recommend testing only symptomatic patients and, to prevent repeat infection, partners of patients with confirmed *M. genitalium* infection.[52]

Antimicrobial resistance in *M. genitalium* has increased, including resistance to azithromycin and moxifloxacin, which have both been used for treatment. Macrolide resistance is mediated by mutations in the 23S ribosomal RNA gene, and fluoroquinolone resistance by mutations in the *parC* and *gyrA* genes.[53] Depending on the geographic region, macrolide resistance has reportedly ranged from 30 to 100%, with the highest rates of resistance detected in samples from MSM.[54,55] In some countries, treatment guidelines for nongonococcal urethritis have shifted away from single-dose azithromycin as first-line treatment, in part because of macrolide resistance in *M. genitalium*.[54,56] Treatment regimens for *M. genitalium* infection are evolving, with emerging reports of dual resistance to both macrolides and fluoroquinolones.[55,57] Some nucleic acid amplification tests also detect mutations associated with macrolide resistance, and this information can guide therapy.[54]

## EMERGING SEXUALLY TRANSMISSIBLE VIRUSES

### ZIKA VIRUS

Zika virus (ZIKV) is a flavivirus transmitted by aedes mosquitoes, which causes a self-limiting denguelike illness, with symptoms including fever, rash, headache, and arthralgia. Of particular concern is the effect of ZIKV infection during pregnancy, which can result in microcephaly and other fetal brain anomalies.[58] The first presumed case of sexual transmission of ZIKV, in 2008, involved a man who had returned to the United States from Senegal and his wife, who had not traveled abroad.[59] Both had acute ZIKV infection and serologic evidence of the virus. In 2013, ZIKV was detected in the semen and urine of a man from Tahiti with acute ZIKV infection, indicating the biologic plausibility of sexual transmission.[60] Linked transmission has been shown by genome sequencing of ZIKV from the saliva of a woman and semen from her male sexual partner.[61] Additional cases of sexual transmission of ZIKV have been reported, most of which have involved sexual transmission from men with acute ZIKV infection to women through vaginal intercourse, with the virus detected in urine or semen.[62] In a prospective study involving persons with acute ZIKV infection, the median time to the clearance of viral RNA from semen was 42 days, with 95% clearance by 4 months, although detection of ZIKV RNA does not necessarily indicate viral viability or infectiousness.[63] ZIKV was infrequently detected in saliva or vaginal secretions.[63]

Although the number of sexual transmissions of ZIKV is difficult to estimate in areas with mosquito-transmitted infection, the total number of confirmed sexual transmissions to date is much smaller than the total number of ZIKV infections globally, and the population-attributable fraction of ZIKV transmission due to sexual transmission is likely to be low. To reduce the risk of sexual transmission of ZIKV, World Health Organization (WHO) guidelines recommend that men and women use condoms consistently or abstain from sex for at least 3 and 2 months, respectively, after possible exposure to ZIKV or in the case of known or presumed infection.[64] Women should avoid sex that could result in pregnancy for 2 months after possible exposure or infection so that ZIKV has cleared before conception. Furthermore, pregnant women and their sexual partners should use condoms consistently or abstain from sex during the entire pregnancy if they reside in an area with ongoing ZIKV transmission or if the partner is returning from such an area.[64]

### EBOLA VIRUS

Cases of sexual transmission of Ebola virus have been reported since the large outbreak of Ebola that occurred in West Africa between 2014 and 2016.[65] Ebola virus can be found in the semen of male survivors of Ebola virus disease, providing a biologic basis for sexual transmission months after recovery.[66] In a prospective study involving male survivors of Ebola virus disease who underwent repeated reverse transcriptase PCR (RT-PCR) testing of semen for Ebola virus, the median duration of persistent viral RNA detection in semen was 158 days after the onset of disease, with a wide range of duration among men; however, RT-PCR positivity does not necessarily indicate the presence of infectious virus.[66] Genome sequencing of Ebola virus from the semen of a man who survived infection and from blood obtained from a female sexual partner who died provided evidence for sexual transmission of Ebola virus 179 days after the onset of disease in the man.[67] The WHO recommends that male survivors of Ebola virus disease be offered RT-PCR semen testing for Ebola virus 3 months after the onset of disease and that those with positive test results abstain from sex or use condoms consistently until monthly semen testing is negative on two occasions.[65]

## NEW ISSUES WITH ESTABLISHED STIs

### SYPHILIS

Syphilis remains a major public health problem globally, with the WHO estimating that there were 6 million new infections worldwide in 2016.[68] Syphilis can result in serious morbidity, including ocular syphilis, neurosyphilis, and congenital infection. Over the past decade, the incidence of syphilis among MSM has increased markedly in many countries. For example, in the United States, the rate of primary or secondary syphilis among MSM increased from 11.7 cases per 100,000 population in 2014 to 18.7 per 100,000 in 2018.[69] The incidence of syphilis has been particularly high among MSM who are receiving preexposure prophylaxis against HIV infection, underscoring the importance of regular syphilis screening together with HIV testing in MSM who are using preexposure prophylaxis against HIV infection.[3] More recently, syphilis has reemerged among heterosexuals in the United States, Japan, and Australia, with increasing reports of congenital infection.[70] The U.S. Preventive Services Task Force recommends screening of persons who are at increased risk for syphilis.[71]

Since primary syphilis can resemble other STIs that cause anogenital ulceration, multiplex PCR testing for the simultaneous detection of pathogens such as *Treponema pallidum* and herpes simplex virus has been used to improve diagnostic accuracy.[72] Anal primary infections in MSM may remain unnoticed, and in the absence of lesions, *T. pallidum* can be detected with the use of nucleic acid amplification tests.[73] Similarly, in cases of secondary syphilis without oral ulcers in MSM, *T. pallidum* has been detected by PCR testing in the oral cavity.[74] Collectively, these studies point to the potential for the transmission of *T. pallidum* from asymptomatic sites. Congenital syphilis is preventable if maternal infection is detected and treated early in pregnancy. After efforts to increase antenatal screening for syphilis in China, the number of reported congenital infections fell precipitously, from a peak of more than 12,000 cases in 2011 to approximately 4000 cases in 2016.[75] Genome sequencing has revealed the simultaneous circulation of several *T. pallidum* lineages across multiple countries and may prove useful for tracking networks of syphilis transmission.[76]

### GONORRHEA

Another key emerging issue is increasing antimicrobial resistance in *N. gonorrhoeae*, which the CDC has identified as an urgent threat to public health in the United States.[77] It is estimated that there are approximately 550,000 drug-resistant *N. gonorrhoeae* infections per year in the United States. Of particular concern is reduced susceptibility to ceftriaxone, azithromycin, or both — the two major drugs recommended for first-line treatment in most high-income countries.

Since 2017, an internationally disseminated, ceftriaxone-resistant *N. gonorrhoeae* clone (the FC428 clone) has been sporadically reported, initially from Japan and subsequently from Europe, Southeast Asia, and Australia.[1] Furthermore, in 2018, the first three cases of *N. gonorrhoeae* infections with both ceftriaxone and high-level azithromycin resistance were reported from the United Kingdom and Australia, termed extensively drug-resistant *N. gonorrhoeae*. Genom-

ic analysis showed intercontinental dissemination of this lineage (the A2543 clone), with a possible reservoir in Southeast Asia.[78] Because of the lack of adequate culture-based surveillance globally, it is likely that most gonococcal infections escape antimicrobial-resistance testing and surveillance, impeding control efforts.[1] The pharynx and rectum serve as reservoirs of infection with *N. gonorrhoeae*; pharyngeal and rectal infections are usually asymptomatic but detectable with nucleic acid amplification testing. The pharynx is believed to be an important site for the development of antimicrobial resistance in *N. gonorrhoeae* and may be a site where treatment fails because of inadequate antibiotic penetration. Although the number of verified treatment failures with ceftriaxone have to date been limited, *N. gonorrhoeae* has shown a remarkable propensity for developing resistance over time, and new, effective antibiotics are urgently required. Recent clinical trials have examined the efficacy of newer antimicrobial agents such as solithromycin,[79] zoliflodacin,[80] and gepotidacin.[81]

## CONCLUSIONS

Rates of established STIs in many countries are approaching levels not seen since the 1970s, with concerns about public health priorities such as increasing antimicrobial resistance in *N. gonorrhoeae* and the rising incidence of congenital syphilis. New or reemerging sexually transmissible pathogens with potentially serious morbidity present additional challenges to public health control, health services, and community responses. The incidence of these STIs will probably continue to increase as a result of enhanced human interconnectedness due to growth in international travel, in online social networking, and in numbers of people taking preexposure prophylaxis. Timely testing and treatment have been critical for the control of STIs, and this applies equally to newer sexually transmissible pathogens.

Access to health care and clinical services for at-risk individuals and groups is essential, particularly for mobile, vulnerable, and marginalized populations, and will require adequate resources and funding. Effective control of emerging STIs will also require dedicated, multimodal public health responses that include health promotion and biomedical prevention (e.g., development and use of effective vaccines). Robust surveillance systems that include laboratory culture of pathogens are necessary for identifying new outbreaks and for evaluating the effectiveness of interventions. The incorporation of genomic technologies into STI surveillance offers great promise in defining transmission networks, including those caused by antimicrobial-resistant pathogens, and may allow improved targeting of public health interventions. Experience from the global response to HIV infection suggests that adequate control of STIs can be achieved only through genuine partnerships among governments, nongovernmental organizations, and the private sector, together with community participation and engagement.

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## REFERENCES

1. Eyre DW, Town K, Street T, et al. Detection in the United Kingdom of the *Neisseria gonorrhoeae* FC428 clone, with ceftriaxone resistance and intermediate resistance to azithromycin, October to December 2018. Euro Surveill 2019;24(10):1900147.
2. Beymer MR, Weiss RE, Bolan RK, et al. Sex on demand: geosocial networking phone apps and risk of sexually transmitted infections among a cross-sectional sample of men who have sex with men in Los Angeles County. Sex Transm Infect 2014;90:567-72.
3. Werner RN, Gaskins M, Nast A, Dressler C. Incidence of sexually transmitted infections in men who have sex with men and who are at substantial risk of HIV infection ó a meta-analysis of data from trials and observational studies of HIV pre-exposure prophylaxis. PLoS One 2018;13(12):e0208107.
4. Ingle DJ, Easton M, Valcanis M, et al. Co-circulation of multidrug-resistant *Shigella* among men who have sex with men, Australia. Clin Infect Dis 2019;69:1535-44.
5. Murray K, Reddy V, Kornblum JS, et al. Increasing antibiotic resistance in Shigella spp. from infected New York City residents, New York, USA. Emerg Infect Dis 2017;23:332-5.
6. Bowen A, Grass J, Bicknese A, Campbell D, Hurd J, Kirkcaldy RD. Elevated risk for antimicrobial drug-resistant *Shigella* infection among men who have sex with men, United States, 2011-2015. Emerg Infect Dis 2016;22:1613-6.
7. Arag n TJ, Vugia DJ, Shallow S, et al. Case-control study of shigellosis in San Francisco: the role of sexual transmission and HIV infection. Clin Infect Dis 2007;44:327-34.
8. Gilbart VL, Simms I, Jenkins C, et al. Sex, drugs and smart phone applications:

findings from semistructured interviews with men who have sex with men diagnosed with *Shigella flexneri* 3a in England and Wales. Sex Transm Infect 2015;91:598-602.
**9.** Wu H-H, Shen Y-T, Chiou C-S, Fang C-T, Lo Y-C. Shigellosis outbreak among MSM living with HIV: a case-control study in Taiwan, 2015-2016. Sex Transm Infect 2019;95:67-70.
**10.** Mohan K, Hibbert M, Rooney G, et al. What is the overlap between HIV and shigellosis epidemics in England: further evidence of MSM transmission? Sex Transm Infect 2018;94:67-71.
**11.** Chiou C-S, Izumiya H, Kawamura M, et al. The worldwide spread of ciprofloxacin-resistant *Shigella sonnei* among HIV-infected men who have sex with men, Taiwan. Clin Microbiol Infect 2016;22(4):383.e11-383.e16.
**12.** Baker KS, Dallman TJ, Ashton PM, et al. Intercontinental dissemination of azithromycin-resistant shigellosis through sexual transmission: a cross-sectional study. Lancet Infect Dis 2015;15:913-21.
**13.** Williamson D, Ingle D, Howden B. Extensively drug-resistant shigellosis in Australia among men who have sex with men. N Engl J Med 2019;381:2477-9.
**14.** Hepatitis A outbreaks in the EU/EEA mostly affecting men who have sex with men: third update, 28 June 2017. Stockholm: European Centre for Disease Prevention and Control, 2017 (https://www.ecdc.europa.eu/sites/portal/files/documents/RRA%20hep%20A%20outbreak%20EU%20EEA%20in%20MSM%20third%20update%2028%20June%202017_0.pdf).
**15.** Ndumbi P, Freidl GS, Williams CJ, et al. Hepatitis A outbreak disproportionately affecting men who have sex with men (MSM) in the European Union and European Economic Area, June 2016 to May 2017. Euro Surveill 2018;23:27.
**16.** Chen W-C, Chiang P-H, Liao Y-H, et al. Outbreak of hepatitis A virus infection in Taiwan, June 2015 to September 2017. Euro Surveill 2019;24(14):1800133.
**17.** Rivas V, Barrera A, Pino K, et al. Hepatitis A outbreak since November 2016 affecting men who have sex with men (MSM) in Chile connected to the current outbreak in MSM in Europe, situation up to October 2017. Euro Surveill 2018;23(9):18-00060.
**18.** Foster MA, Hofmeister MG, Kupronis BA, et al. Increase in hepatitis A virus infections ó United States, 2013 2018. MMWR Morb Mortal Wkly Rep 2019;68:413-5.
**19.** Chen G-J, Lin K-Y, Hung C-C, Chang S-C. Hepatitis A outbreak among men who have sex with men in a country of low endemicity of hepatitis A infection. J Infect Dis 2017;215:1339-40.
**20.** Ruscher C, Werber D, Thoulass J, et al. Dating apps and websites as tools to reach anonymous sexual contacts during an outbreak of hepatitis A among men who have sex with men, Berlin, 2017. Euro Surveill 2019;24(21):1800460.
**21.** Brennan J, Moore K, Sizemore L, et al. Acute hepatitis A virus infection among previously vaccinated persons with HIV infection ó Tennessee, 2018. MMWR Morb Mortal Wkly Rep 2019;68:328-9.
**22.** Gaudreau C, Rodrigues-Coutl e S, Pilon PA, Coutl e F, Bekal S. Long-lasting outbreak of erythromycin- and ciprofloxacin-resistant *Campylobacter jejuni* subspecies *jejuni* from 2003 to 2013 in men who have sex with men, Quebec, Canada. Clin Infect Dis 2015;61:1549-52.
**23.** Simms I, Gilbart VL, Byrne L, et al. Identification of verocytotoxin-producing *Escherichia coli* O117:H7 in men who have sex with men, England, November 2013 to August 2014. Euro Surveill 2014;19(43):20946.
**24.** Escol -Verg L, Arando M, Vall M, et al. Outbreak of intestinal amoebiasis among men who have sex with men, Barcelona (Spain), October 2016 and January 2017. Euro Surveill 2017;22(30):30581.
**25.** Hung CC, Chang SY, Ji DD. *Entamoeba histolytica* infection in men who have sex with men. Lancet Infect Dis 2012;12:729-36.
**26.** Shea S, Kubota KA, Maguire H, et al. Clinical microbiology laboratories adoption of culture-independent diagnostic tests is a threat to foodborne-disease surveillance in the United States. J Clin Microbiol 2017;55:10-9.
**27.** Newman KL, Newman GS, Cybulski RJ, Fang FC. Gastroenteritis in men who have sex with men in Seattle, Washington, 2017-2018. Clin Infect Dis 2019 October 17 (Epub ahead of print).
**28.** Janda WM, Bohnoff M, Morello JA, Lerner SA. Prevalence and site-pathogen studies of Neisseria meningitidis and N gonorrhoeae in homosexual men. JAMA 1980;244:2060-4.
**29.** Toh E, Gangaiah D, Batteiger BE, et al. *Neisseria meningitidis* ST11 complex isolates associated with nongonococcal urethritis, Indiana, USA, 2015-2016. Emerg Infect Dis 2017;23:336-9.
**30.** Retchless AC, Kretz CB, Chang HY, et al. Expansion of a urethritis-associated *Neisseria meningitidis* clade in the United States with concurrent acquisition of *N. gonorrhoeae* alleles. BMC Genomics 2018;19:176.
**31.** Bazan JA, Turner AN, Kirkcaldy RD, et al. Large cluster of *Neisseria meningitidis* urethritis in Columbus, Ohio, 2015. Clin Infect Dis 2017;65:92-9.
**32.** Kamiya H, MacNeil J, Blain A, et al. Meningococcal disease among men who have sex with men ó United States, January 2012 June 2015. MMWR Morb Mortal Wkly Rep 2015;64:1256-7.
**33.** Koch J, Hellenbrand W, Schink S, et al. Evaluation of a temporary vaccination recommendation in response to an outbreak of invasive meningococcal serogroup C disease in men who have sex with men in Berlin, 2013-2014. Euro Surveill 2016;21:12-22.
**34.** Nanduri S, Foo C, Ngo V, et al. Outbreak of Serogroup C meningococcal disease primarily affecting men who have sex with men ó Southern California, 2016. MMWR Morb Mortal Wkly Rep 2016;65:939-40.
**35.** Folaranmi TA, Kretz CB, Kamiya H, et al. Increased risk for meningococcal disease among men who have sex with men in the United States, 2012-2015. Clin Infect Dis 2017;65:756-63.
**36.** Miglietta A, Fazio C, Neri A, et al. Interconnected clusters of invasive meningococcal disease due to *Neisseria meningitidis* serogroup C ST-11 (cc11), involving bisexuals and men who have sex with men, with discos and gay-venues hotspots of transmission, Tuscany, Italy, 2015 to 2016. Euro Surveill 2018;23(34):1700636.
**37.** Ma KC, Unemo M, Jeverica S, et al. Genomic characterization of urethritis-associated *Neisseria meningitidis* shows that a wide range of *N. meningitidis* strains can cause urethritis. J Clin Microbiol 2017;55:3374-83.
**38.** Bozio CH, Blain A, MacNeil J, et al. Meningococcal disease surveillance in men who have sex with men ó United States, 2015 2016. MMWR Morb Mortal Wkly Rep 2018;67:1060-3.
**39.** MacNeil JR, Rubin LG, Patton M, Ortega-Sanchez IR, Martin SW. Recommendations for use of meningococcal conjugate vaccines in HIV-infected persons ó Advisory Committee on Immunization Practices, 2016. MMWR Morb Mortal Wkly Rep 2016;65:1189-94.
**40.** Simons R, Candfield S, French P, White JA. Observed treatment responses to short-course doxycycline therapy for rectal lymphogranuloma venereum in men who have sex with men. Sex Transm Dis 2018;45:406-8.
**41.** de Vries HJC. Lymphoganuloma venereum in the Western world, 15 years after its re-emergence: new perspectives and research priorities. Curr Opin Infect Dis 2019;32:43-50.
**42.** Spaargaren J, Schachter J, Moncada J, et al. Slow epidemic of lymphogranuloma venereum L2b strain. Emerg Infect Dis 2005;11:1787-8.
**43.** Hughes G, Alexander S, Simms I, et al. Lymphogranuloma venereum diagnoses among men who have sex with men in the U.K.: interpreting a cross-sectional study using an epidemic phase-specific framework. Sex Transm Infect 2013;89:542-7.
**44.** European Centre for Disease Prevention and Control. Lymphogranuloma venereum. In: Annual epidemiological report for 2016. Stockholm: ECDC, 2018 (https://www.ecdc.europa.eu/sites/default/files/documents/AER_for_2016-lymphogranuloma-venereum.pdf).

**45.** de Vries HJC, de Barbeyrac B, de Vrieze NHN, et al. 2019 European guideline on the management of lymphogranuloma venereum. J Eur Acad Dermatol Venereol 2019;33:1821-8.
**46.** Bissessor M, Fairley CK, Read T, Denham I, Bradshaw C, Chen M. The etiology of infectious proctitis in men who have sex with men differs according to HIV status. Sex Transm Dis 2013;40:768-70.
**47.** Leeyaphan C, Ong JJ, Chow EP, et al. Systematic review and meta-analysis of doxycycline efficacy for rectal lymphogranuloma venereum in men who have sex with men. Emerg Infect Dis 2016;22:1778-84.
**48.** Handsfield HH. Lymphogranuloma venereum treatment and terminology. Sex Transm Dis 2018;45:409-11.
**49.** Tully JG, Taylor-Robinson D, Cole RM, Rose DL. A newly discovered mycoplasma in the human urogenital tract. Lancet 1981;1:1288-91.
**50.** Gaydos CA, Manhart LE, Taylor SN, et al. Molecular testing for *Mycoplasma genitalium* in the United States: results from the AMES Prospective Multicenter Clinical Study. J Clin Microbiol 2019;57(11):e01125-e19.
**51.** Golden MR, Workowski KA, Bolan G. Developing a public health response to *Mycoplasma genitalium.* J Infect Dis 2017;216:suppl_2:S420-S426.
**52.** Jensen JS, Cusini M, Gomberg M, Moi H. 2016 European guideline on *Mycoplasma genitalium* infections. J Eur Acad Dermatol Venereol 2016;30:1650-6.
**53.** Taylor-Robinson D, Jensen JS. *Mycoplasma genitalium*: from chrysalis to multicolored butterfly. Clin Microbiol Rev 2011;24:498-514.
**54.** Durukan D, Read TRH, Murray G, et al. Resistance-guided antimicrobial therapy using doxycycline-moxifloxacin and doxycycline-2.5g azithromycin for the treatment of Mycoplasma genitalium infection: efficacy and tolerability. Clin Infect Dis 2019 October 20 (Epub ahead of print).
**55.** Dionne-Odom J, Geisler WM, Aaron KJ, et al. High prevalence of multidrug-resistant *Mycoplasma genitalium* in human immunodeficiency virus-infected men who have sex with men in Alabama. Clin Infect Dis 2018;66:796-8.
**56.** Soni S, Horner P, Rayment M, et al. British Association for Sexual Health and HIV national guideline for the management of infection with *Mycoplasma genitalium* (2018). Int J STD AIDS 2019;30:938-50.
**57.** Murray GL, Bradshaw CS, Bissessor M, et al. Increasing macrolide and fluoroquinolone resistance in *Mycoplasma genitalium.* Emerg Infect Dis 2017;23:809-12.
**58.** Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika virus and birth defects ó reviewing the evidence for causality. N Engl J Med 2016;374:1981-7.
**59.** Foy BD, Kobylinski KC, Chilson Foy JL, et al. Probable non-vector-borne transmission of Zika virus, Colorado, USA. Emerg Infect Dis 2011;17:880-2.
**60.** Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus. Emerg Infect Dis 2015;21:359-61.
**61.** D Ortenzio E, Matheron S, Yazdanpanah Y, et al. Evidence of sexual transmission of Zika virus. N Engl J Med 2016;374:2195-8.
**62.** Moreira J, Peixoto TM, Siqueira AM, Lamas CC. Sexually acquired Zika virus: a systematic review. Clin Microbiol Infect 2017;23:296-305.
**63.** Paz-Bailey G, Rosenberg ES, Doyle K, et al. Persistence of Zika virus in body fluids ó final report. N Engl J Med 2017;379:1234-43.
**64.** WHO guidelines for the prevention of sexual transmission of Zika virus: executive summary. Geneva: World Health Organization, 2019 (https://apps.who.int/iris/bitstream/handle/10665/311026/WHO-RHR-19.4-eng.pdf?ua=1).
**65.** Ebola virus disease fact sheet. Geneva: World Health Organization, 2020 (https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease).
**66.** Sissoko D, Duraffour S, Kerber R, et al. Persistence and clearance of Ebola virus RNA from seminal fluid of Ebola virus disease survivors: a longitudinal analysis and modelling study. Lancet Glob Health 2017;5(1):e80-e88.
**67.** Mate SE, Kugelman JR, Nyenswah TG, et al. Molecular evidence of sexual transmission of Ebola virus. N Engl J Med 2015;373:2448-54.
**68.** Report on global sexually transmitted infection surveillance 2018. Geneva: World Health Organization, 2018 (https://www.who.int/reproductivehealth/publications/stis-surveillance-2018/en/).
**69.** Sexually transmitted disease surveillance 2018. Atlanta: Centers for Disease Control and Prevention, 2018.
**70.** Stafford IA, S nchez PJ, Stoll BJ. Ending congenital syphilis. JAMA 2019 November 11 (Epub ahead of print).
**71.** US Preventive Services Task Force. Screening for syphilis infection in nonpregnant adults and adolescents: US Preventive Services Task Force recommendation statement. JAMA 2016;315:2321-7.
**72.** Towns JM, Leslie DE, Denham I, Azzato F, Fairley CK, Chen M. Painful and multiple anogenital lesions are common in men with *Treponema pallidum* PCR-positive primary syphilis without herpes simplex virus coinfection: a cross-sectional clinic-based study. Sex Transm Infect 2016;92:110-5.
**73.** Golden M, O Donnell M, Lukehart S, et al. *Treponema pallidum* nucleic acid amplification testing to augment syphilis screening among men who have sex with men. J Clin Microbiol 2019;57:57.
**74.** Yang CJ, Chang SY, Wu BR, et al. Unexpectedly high prevalence of *Treponema pallidum* infection in the oral cavity of human immunodeficiency virus-infected patients with early syphilis who had engaged in unprotected sex practices. Clin Microbiol Infect 2015;21(8):787.e1-787.e7.
**75.** Tao Y, Chen MY, Tucker JD, et al. A nationwide spatiotemporal analysis of syphilis over 21 years and implications for prevention and control in China. Clin Infect Dis 2020;70:136-9.
**76.** Beale MA, Marks M, Sahi SK, et al. Genomic epidemiology of syphilis reveals independent emergence of macrolide resistance across multiple circulating lineages. Nat Commun 2019;10:3255.
**77.** Antibiotic resistance threats in the United States, 2019. Atlanta: Centers for Disease Control and Prevention, 2019.
**78.** Jennison AV, Whiley D, Lahra MM, et al. Genetic relatedness of ceftriaxone-resistant and high-level azithromycin-resistant *Neisseria gonorrhoeae* cases, United Kingdom and Australia, February to April 2018. Euro Surveill 2019;24(8):1900118.
**79.** Chen MY, McNulty A, Avery A, et al. Solithromycin versus ceftriaxone plus azithromycin for the treatment of uncomplicated genital gonorrhoea (SOLITAIRE-U): a randomised phase 3 non-inferiority trial. Lancet Infect Dis 2019;19:833-42.
**80.** Taylor SN, Marrazzo J, Batteiger BE, et al. Single-dose zoliflodacin (ETX0914) for treatment of urogenital gonorrhea. N Engl J Med 2018;379:1835-45.
**81.** Taylor SN, Morris DH, Avery AK, et al. Gepotidacin for the treatment of uncomplicated urogenital gonorrhea: a phase 2, randomized, dose-ranging, single-oral dose evaluation. Clin Infect Dis 2018;67:504-12.