

Genital Mycoplasma, Shigellosis, Zika, Pubic Lice, and Other Sexually Transmitted Infections: Neither Gone Nor Forgotten

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Abstract: Most estimates of the combined burden and cost of sexually transmitted infections (STIs) in the United States have focused on 8 common STIs with established national surveillance strategies (chlamydia, gonorrhea, syphilis, trichomoniasis, genital herpes, human papillomavirus, and sexually transmitted human immunodeficiency virus and hepatitis B). However, over 30 STIs are primarily sexually transmitted or sexually transmissible. In this article, we review what is known about the burden of “other STIs” in the United States, including those where sexual transmission is not the primary transmission route of infection. Although the combined burden of these other STIs may be substantial, accurately estimating their burden due to sexual transmission is difficult due to diagnostic and surveillance challenges. Developing better estimates will require innovative strategies, such as leveraging existing surveillance systems, partnering with public health and academic researchers outside of the STI field, and developing methodology to estimate the frequency of sexual transmission, particularly for new and emerging STIs.

Monitoring the burden of sexually transmitted infections (STIs) in the United States is critical to inform and evaluate interventions and guide public health action. Most estimates of the combined burden of STIs in the United States have focused on eight common STIs with established national surveillance strategies (chlamydia, gonorrhea, syphilis, trichomoniasis, genital herpes, human papillomavirus and sexually transmitted human immunodeficiency virus [HIV], and hepatitis B)^{1–5}; however, there are over 30

pathogens that are sexually transmitted or transmissible,^{6–8} and these combined estimates underestimate the total burden and economic impact of STIs. “Other STIs” include infections that are primarily sexually transmitted in adults, but their public health significance has not been well established or there are no specific prevention or control programs for them (eg, pubic lice, *Mycoplasma genitalium*) and infections where sexual transmission is not the primary transmission route (eg, shigella, Zika). In this article, we describe what is known about the burden (eg, prevalence or incidence) of “other STIs” in the US based on a review of published articles and surveillance reports and identify strategies that could be used to better estimate their burden.

OTHER INFECTIONS THAT ARE PRIMARILY SEXUALLY TRANSMITTED IN ADULTS

Chancroid

Chancroid is caused by the Gram-negative bacterium *Haemophilus ducreyi* and is usually characterized by multiple painful anogenital ulcers that are often accompanied by regional lymphadenopathy or buboes.⁹ Complications include phimosis in men, further ulceration due to secondary bacterial infection, and infection and inflammation that can facilitate the acquisition and transmission of HIV. Transmission is primarily sexual through contact with open sores, although nonsexual transmission can occur.¹⁰ A definitive diagnosis requires the identification of *H. ducreyi* on special culture media that is not widely available from commercial sources; even when these media are used, sensitivity is less than 80%. No Food and Drug Administration (FDA)-cleared nucleic acid amplification test (NAAT) for *H. ducreyi* is available in the United States, but such testing can be performed by some clinical laboratories with a Clinical Laboratory Improvement Amendments waiver. There are multiple effective, first-line treatment regimens, including 2 single-dose regimens: azithromycin 1 g orally once and ceftriaxone 250 mg intramuscularly once.¹¹

Chancroid is nationally notifiable with case reports provided to the Centers for Disease Control and Prevention (CDC) through the Nationally Notifiable Disease Surveillance System (NNDSS). During the 1980s, localized outbreaks of chancroid occurred in the United States; some of which were linked to commercial sex work and case counts neared 5000 in 1987. Chancroid has declined in the United States since, and the annual number of reported cases has been less than 25 since 2010. In 2018, there were only 3 reported cases from 3 US states.¹² Although national in scope, chancroid case report data should be interpreted cautiously as some chancroid infections are likely missed because of diagnostic challenges; however, the CDC Atlanta STD laboratory reports no genital lesion specimens sent from US state or local jurisdictions for confirmatory NAAT have tested positive in more than 10 years (person communication, A. Pillay CDC), suggesting

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low burden of disease. Additionally, genital ulcerative disease (GUD) etiologic studies conducted since 2000 in various international settings have described a sustained reduction in the proportion of GUD caused by *H. ducreyi*.¹³ Understanding the burden of chancroid in the United States will be difficult without expanded access to diagnostics; sentinel surveillance and special studies could be used to establish point prevalence estimates.

Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is an ulcerative disease caused by infection with invasive *Chlamydia trachomatis* serovars L1–L3 and is sexually transmitted.¹⁴ Genital LGV is characterized by the presence of 1 or more transient genital ulcers or papules, typically followed by unilateral inguinal or femoral lymphadenopathy. Over the past decade, classical inguinal presentations of LGV in the United States have become increasingly uncommon with proctitis and proctocolitis now the more commonly reported clinical manifestations of LGV, particularly among gay, bisexual and other men who have sex with men (MSM). If untreated, LGV can lead to a systemic infection resulting in chronic colorectal fistulas and strictures.¹⁵ Currently, CDC recommends that LGV be treated with 100 mg doxycycline twice daily for 21 days.¹¹

Lymphogranuloma venereum, separate from *C. trachomatis*, is not a nationally notifiable condition and there is no routine national surveillance for LGV in the United States. Newer molecular methods to differentiate LGV (L1–L3) from non-LGV strains (A–K) are not widely available outside of research or specialized public health settings.^{16,17} Consequently, LGV diagnoses are largely based on medical history and clinical presentation, which can lead to misclassification since symptoms often overlap with that of other sexually transmitted diseases (STD) and some gastrointestinal disorders, like inflammatory syndrome. Further complicating surveillance, a notable proportion of infections are also asymptomatic (14%–27%)¹⁸ and likely undiagnosed and untreated. Published LGV burden estimates are limited to case reports and sentinel surveillance studies. Lymphogranuloma venereum appears common among MSM (eg, about one in five male anorectal chlamydial infections in New York City are estimated to be LGV¹⁹ but are likely less frequent among women.²⁰ Additional studies and expanded sentinel surveillance including symptomatic and asymptomatic men and women would help better understand the burden of LGV.

Mycoplasma genitalium

The bacterium *M. genitalium* is sexually transmitted and can infect the urogenital system of men and women, as well as the rectum. Infection can cause urethritis in men, often with dysuria, pruritus, and discharge; proctitis has been reported among MSM. Among women, infection can cause cervicitis and ascend into the upper genital tract leading to pelvic inflammatory disease. *M. genitalium* is difficult to culture and until recently, NAATs were only available in research settings. As a result, most infected patients are treated in the context of empiric treatment for urethritis or cervicitis, usually with an azithromycin-containing regimen; however, *M. genitalium* resistance to azithromycin is a growing concern.²¹ Infected patients failing first-line therapy are usually provided moxifloxacin, which has a higher cure rate.¹¹ In January 2019, the FDA approved a NAAT to diagnose *M. genitalium*, facilitating more targeted treatment of infected patients failing first line treatment.²²

Estimates of the burden of *M. genitalium* in the United States are limited to findings from special studies and clinic-based surveillance. Based on a population-based survey of adolescents

and young adults in 2001 to 2002, national prevalence was estimated to be 1.0% and was similar among men and women.²³ Clinic-based positivity estimates are higher. Among men presenting with urethritis in select STD clinics, 28.7% were positive for *M. genitalium*²⁴ and among high-risk women tested in an STD clinic in Seattle, 26% were found to be infected when tested.²⁵ A meta-analysis of prevalence among MSM found that urethral (5.0%) and rectal (6.2%) infections were more common than pharyngeal infections (1.0%).²⁶ Given recently expanded NAAT availability, sentinel surveillance and national surveys could be expanded to better establish the burden of *M. genitalium* in the United States.

Pubic Lice

Pubic lice are an infestation of the pubic hair caused by the blood sucking arthropod *Phthirus pubis*.²⁷ Bites cause itching, typically within the pubic hair, and occasionally results in discrete, erythematous lesions caused by scratching. The infestation, also known as “crabs,” is spread through sexual contact but may also spread by close and prolonged contact with items that have been used by an infested person, such as clothing, bedding, and towels. Topical permethrin lotion or pyrethrin with piperonyl butoxide are first-line treatments, though ivermectin and topical malathion may also be used if first-line therapy is not tolerated.¹¹ Sexual partners must also be treated and bedding decontaminated.

The prevalence of pubic lice in the United States is unknown. One prospective study performed in a Spanish STI unit from 1988 to 2001 demonstrated a yearly infestation rate of 1.3% to 4.6%.²⁸ Evidence suggests prevalence has fallen, in part, because of increased pubic hair removal. Rates in a British genitourinary clinic dropped significantly from 1997 to 2003 (odds ratio [OR], 0.41; 95% confidence interval [CI], 0.23–0.70), which was attributed to the popularity of the “Brazilian” wax starting in 2000 to 2001.²⁹ In another center in the United Kingdom, researchers found a continuous, significant fall in pubic lice incidence during 2003 to 2013, from 1.82% to 0.07%; moreover, a strong correlation between infestation and increased pubic hair removal was found ($r = 0.97$; 95% CI, 0.88–0.99).³⁰ In the United States, a nationally representative probability sample found 74% of respondents reported grooming their pubic hair.³¹ In this study, low-frequency grooming was associated with pubic lice (OR, 2.0; 95% CI, 1.3–3.1), but confounding may have been present. Careful combing through available data sources, such as military medical registries, might provide future clarity on the burden of pubic lice.

Granuloma Inguinale

The gram-negative bacterium *Klebsiella granulomatis* causes the GUD granuloma inguinale, also known as donovanosis.³² The disease is usually characterized by painless, ulcerative anogenital lesions that are highly vascular; subcutaneous granulomas (pseudobuboes) can also occur. Most diagnoses are presumptive based on clinical evaluation; confirmatory diagnoses require visualization of Donovan bodies on a crush preparation smear or biopsy. Currently there are no-FDA cleared molecular tests for *K. granulomatis*. Treatment with an antimicrobial regimen (eg, azithromycin or doxycycline) can halt the progression of lesions; however, prolonged treatment can be required for large lesions and relapse can occur.¹¹ There are no surveillance systems in place for *K. granulomatis*; however, transmission is thought to occur very rarely in the United States, with only a few case reports in recent years.³³

OTHER SEXUALLY TRANSMISSIBLE INFECTIONS

Scabies

Scabies is a skin infestation caused by the mite *Sarcoptes scabiei*.²⁷ The condition is characterized by an intensely itchy skin rash, usually worse at night, caused by female mites burrowing into the skin to lay their eggs. The rash is classically distributed in the axillae, bends of elbows and knees, genitalia, and in between fingers; however, heavier infestation (crusted scabies) can occur in the setting of cellular immunocompromise and results in thick crusting scales widely distributed on the skin. Scabies transmission usually occurs from direct, prolonged skin-to-skin contact, although it can occur through fomites. First-line treatment of scabies includes topical permethrin or oral ivermectin, and other agents can also be used.¹¹ Bedding and clothing should be decontaminated, and any sex partners within the previous month should also be treated.

Scabies is not a reportable disease in the United States, and information on prevalence is extremely limited. One study recently assessed the global burden of scabies using available prevalence estimates with a disability weight³⁴; this study demonstrated that disability-adjusted life years from scabies ranged from 0 to 10 per 100,000 persons in North America, including the United States, Canada, and Greenland. Another nationally representative analysis of persons visiting US emergency departments during 2013 to 2015 found 85.7 per 100,000 visits were due to scabies.³⁵ Additional analyses of existing data, including claims and electronic health record data, could be used to further define the burden of scabies; however, defining the burden of sexually transmitted scabies will be difficult.

Shigella spp.

Shigellosis is a diarrheal illness, caused by *Shigella* spp., which can present with abrupt onset of watery (and infrequently bloody) diarrhea, fever, and abdominal pain. Although transmission of *Shigella* spp. most commonly occurs through contaminated food and water, sexual transmission may occur. Sexual transmission of *Shigella* spp., particularly *S. flexneri* and *S. sonnei*, likely occurs through exposure to fecal material during sex by direct oral-anal contact, such as during anilingus (“rimming”), or indirect exposure (eg, anal fisting).³⁶ Shigellosis outbreaks, possibly owing to sexual transmission, have been reported among MSM.³⁷

In the United States, 16,333 shigellosis cases were reported in 2018.³⁸ Of these cases, 9,347 were among adolescents and adults aged 15 to 64 years. Additional demographic data are available for cases reported through FoodNet, which includes 10 sites covering 15% of the US population.³⁹ In 2018, 1,796 cases were reported to FoodNet among persons 10–64 years of age; 153 cases were among those 10 to 19 (2.4 per 100,000) and 1,643 were among those 20 to 64 (5.5 per 100,000). Among those 10 to 64 years of age, shigellosis cases and rates were higher among men than women, suggesting possible elevated shigellosis rates among MSM. Among men, 1282 shigellosis cases (7.1 per 100,000) were reported; among women, 511 cases (2.8 per 100,000) were reported. However, rates are based on diagnosed and reported infections and likely underestimate the incidence of shigellosis infections. Infections may be mild and/or self-limited, not all persons with shigellosis seek medical care, and healthcare providers may not obtain specimens for laboratory testing.⁴⁰ Data on gender of sex partners, recent sexual behavior, and suspected sexual transmission for each case are not routinely reported as part of shigellosis case reporting in the United States. Thus, data are lacking on the number and proportion of cases (among men and women) that were likely sexually transmitted. Sentinel and enhanced surveillance to collect behavioral data among diagnosed cases could help better understand the burden of sexually transmitted shigella.

Giardia lamblia

G. lamblia is a protozoan parasite that causes sporadic or epidemic diarrheal illness (referred to as giardiasis). Symptoms include diarrhea, malaise, steatorrhea, and abdominal cramping. Chronic giardiasis can cause malabsorption and substantial weight loss. Sexual transmission through direct or indirect fecal exposure may occur, particularly among MSM.^{41–43}

In 2018, 15,579 giardiasis cases were reported to CDC; 9561 from males, 5966 from females.⁴⁴ Among persons aged 15 to 64 years, 10,747 cases were reported. Reported cases likely underestimate disease incidence; previous estimates suggest only ~1.6% of giardia infections were diagnosed and reported.³⁸ There are insufficient data on gender of sex partners and recent sexual behavior to identify the likely route of transmission among reported cases; therefore, the burden of sexually transmitted giardiasis is unknown. Collecting behavioral data among a representative sample of diagnosed cases could help better understand the burden of sexually transmitted giardiasis.

Neisseria meningitidis

Neisseria meningitidis is a gram-negative diplococcus that can cause systemic invasive disease, including meningitis and meningococemia. *N. meningitidis* has also been identified as a cause of localized urogenital disease, such as urethritis and cervicitis, since the 1940s.⁴⁵ Symptoms of meningococcal urethritis can be similar to gonorrhea, with discharge, dysuria, urinary frequency, and urgency. Both pathogens are gram-negative intracellular diplococci and appear identical on Gram stain; differentiation is only possible through molecular or confirmatory testing on cultured isolates. Because of the similar symptoms and morphology of the organisms, meningococcal urethritis may be misidentified as *N. gonorrhoeae*. Meningococcal urethritis is usually treated with the same antimicrobial regimen as gonococcal urethritis.⁴⁶ Current evidence is limited to case reports or single clinic assessments regarding the risk of sexual transmission or recurrent infections with meningococcal urethritis. Because of this lack of systematic surveillance, there is limited information to inform public health guidance. Some experts recommend treating sex partners of patients with meningococcal urethritis with the same regimens as for exposure to gonorrhea.¹¹

The prevalence of meningococcal urethritis is unknown. Unlike gonorrhea, meningococcal urethritis is not a reportable condition. The CDC has conducted surveillance through select clinics involved in gonococcal sentinel surveillance to assess the prevalence of and characterize meningococcal urethritis; results are forthcoming. A preliminary evaluation at 2 STI clinics showed that 1.5% to 2.0% of men with suspected gonorrhea were subsequently diagnosed with meningococcal urethritis. (personal communication; S. Oliver, CDC) However, these estimates are not nationally representative. With more than 500,000 cases of gonorrhea reported in the United States each year,¹² there could be thousands of unrecognized cases of meningococcal urethritis. Continuing to leverage existing enhanced *N. gonorrhoeae* sentinel surveillance systems could help further inform the burden of meningococcal urethritis.

Hepatitis A

Hepatitis A is a vaccine-preventable disease caused by the hepatitis A virus (HAV). When symptoms are present, they are indistinguishable from other viral hepatitis infections and can include fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, dark urine, diarrhea, clay-colored bowel movements, joint pain, and jaundice. When present, symptoms usually last less than 2 months, although 10% to 15% of symptomatic persons have

prolonged or relapsing illness lasting up to 6 months.^{47–51} Although most cases of hepatitis A are mild, some can be severe enough to result in hospitalization or, in rare cases, death.⁵² Hepatitis A virus replicates in the liver and is shed in the stool, resulting in transmission primarily through the fecal-oral route.⁵³ Although exposures to food or water contaminated with HAV can cause common-source outbreaks, person-to-person transmission is the most common route of transmission in the United States. Epidemiologic and molecular data implicate certain sexual practices as important modes of transmission, including oral-anal contact, digital-anal contact, and anal intercourse.⁵³

Although hepatitis A is a nationally notifiable disease, underdiagnosis results in underreporting through NNDSS.⁵² Furthermore, data on risk are missing for many reported cases limiting accurate characterization and monitoring of associated risk behaviors. In 2018, 12,474 cases of hepatitis A were reported, far less than the expected 24,900 (95% CI, 17,500–27,400) HAV infections. Among the reported cases in 2018, risk data were missing for 26%.⁵² For those case reports that contained data on risk, the most common risks or behaviors reported (not mutually exclusive) were injection-drug use (50.1%), being a man who has sex with men (12.5%), having nonsexual or nonhousehold contact with a person known to have hepatitis A (6.2%), or sexual contact with a person known to have hepatitis A (5.9%). Seroprevalence of HAV infection in STD clinic settings ranges from 30% to 40%.^{54–61} and hepatitis A outbreaks among MSM are common. The large increases in hepatitis A incidence in recent years highlights the importance of vaccination and emphasizes the need for improvements in public health surveillance that can improve outbreak identification and response, including better collection of behavioral data among diagnosed cases.

Hepatitis C

Hepatitis C is a bloodborne infection caused by the hepatitis C virus (HCV). More than half of persons who become infected with HCV will develop chronic infection which, if left untreated, can progress into severe liver disease.^{61, 62} Because this chronic disease process usually occurs slowly and without any symptoms, CDC recommends that all adults be screened at least once in their lifetime for hepatitis C.⁶³ Injection drug use is the most common means of HCV transmission in the United States.⁶⁴ Although compared with hepatitis B virus, HCV is less efficiently sexually transmitted, high-risk behaviors such as unprotected anal sex, primarily among persons with HIV are also important modes of transmission for HCV.^{64, 65} Other possible exposures include invasive medical procedures without proper infection-control procedures, birth to a mother with hepatitis C, needlestick injuries among healthcare personnel, and sharing of personal items contaminated with blood (eg, razors).⁶³

Without routine screening, hepatitis C goes largely undiagnosed and thus is difficult to capture accurately in surveillance systems.^{52, 66} In 2018, 3621 acute hepatitis C cases were reported in NNDSS, far fewer than the estimated 50,300 (95% CI, 39,800–171,600) HCV infections.⁵² Risk data were missing for almost half (49%) of these reported cases. Among case reports with data on risk, the most common risks or behaviors reported (not mutually exclusive) were injection drug use (71.8%), having multiple sex partners (31.5%), or having sexual contact with a person known to have hepatitis C (27.4%). However, given the cocurrence of many of these risk factors, the extent to which hepatitis C is transmitted sexually has been difficult to characterize. A meta-analysis of literature from 1995 to 2009 revealed that after adjusting for other risk factors (eg, injection drug use) there was no increased risk of sexual transmission of HCV among

heterosexual couples in regular relationships.⁶⁷ However, this same analysis revealed increased risk of sexual transmission among several other groups, including persons with multiple sex partners (adjusted OR [aOR] range, 2.2–2.9), women with HIV or other STIs (aOR range, 3.3–3.9), and men infected with HIV who have sex with men (aOR range, 4.1–5.7). In general, sexual transmission of HCV seems to be inefficient but may occur more frequently in the presence of HIV and other STI coinfections or during sexual practices that can result in mucosal damage or result in exposure to blood.⁵³

Ebola

Ebola virus disease (EVD) is a deadly viral hemorrhagic disease spread by direct contact with the body fluids of an infected person. Ebola virus disease was first identified in the Democratic Republic of Congo in 1976 and recent outbreaks have been sporadic and have occurred primarily in Africa.⁶⁸ Most EVD survivors clear their infections from their blood stream shortly after symptom resolution. However, anatomic sites such as the eyes, brain, and testes may harbor persistent virus.⁶⁹ Although there have been anecdotal reports of sexual transmission of EVD from male survivors to their sexual partners, a well-documented case in Liberia provided strong evidence that sexual transmission is possible.^{7, 70} Several cohort studies have further established the evidence that the Ebola virus does persist in semen, with some estimates up to 40 months after release from an Ebola Treatment Unit.^{71–73}

The proportion of EVD cases that result from sexual transmission is unknown, although it is believed to be small.⁶⁹ A recent modeling study suggests that 3% to 7% of the overall reproductive rate for Ebola could be attributed to sexual transmission.⁷⁴ World Health Organization recommends male EVD survivors should be offered semen testing and abstain from unprotected sexual activity until 2 consecutive semen specimens test negative for the Ebola virus.⁷⁵ Ensuring robust surveillance of mode of transmission and refining mathematical models will be helpful to determine the burden of sexually transmitted EVD in future outbreaks.

Zika

The Zika virus (ZIKV) is a flavivirus transmitted primarily by the *Aedes Culicidae* mosquito.⁷⁶ Although most people infected with ZIKV will have mild symptoms (eg, fever, muscle pain) or will be asymptomatic, infection can be passed from a pregnant person to her fetus potentially resulting in severe microcephaly, decreased brain tissue, and vision damage.⁷⁶ Zika virus was first isolated in 1947 and occurred sporadically in Africa and Asia until outbreaks were reported in Micronesia and French Polynesia beginning in 2007.^{77, 78} A large outbreak in Brazil was identified in 2015 affecting 440,000 to 1.3 million people.⁷⁹ Although primarily vector-borne, several documented sexually transmitted cases have been reported.⁸⁰ The first case of sexually transmitted ZIKV was reported in 2008.⁸¹ Sexual transmission has now been reported in 36 human couples, the majority involving male-to-female transmission^{8, 80}; however, the contribution of sexual transmission to overall ZIKV incidence is unknown. The CDC recommends that couples planning to conceive wait at least 3 months after the male partners travel or experience symptom onset; for that time, couples should either use condoms or abstain from sex.⁸² Mathematical modeling of the contribution of sexual transmission to overall ZIKV transmission could help inform estimates of the burden in the United States.

OTHER SEXUALLY TRANSMISSIBLE INFECTIONS

There are numerous other pathogens that are sexually transmissible in adults, including bacteria such as *Staphylococcus*

aureus, *Campylobacter* spp., and *Salmonella enterica*, viruses, such as Molluscum contagiosum and cytomegalovirus, and protozoa, such as *Entamoeba histolytica*.^{6, 82, 84} As with other infections where sexual contact is not the primary mode of transmission, it is difficult to estimate the sexually transmitted burden of these infections. It is likely that the burden of sexual transmission of these infections is low in the United States, relative to other STIs, such as chlamydia and human papillomavirus; however, some may be associated with significant economic costs given diagnostic and treatment challenges. Ensuring that existing surveillance platforms are flexible and adaptable would allow for periodic special studies to inform burden estimates for these other sexually transmissible infections.

CONCLUSIONS

Recent estimates of the burden of eight common STIs in the United States are substantial, with an estimated 67.6 million prevalent and 26.2 million incident infections³ and an annual direct medical cost of \$16.0 billion in 2018⁵; however, these estimates exclude the burden of other STIs, including infections that can lead to severe sequelae. When discussing the burden of STIs in the United States, it is important to highlight that published combined estimates, such as the ones published in this special issue, represent the minimum burden of STIs in the United States.

However, accurately estimating the burden of other STIs is difficult. As described above, diagnostic and surveillance challenges are common, particularly for pathogens whose primary route of transmission is not sexual. Developing better estimates will require innovative strategies, such as leveraging existing surveillance systems to include other STIs, partnering with public health and academic researchers outside of the STD field, such as communicable disease and enteric experts, developing methodology to estimate the frequency of sexual transmission, particularly for new and emerging STIs, as well as considering data sources increasingly being recognized for public health use, such as examining trends in internet search data and conducting content analysis of online discussion forums.^{85, 86}

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For further references, please see “Supplemental References,” <http://links.lww.com/OLQ/A608>.