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Sexually transmitted infections and female reproductive health

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Women are disproportionately affected by sexually transmitted infections (STIs) throughout life. In addition to their high prevalence in women, STIs have debilitating effects on female reproductive health due to female urogenital anatomy, socio-cultural and economic factors. In this Review, we discuss the prevalence and impact of non-HIV bacterial, viral and parasitic STIs on the reproductive and sexual health of cisgender women worldwide. We analyse factors affecting STI prevalence among transgender women and women in low-income settings, and describe the specific challenges and barriers to improved sexual health faced by these population groups. We also synthesize the latest advances in diagnosis, treatment and prevention of STIs.

Sexually transmitted infections (STIs) cause reproductive morbidity worldwide. In 2019, the World Health Organization (WHO) estimated that there were 376 million new episodes of chlamydia, gonorrhoea, syphilis and trichomoniasis (Fig. 1)[1]. In 2019, the United States Centers for Disease Control and Prevention (CDC) reported a nearly 30% increase in chlamydia, gonorrhoea and syphilis between 2015–2019 and a rising incidence of all STIs for the sixth consecutive year[2]. In the United States in 2018, several STIs were estimated to be more prevalent among women than men, including gonorrhoea, chlamydia and trichomoniasis[3]. Women often experience complications from STIs, including infertility and chronic pelvic pain, that can have lifelong impact[4]. STIs can increase peripartum morbidity and mortality in both industrialized areas and in rural and underserved areas of developed countries.

The larger impact of STIs in women compared with men is in part due to the female anatomy (Fig. 2). A woman's urogenital anatomy is more exposed and vulnerable to STIs compared with the male urogenital anatomy, particularly because the vaginal mucosa is thin, delicate and easily penetrated by infectious agents[5]. The cervix at the distal end of the vagina leads to the upper genital tract including the uterus, endometrium, fallopian tubes and ovaries. STIs can produce a variety of symptoms and effects at different parts of the female reproductive tract, including genital ulcer disease, vaginitis, pelvic inflammatory disease (PID) and infertility[6].

In this Review, we focus on the impact of non-HIV bacterial, viral and parasitic STIs on the sexual and reproductive health of cisgender women (Table 1). We discuss adverse outcomes of STIs, treatment and prevention, including vaccine development. STIs in transgender women (TGW) are discussed in brief because an exhaustive review of STIs in this population has recently been published[7,8]. We do not review developments in HIV prevention or treatments in women and refer readers to reviews published elsewhere[9–13]. Hepatitis B was also excluded as it would merit its own dedicated review.

Viral STIs

HPV. Human papilloma virus (HPV) is a small circular double-stranded DNA papilloma virus that infects cutaneous or mucosal epithelial tissues in humans[14]. More than 200 genotypes of HPV have been identified, including at least 40 that affect the genitals, and are grouped into high- or low-risk[15]. Although HPV infection is often asymptomatic and self-limiting, symptoms can include anogenital warts, respiratory papillomatosis, and precancerous or cancerous cervical, penile, vulvar, vaginal, anal and oropharyngeal lesions[16]. HPV is the most common STI worldwide, with most sexually active people exposed to it during their lifetime[17]. Among women, HPV prevalence is highest among those in low- and middle-income countries (LMICs), peaking at <25 years old[18]. While most women clear HPV spontaneously, persistent infection can cause cervical, anal, or head and neck cancer[19]. Cervical cancer has been a leading cause of mortality among women for decades; in 2012, there were 266,000 HPV-related cervical cancer deaths worldwide, accounting for 8% of all female cancer deaths that year[20]. Cervical cancer also causes substantial genitourinary morbidity, including radiation treatment-related infertility and urinary or faecal incontinence[21]. Persistent infection with high-risk HPV types is responsible for 99.7% of cervical squamous cell cancer cases[22].

In women with HPV, one factor that increases the risk of progression to cervical cancer is co-infection with a different STI[23]. HIV, for example, increased the oncogenic potential of HPV, especially in immunosuppressed women[24]. Women adherent to antiretroviral therapy are less likely to acquire high-risk HPV types, and progression to pre-malignant or malignant lesions is reduced[25]. In HIV-negative women, persistent HPV increases the risk of acquiring HIV, but the underlying mechanism is unclear[23]. Persistent HPV and *Chlamydia trachomatis* co-infection has also been proposed as a cofactor in the progression of cervical malignancy in women, with chronic inflammation as a mediating factor[26]. For these reasons, primary prevention using HPV vaccination is essential.

HPV vaccine development is one the most important medical achievements of the twenty-first century. Universal HPV vaccination has the potential to prevent between 70% to 90% of HPV-related disease, including anogenital warts and HPV-associated cancers[27]. The global strategy of the WHO is to vaccinate 90% of females by age 15, in addition to screening and treating older females, with the goal of eliminating cervical cancer in the next century[28]. There are four available HPV vaccines: Gardasil (Merck, 2006), Ceravrix (GlaxoSmithKline, 2007), Gardasil 9 (Merck, 2014) and Cecolin (Xiamen Innovax Biotech Co., 2021)[27]. All offer protection against HPV16 and HPV18 high-risk genotypes, which account for 66% of all cervical cancers (Table 2). Gardasil 9 targets 5 additional

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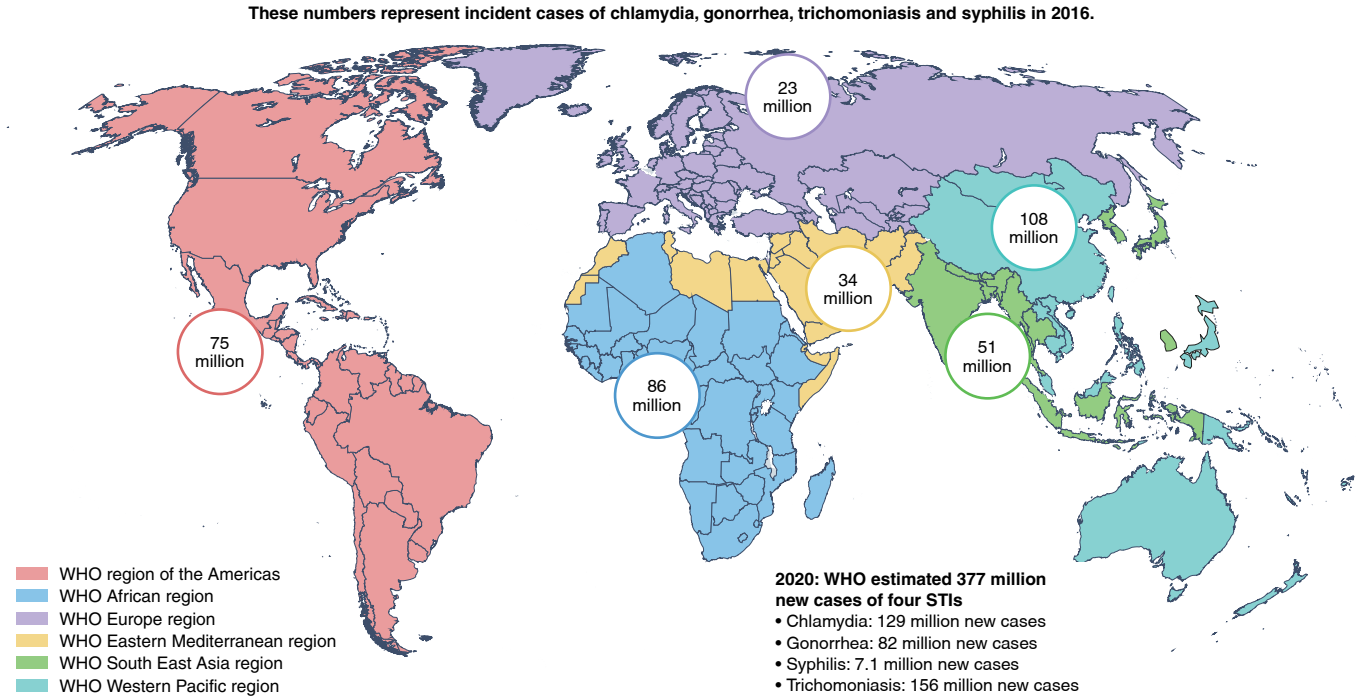

Fig. 1 | Incident cases of chlamydia, gonorrhoea, trichomoniasis and syphilis in 2016. WHO global regions and the incident cases of four STIs (chlamydia, gonorrhoea, trichomoniasis and syphilis) from 2016 estimates. The WHO estimates of new cases of these four STIs worldwide in 2020 are shown at the bottom right of the figure.

oncogenic HPV types (HPV31, 33, 45, 52, 58) that account for another 15% of cervical cancers. Gardasil products also offer protection against HPV6 and HPV11, which cause >90% of genital warts[16]. Cervarix and Cecolin offer protection only against HPV16 and HPV18[29].

HPV vaccination programmes have resulted in a profound reduction in pre-malignant and malignant cancers in women[30]. In England since 2008, HPV immunization has been routinely recommended for girls aged 12–13 years, with a catch-up programme at 14–18 years. A 2019 observational study of this population reported that for those vaccinated at ages 12–13, there was an estimated 87% relative reduction in cervical cancer rates and a 97% risk reduction for cervical intraepithelial neoplasia 3 compared with a reference unvaccinated cohort. Among vaccinated cohorts in the same study, since 2008, investigators estimated 448 fewer cervical cancers and 17,235 fewer cervical intraepithelial neoplasia 3 cases than expected by 2019[31]. The study authors concluded that the immunization programme in England has almost eliminated cervical cancer in women born since 1995. Programmes in Denmark and Sweden have reported similar levels of success[30].

These findings show that elimination of cervical cancer in the short term is possible with primary prevention programmes, at least in adequately resourced countries. In other settings, infrastructural and cultural challenges can make establishment of such programmes difficult. Efforts to implement HPV vaccination programmes in all areas are essential, especially to vaccinate girls before sexual debut and complete all doses in the vaccination series[32].

HPV-related anal cancer is also of concern for women, especially those with HIV[33]. HPV has been linked to 80% of anal cancer cases in the United States[34]. Women living with HIV have a 7.8-fold higher risk of anal carcinoma in situ and a 10-fold higher risk of anal squamous cell carcinoma compared with women without HIV[35,36]. In contrast to cervical cancer, it is less clear whether screening for HPV-associated precancerous lesions will impact the incidence of anal cancers. The Anal Cancer HSIL Outcomes Research (ANCHOR) study is an ongoing trial investigating whether treatment of precancerous high-grade squamous intraepithelial lesions (HSIL) is effective in reducing the incidence of anal cancer in people with HIV, including women (NCT02135419). Preliminary results in 4,446 participants demonstrated that removal of HSILs identified on screening anal Papanicolaou smears notably reduced the risk of progression to anal cancer[37]. Currently, there are no routine screening recommendations for anal cancer for women[16].

Detection of high-risk HPV based on cytology screening of precancerous anal lesions is challenging because sensitivity is limited and diagnosis requires the provision of adequate follow-up infrastructure (for example, high-resolution anoscopy). Molecular assays might reduce the number of unnecessary high-resolution anoscopies performed[38,39].

HSV. Genital herpes is caused by herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2), which are members of the *Herpesviridae* family. In 2016, the WHO estimated that up to 192 million people were affected by genital HSV-1 and 491 million people by HSV-2[40]. Although HSV-1 is more commonly associated with oral disease ('cold sores'), the proportion of sexually transmitted anogenital herpes attributed to HSV-1 has increased over time, especially among women aged 18–30 years old[41]. HSV-2 is the primary causative agent of genital herpes infections globally[42]. Although HSV infection is chronic and lifelong, many women experience few or no symptoms. When present, symptoms range from painful genital sores to discomfort that is sometimes misdiagnosed as recurrent vulvovaginal candidiasis. HSV infections can be managed with oral antivirals including suppressive therapy, such as valacylovir (Table 3)[16].

One devasting consequence of HSV infection in pregnant women is neonatal herpes. In the U.S., the incidence of neonatal HSV has increased, with 5.3/10,000 infants affected in 2015, up from 3.75/10,000 births in the early 2000s[43,44]. Neonatal herpes manifests when neonates are infected with HSV during vaginal birth. Neonatal infection can affect the skin, eyes or mouth, but the central nervous

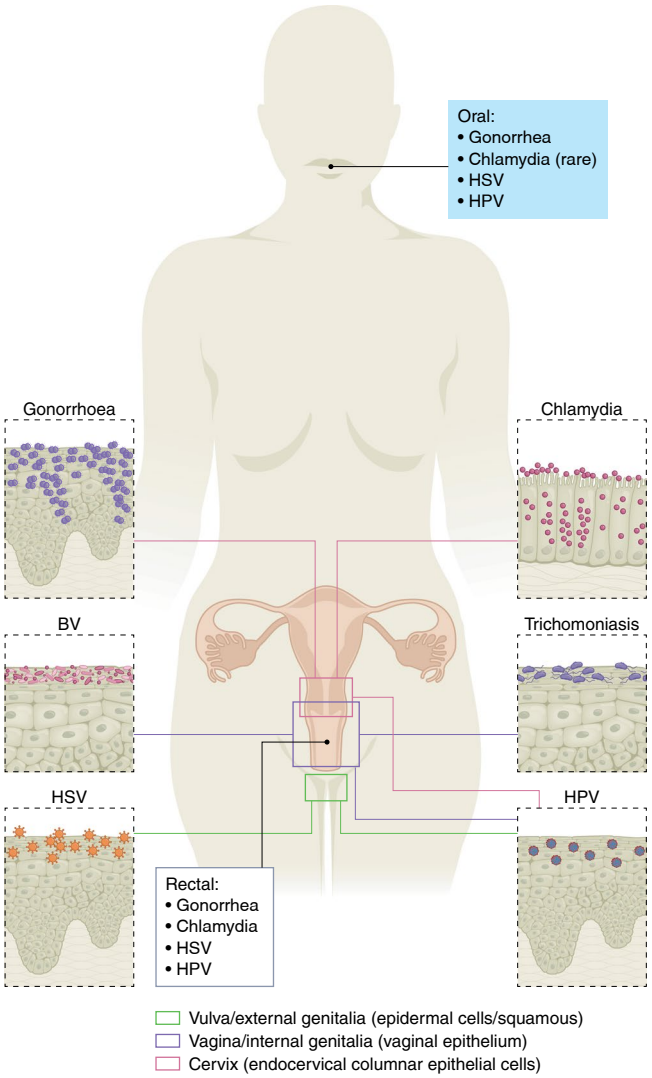

Fig. 2 | Anatomical sites affected by selected STIs. STIs can affect genital and extragenital sites in women. Gonorrhoea and chlamydia typically present as cervicitis. Bacterial vaginosis (BV) and trichomoniasis can also cause cervicitis, but more commonly manifest as vaginitis. HSV and HPV most typically affect the vulva or external genitalia of women.

system or multiple organs can also become infected; incidence of central nervous system manifestations of neonatal herpes is estimated to be between 1 in 3,000 and 1 in 20,000 live births. Mortality in such cases without treatment is as high as 85%, with a high likelihood of long-term neurological sequalae in those infants who do survive[45]. Mother-to-child transmission is preventable by elective Caesarian-section delivery in mothers with active herpetic lesions.

HSV-2 infection in women is associated with a threefold increased risk of HIV acquisition and horizontal transmission[46,47]. One analysis concluded that an estimated 420,000/1.4 million HIV infections (population attributable fraction 29.6% (22.9–37.1)) were attributed to HSV-2 infections worldwide[48].

Diagnosis of genital herpes is challenging because characteristic lesions often resolve by the time patients present to care. A presumptive diagnosis can be made by physical examination but should be confirmed with type-specific nucleic acid amplification testing (NAAT) or culture[16]. The use of HSV serologies is discussed in detail elsewhere[16,49].

Episodic and suppressive treatments for HSV do not prevent recurrence. Even if indefinite suppressive antivirals are administered, HSV shedding can still occur[50]. Lifelong antivirals are not cost effective and perfect adherence can be challenging for patients[16]. Therefore, there is continued interest in developing vaccines for HSV-2 (Table 2). Despite extensive investigation of many candidate HSV vaccines, none have performed well enough in clinical trials to be brought to the market. In the 1990s, initial studies investigated subunit vaccines, which aimed to select targets that induce immune responses against HSV-2[51]. One such vaccine candidate, Simplirix (GSK), targeted the glycoprotein D subunit (gD), which facilitates host cell entry by HSV. Initial trials demonstrated 74% efficacy in HSV-1/HSV-2 seronegative women with seropositive partners, but these results were not replicated in seronegative men[52]. Given the promising initial efficacy findings among seronegative women, additional trials were performed in women; however, they largely failed to meet primary endpoints. Most notably, efficacy of the same GSK gD subunit vaccine in the Herpevac trial was only 58% and 20% against HSV-1 and HSV-2, respectively[53]. The discrepancy in results between these two studies is puzzling, but given that gD is known to elicit a strong immune response, it has been a component in several additional vaccine candidates[51,54]. A major concern with HSV subunit vaccines is cost, so research and development strategies have pivoted towards cheaper nucleic acid-based vaccine platforms and the potential of live-attenuated vaccines[55–57]. Given the complex immunology of HSV, there is interest in understanding the role of mucosal immunity in the genital tract to aid the development of a successful vaccine against HSV-2[58].

Bacterial STIs

Syphilis. Syphilis is caused by the spirochaete *Treponema pallidum* subspecies *pallidum*. Main symptoms of syphilis include anogenital or oral painless chancres in primary syphilis, diffuse rash in secondary syphilis, aseptic meningitis and pan uveitis[59]. The impact of syphilis on women has intensified over the past decade. In the United States between 2014 and 2018, rates of primary and secondary syphilis among women doubled and similar trends have been noted globally[1,60]. Rates of primary and secondary syphilis are lower among US women compared with men who have sex with men (MSM), but cases among heterosexual women increased by 178.6% between 2015 and 2019, suggesting an epidemic mediated by heterosexual transmission[60]. Increasing primary and secondary syphilis cases among women are also predominant among those of childbearing age[60]. Therefore, the rising rates of congenital syphilis are not surprising; in 2013, congenital syphilis occurred in 9.2 cases per 100,000 live births and in 2020 increased to 57.3 cases per 100,000 live births[60]. Tragically, this trajectory has resulted in increasing numbers of syphilitic stillbirths and congenital syphilis-related infant deaths[60]. Syphilis in pregnancy is the second leading cause of stillbirth globally and has been associated with low birth weight, neonatal infections and preterm delivery[61]. Congenital syphilis is preventable with early detection and prompt treatment of maternal infection; however, many women lack access to adequate syphilis treatment, even with early diagnosis[62]. Limited prenatal care and timely syphilis testing are barriers to preventing congenital syphilis, especially in LMICs where prenatal care and syphilis screening resources are limited[63]. Currently, the CDC and WHO recommend routine serologic screening of pregnant women at their initial prenatal visit, at 28 weeks' gestation and at the time of delivery in high-prevalence settings, although recommendations vary geographically[16,64].

Consequences of untreated syphilis in pregnancy are dire for both mother and neonate. Options for effective treatment are straightforward because syphilis is treatable with penicillin G and antimicrobial resistance is essentially non-existent[16]. Depending on the stage and site of infection, treatment regimens differ in terms of penicillin dose frequency and route of administration, as discussed elsewhere[16]. Doxycycline can be given in certain situations

Table 1 | Modes of transmission and sites of replication of non-HIV STIs affecting women

STI	Mode of transmission	Main site of replication
HPV	Primary mode: •Sexual transmission (for example, genital skin–skin or skin–mucosal contact)[143] Secondary modes: •Horizontal transmission (for example, fomites, fingers, non-sexual skin contact)[144] •Self-inoculation[144] •Vertical transmission[145]	Viral DNA replication occurs inside host epithelial cells → newly encoded viral particles released into cervical canal → abnormal growth of cervical squamous cells[146]. Replication can also occur in the oropharyngeal and rectal mucosa as well as the skin[146].
HSV-1 and HSV-2	Primary mode: •Sexual transmission (for example, skin–skin or skin–mucosal contact in the setting of shedding virus from epithelial cells or secretions)[147] •Transmission can occur through genital-genital, oral-genital, genital-oral, and anal-genital contact Secondary modes: •Vertical transmission during delivery through direct mucosal or skin contact with herpetic lesions[148] •Fomite transmission is possible, but unlikely[149]	Primary infection: Virus penetrates mucosal surfaces or traverses through breaks in those surfaces (that is, skin, urogenital epithelium) → travels from epithelial cells to peripheral nerve endings up to nerve cell bodies in sacral and paraspinal ganglia → enters latency and indefinitely resides in ganglia reservoir (expression of viral microRNA and latency-associated transcription factors maintain latency). Reactivation[150]: Typically induced by neuronal stress → transcription of immediate-early viral genes → translation into viral proteins → subsequent viral transport down the axon to epithelial cells → viral replication → asymptomatic viral shedding or clinically symptomatic genital ulcer disease.
Syphilis	Primary mode: •Sexual transmission[151] Secondary modes: •Vertical transmission (in utero or less commonly during passage through the birth canal) •Transmission via blood products (rare since implementation of screening of the blood supply and refrigeration of blood products) •Transmission via organ donation (rare)[152] •Occupational exposure (rare)[153]	Direct spirochaete inoculation at genital-mucosal sites leads to the development of primary syphilitic chancre(s) within weeks of infection. The spirochaete adheres to epithelial cells and extracellular matrix components in these areas. Once below the epithelium, organisms multiply locally and begin to disseminate through the lymphatics and bloodstream. Replication after widespread dissemination leads to signs and symptoms of secondary syphilis within months and years later, tertiary syphilis[154]. Syphilis can also have systemic manifestations[154].
Chlamydia	Primary mode: •Sexual transmission[155] Secondary mode: •Vertical transmission	Chlamydial elementary bodies bind to host vaginal, rectal or oral (rare) epithelial cells, initiated by the formation of a trimolecularbridge between bacterial adhesins, host receptors and host heparin sulfate proteoglycans. Type III secretion system effectors are injected into the host cell, some of which initiate cytoskeletal rearrangements to facilitate internalization. The elementary body is endocytosed. Bacterial protein synthesis begins. Elementary bodies convert to reticulate bodies and newly secreted inclusion membrane proteins promote nutrient acquisition[156].
Gonorrhoea	Primary mode: •Sexual transmission[157] Secondary mode •Vertical transmission	*N. gonorrhoeae* attaches to mucosal cell surfaces of the throat, vagina or rectum through type IV pili, leading to local penetration into cells, proliferation and a local inflammatory response. Other outer membrane structures involved in attachment include PilC proteins, Opa (opacity-associated proteins or protein II), PorB, gonococcal lipooligosaccharide (LOS), gonococcal ribosomal protein L12, *N. gonorrhoeae* outer membrane protein A (Ng-OmpA), and MetQ. Systemic dissemination can occur in some cases[158]. *N. gonorrhoeae* can also have systemic manifestations[157].
Trichomoniasis	Primary mode: •Sexual transmission[159] Secondary modes: •Fomites (for example, wet wash cloths)[159] •Pit latrines (rare)[160] •Iatrogenic transmission (rare)[161]	The parasite invades the squamous epithelium of the urogenital tract and becomes an adherent amoeboid within minutes of exposure to host epithelial tissue; subsequent adherence is cytotoxic and results in lysis of host cells[162].

to non-pregnant women (that is, in cases of true penicillin allergy) to effectively treat primary, secondary or latent syphilis; however, penicillin G is the only antimicrobial agent that has demonstrated efficacy in preventing congenital syphilis[65]. Thus, treatment of women with a true penicillin allergy and those who are unable to access penicillin G is challenging. The ideal dosing regimen of penicillin G for syphilis treatment during pregnancy is not clear, but evidence suggests that an additional injection of benzathine penicillin G after the initial dose reduces the risk of congenital syphilis[65–67].

Chlamydia. *Chlamydia trachomatis* is an obligate intracellular Gram-negative bacterium that can replicate only inside a host cell[68]. Although usually asymptomatic in women, *C. trachomatis* infection can result in reproductive damage, and when untreated, it can be associated with PID, ectopic pregnancy, chronic pelvic pain and tubal infertility. In the U.S., women <25 years account for most infections, so annual screening in this age group is recommended to reduce the frequency of PID and other adverse health outcomes[16,60,69]. Perinatal maternal *Chlamydia* infection is associated

Table 2 | Selected sexually transmitted vaccine and vaccine candidate products

STI	Mechanism/components	Vaccine product/ candidate	Manufacturer/developer	Stage of development/ availability	Indications
HPV	Recombinant L1 VLP (2-valent, HPV types 16, 18)	Cervarix	GlaxoSmithKline (GSK) Biologicals	Licensed for use and available[a]	Females, 9–25 years old
	Recombinant L1 VLP (4-valent, HPV types 6, 11, 16, 18)	Gardasil	Merck	Licensed for use and available[a]	Females and males, 9–26 years old
	Recombinant L1 VLP (9-valent, HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58)	Gardasil 9	Merck	Licensed for use and available[a]	Females and males, 9–45 years old
	Recombinant L1 VLP (2-valent, HPV16, 18)	Cecolin	Xiamen Innovax Biotech	Licensed for use and available[a]	Females, 9–45 years old
HSV	Subunit vaccine	gD2; gD2/gB2	Novartis	Stopped after Phase II trials	n/a
	Subunit vaccine	Simplirix/Herpevac (gD2 and AS04)	GSK	Stopped after Phase III trials	n/a
	Subunit vaccine	GEN-003 (gD2 and matrix M2)	Genocea	Stopped after Phase II trial	n/a
	Subunit vaccine	HerpV (peptide vaccine + QS-21 stimulon)	Agenus	Stopped after Phase II trial	n/a
	Live-attenuated vaccine	HSV529 (Defective replication of HSV-2, UL5/UL29 deletion)	Sanofi Pasteur	Phase II trial ongoing	n/a
	DNA vaccine	COR-1 (gD2 codon optimized DNA vaccine)	Anteris	Stopped after Phase I/IIa trial	n/a
Gonorrhoea	Meningococcal and gonococcal OMV vaccine	VA-MENGOC-BC	Cuban government	Observational data suggest association with lower rates of gonorrhoea among immunized people	n/a
	Mixed OMV and protein subunit vaccines (MeNZB OMV antigens with additional protein subunit antigens)	Bexsero	GlaxoSmithKline Biologicals	Phase III trials ongoing	n/a
	Immunotherapeutic vaccines	OMV vaccine with IL-2 aduvant, 2C7 LOS epitope mimic antigenic peptide vaccine	University of Buffalo, University of Massachusetts	Preclinical trials completed	n/a
Chlamydia	Recombinant major outer membrane protein and native major outer membrane protein vaccines	major outer membrane protein in murine models	MRC Clinical Research Centre (UK), Wenzhou Medical University (China), University of California, Irvine	Preclinical trials ongoing	n/a

[a]Availability differs by country-specific licensure and relative prioritization for HPV immunization with the 9-valent HPV vaccine (Gardasil 9). OMV, outer membrane vesicle.

with preterm birth, stillbirth, low birth weight and neonatal infections such as pneumonia and conjunctivitis[69–71].

The composition of the vaginal microbiome probably has a role in host defence against chlamydial infection. An optimal vaginal microbiota is dominated by *Lactobacillus crispatus*, which produces lactic acid that has antimicrobial properties and can inactivate *C. trachomatis*, decreasing the likelihood of ascension of this pathogen into the upper genital tract[72]. Women with bacterial vaginosis, defined by a paucity of *L. crispatus* and other favourable vaginal lactobacilli, and an increased abundance of facultative and strict anaerobes, may have reduced immune defence against *C. trachomatis*, leading to increased risk of acquiring this pathogen as well as *Neisseria gonorrhoeae* and *Trichomonas vaginalis*[73].

Prompt diagnosis and treatment are the best approaches to preventing the reproductive morbidity and sequelae associated with chlamydia (Table 3). For decades, single-dose oral azithromycin (2 g) was a first-line treatment option for *C. trachomatis*, offering the option of directly observed therapy. Recent data suggest that this regimen is inferior to oral doxycycline given twice daily for 7 days, specifically for women and men with urogenital and rectal infection[74]. Thus, the only currently recommended first-line agent for uncomplicated urogenital or rectal chlamydia is multidose doxycycline[16]. This change in guidance in 2021 was driven by data related to men with chlamydia; more efficacy studies are needed in women[75]. However, rectal chlamydial infection has been found to occur in women more frequently than previously thought. In addition to

Table 3 | First-line treatment regimens for common STIs in women

STI	Treatment
Genital HSV	**First clinical episode**
	Acyclovir, 400 mg orally three times daily for 7–10 days[a,b]
	Acyclovir, 200 mg orally five times daily for 7 days[a]
	Famciclovir, 250 mg orally three times daily for 7–10 days[a,b]
	Valacyclovir, 1 g orally twice daily for 7–10 days[a,b]
	Suppressive therapy
	Acyclovir, 400 g orally twice daily[a,b]
	Valacyclovir, 500 mg orally daily[a,b]
	Valacyclovir, 1 g orally daily[a,b]
	Famiciclovir, 250 mg orally twice daily[a,b]
	Episodic therapy for recurrent infection
	Acyclovir, 800 mg orally twice or three times daily for 5 days[a,b]
	Acyclovir, 200 mg orally five times daily for 5 days[b]
	Acyclovir, 400 mg orally three times daily for 5 days[b]
	Famiciclovir, 1 g orally twice daily for 1 day[a]
	Famiciclovir, 500 mg orally once, followed by 250 mg twice daily for 2 days[a]
	Famiciclovir, 125 mg orally twice daily for 5 days[a,b]
	Valacyclovir, 500 mg orally twice daily for 3–5 days[a,b]
	Valacyclovir, 1 g orally once daily for 5 days[a,b]
Syphilis	**Primary and secondary syphilis and early latent syphilis**
	Benzathine penicillin G, 2.4 million units intramuscularly once[a,b]
	Late latent syphilis
	Benzathine penicillin G, 2.4 million units intramuscularly once weekly for three consecutive weeks[a,b]
	Neurosyphilis, ocular syphilis and otosyphilis
	Aqueous crystalline penicillin G, 18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion for 10–14 days[a]
	Aqueous benzylpenicillin,12–24 million IU by intravenous injection, administered daily in doses of 2–4 million IU, every 4 hours for 14 days[b]
Chlamydia	Doxycycline[c], 100 mg orally twice daily for 7 days[a,b]
	Azithromycin, 1 g orally once[b]
Gonorrhoea	**Uncomplicated anogenital infection**
	Ceftriaxone, 500 mg[d] intramuscularly as a single dose[a]
	Ceftriaxone, 125 mg intramuscularly as a single dose[b]
	Ciprofloxacin[c], 500 mg orally as a single dose[b]
	Cefixime, 400 mg orally as a single dose[b]
	Spectinomycin, 2 g intramuscularly as a single dose[b]
Trichomoniasis	Metronidazole, 500 mg orally twice daily for 7 days[a]
	Metronidazole, 2 g orally as a single dose[b]
	Tinidazole, 2 g orally as a single dose[b]

[a]*STI Treatment Guidelines* (US Centers for Disease Control and Prevention, 2021). [b]*Guidelines for the Management of Sexually Transmitted Infections* (WHO, 2016). [c]Contraindicated in pregnancy. [d]For patients weighing over 150 kg, intramuscular ceftriaxone, 1 g single dose.

receptive anal sex, auto-inoculation from cervicovaginal chlamydial infection may yield rectal infection[76,77]. While single-dose azithromycin is efficacious for urogenital *C. trachomatis* in women, the possibility that concomitant rectal infection that may not be adequately treated with this regimen is concerning[78]. Single-dose azithromycin is also recommended for the treatment of chlamydia in pregnant women as doxycycline is not safe in pregnancy[16].

Currently, no vaccines are available for *C. trachomatis*[79]. Given the high rates of re-infection, especially among young women[80], vaccines offer the promise of both protecting from disease and reducing antibiotic use, treatment burden, preventing development of antimicrobial resistance in other infections (for example, gonorrhoea) and decreasing reproductive morbidity[81,82]. A major challenge in *C. trachomatis* vaccine research has been targeting both humoral and cell-mediated immune responses in infected individuals; complete protection requires activity in both pathways[83,84]. Comprehensive monitoring of this complicated immune response is difficult. Despite approximately 220 chlamydial vaccine trials having been conducted from 1946 until the present—over seven decades—an effective vaccine remains elusive (Table 2).

Gonorrhoea. Gonorrhoea is caused by *N. gonorrhoeae*, a Gram-negative diplococcal bacterium. *N. gonorrhoeae* can yield mucosal infections in epithelia of the urogenital tract and the ectocervix[85]. Gonorrhoea is extremely common worldwide, with an estimated global annual incidence of 86.9 million adults and a prevalence among women of 0.9%, with the greatest burden among women in LMICs[1]. Genitourinary gonorrhoea can present in women as cervicitis or urethritis but is mostly asymptomatic[86]. If untreated, gonococcal infections can result in serious complications such as PID, tubal infertility, ectopic pregnancy and disseminated gonococcal infection[87–89]. Gonorrhoea also facilitates transmission of HIV and other STIs[86]. Similar to other bacterial STIs, untreated gonorrhoea has been associated with adverse birth outcomes such as preterm birth, low birth weight and premature rupture of membranes[90,91]. Perinatal exposure to an infected cervix puts neonates at risk for serious complications such as gonococcal sepsis and ophthalmia neonatorum, the latter of which can lead to blindness if untreated[92].

When detected in a timely manner, gonorrhoea can be treated and its negative sequelae can be avoided. The landscape of gonorrhoea treatment, however, has been in flux over the past several decades due to the emergence of resistance to multiple antimicrobials among gonococcal isolates worldwide[60,93]. The Gonococcal Isolate Surveillance Program (GISP) was established in the United States in 1986 to monitor trends in antimicrobial resistance among urethral *N. gonorrhoeae* isolates. This programme is integral in generating clinical guidance on gonococcal therapy[94]. Since the generation of GISP, notable gonococcal resistance has emerged to several antimicrobial drug classes, including fluoroquinolones (for example, ciprofloxacin) and macrolides (for example, azithromycin); use of these agents is no longer recommended in national treatment guidelines[16,95]. The 2021 CDC STI treatment guidelines currently recommend cephalosporins for first-line gonorrhoea treatment, specifically 500 mg intramuscular ceftriaxone for people weighing less than 150 kg[16]. Oral cephalosporins, such as cefixime, are not recommended as first-line treatment, given many instances of treatment failure and limited efficacy in treating pharyngeal gonococcal infection[96–100]. While ceftriaxone remains a reliable choice in most situations, there is growing concern for widespread ceftriaxone-resistant gonococcal isolates. Such strains have been reported in Denmark, France, Japan, Thailand and the United Kingdom; alternative treatment options are limited[101–104].

In the past 10 years, several novel anti-gonococcal antimicrobials have been conceptualized and developed[105–107]. One example is zoliflodacin, a single-dose spiropyrimidinetrione antimicrobial that works by inhibiting DNA biosynthesis through blocking gyrase complex cleavage[108]. In a multicentre Phase 2 trial in the United States, most patients who received zoliflodacin for uncomplicated urogenital and rectal gonococcal infection were successfully treated. Efficacy for treating pharyngeal infections was less impressive, with only 50% and 82% of those who received 2 g and 3 g of zoliflodacin, respectively, achieving cure. Regardless, several studies have shown that zoliflodacin continues to have excellent in vitro activity against multidrug-resistant gonococcal isolates, including those with resistance to extended-spectrum cephalosporins[109,110].

Given global increases in antimicrobial resistance, vaccines preventing acquisition of gonorrhoea are urgently needed. Modelling studies have demonstrated that a gonococcal vaccine of moderate efficacy and duration would have a substantial impact on disease prevalence and prevention of adverse reproductive sequelae[111]. The WHO has named *N. gonorrhoeae* as a global priority, hence increasing interest and funding have been funnelled into development of candidate gonorrhoea vaccines (Table 2). Fortunately, available tools for other gonococcal species may offer opportunity for *N. gonorrhoeae* prevention, an approach currently under study. The rMenB+OMV NZ vaccine (Bexsero) was first licensed in the European Union in 2013 and in the United States in 2015 for prevention of meningococcal disease caused by *N. meningitidis* serogroup B[112]. An earlier version of a vaccine aimed at a meningococcal B outbreak (MeNZB) was introduced in New Zealand in the early 2000s. A retrospective case-control study revealed that this vaccine programme not only led to a decrease in meningococcal disease, as expected, but had an estimated reduction of future gonorrhoea acquisition of 31% (95% CI: 21–39) in those who received 3 doses of vaccine[113]. Clinical trials are ongoing to assess the efficacy of Bexsero in preventing urogenital and/or rectal gonorrhoea (NCT 04350138).

Parasitic STIs

Trichomoniasis. Globally, trichomoniasis has an enormous impact on women as the most common non-viral STI[1]. It is caused by the parasitic protozoan *Trichomonas vaginalis*, and results in vaginal discharge and dysuria when symptomatic[114]. *T. vaginalis* has also been associated with adverse birth outcomes (for example, preterm birth, low birth weight, preterm rupture of membranes)[115] and an increased risk of HIV acquisition and transmission, PID and cervical cancer related to HPV infection[116–119]. Despite these significant health impacts, has been viewed as a nuisance infection and investigation has been limited until recent years. Globally, trichomoniasis is not currently reportable[120,121]. Marked racial and geographic disparities have also been described in relation to *T. vaginalis* infection. In the United States, according to the most recent National Health and Nutrition Examination Survey data, the overall prevalence of *T. vaginalis* in women in the United States is 1.8%[122], being 6.8% among black women compared with 0.4% among women of other racial/ethnic backgrounds[122]. The global epidemiology of trichomoniasis is less well-defined, but one systematic review including men and women noted a prevalence range of 3.9%–24.6% in LMICs from Latin America and Southern Africa[123].

Diagnosis of *T. vaginalis* has greatly improved in women (and men) over the past decade with the use of highly sensitive and specific NAAT tests[124–127]. Treatment recommendations for women with *T. vaginalis* have been largely unchanged for decades, with 5-nitroimidazoles such as metronidazole (MTZ) and tinidazole (TDZ) remaining mainstays of therapy (Table 3). Guidelines published by the WHO in June 2021 recommend treatment with either a single dose of MTZ (2 g orally) or twice-daily dose of MTZ (500 mg orally) for 7 days[128]. In LMIC and other resource-limited settings where adherence to a multidose MTZ regimen may be difficult, a single-dose treatment option may be advantageous. Accumulating data suggest, however, that single-dose treatment with MTZ for women may not be optimal[129,130]. A recent multicentre randomized controlled trial in the United States compared the multidose oral MTZ regimen to the single-dose regimen among HIV-negative women. Participants who received the multidose regimen were significantly less likely to re-test positive for *T. vaginalis* at 1 month compared with women in the single-dose group; adherence among both groups were similar[130]. Thus, the multidose oral MTZ regimen is now the recommended regimen for all women; this update may influence future global guidelines moving forward[16]. Notably, MTZ is safe for pregnant women at all stages of pregnancy[131]. Therefore, to prevent adverse birth outcomes associated with this infection, prompt treatment is essential[115,131].

Due to limited clinical trial data in men, the single 2 g dose of oral MTZ remains the recommended treatment regimen for *T. vaginalis* in men[16]. This is the first time there has been a discrepancy in the treatment of an STI based on gender. Such a situation could lead to complicated public health logistics in partner treatment of infected women and additional studies are needed to discover the optimal treatment regimen for men[132]. Women are re-infected by their male sex partners if they are either not treated or are inadequately treated for trichomoniasis[133].

Table 4 | Challenges to STI prevention and proposed solutions

Challenges	Proposed solutions
Antimicrobial resistance	•National surveillance programmes for drug resistant STIs •Antimicrobial stewardship •Development of novel drugs •Development of STI vaccines
Lack of engagement of priority populations in research and public health efforts	Increased engagement of the following populations: •Adolescents and young adults •Pregnant women •Sexual and gender minority women (that is, women who have sex with women, transgender women) •Women of diverse racial and ethnic backgrounds
Limited STI surveillance programmes	•Improve reporting efforts of STIs such as *T. vaginalis*, HSV •Develop effective control programmes for key STIs
Structural barriers to appropriate sexual healthcare for women (systemic racism, misogyny, limited access to sexual healthcare resources)	•Provide widespread sexual and reproductive health education programmes •Overcome cultural taboos and barriers in this arena •Emphasize the need for policymakers, organizations and key sectors to promote sexual health programmes •Need for more integration of health services

Oral secnidazole (SEC) was recently approved by the US Food and Drug Administration (FDA) for treatment of *T. vaginalis* in both men and women. Given its microbiologic cure rate of 92.2% in a randomized double-blind placebo-controlled delayed-treatment study, SEC offers a promising new single-dose treatment option for trichomoniasis[134].

STI prevention challenges and disparities in minority populations

Gender minority women. STI prevention poses challenges for women in general, but some populations face additional barriers to sexual healthcare (Table 4). Gender minority women, including transgender women (TGW), or people who were assigned male sex at birth but whose gender identity is female, are at high risk of acquiring STIs through engagement in sexual behaviours such as commercial sex work and condomless anal receptive intercourse[135]. Consequently, STIs disproportionally affect TGW; an estimated 14% of TGW in the United States are living with HIV[136], and global bacterial STI prevalence has been reported to be as high as 50%, 19% and 25% for syphilis, gonorrhoea and chlamydia, respectively[8,135,136]. These high rates may be related to the limited engagement of TGW with effective sexual health services—for example, regular HIV/STI screening—and underutilization of pre-exposure prophylaxis[137,138]. This lack of engagement arises from a suite of factors, including stigma, mistrust of the healthcare system, limited trans-affirming clinical services, previous sexual trauma or competing healthcare priorities such as hormone replacement therapy for gender-affirming therapy[139,140].

Given the combination of this population's unique sexual health needs and mistrust of the medical establishment, community-driven patient-centred prevention efforts are necessary. One qualitative study assessing attitudes related to HIV prevention among TGW in the Southeastern United States found that limited trans-affirming sexual health resources are a major barrier to engaging in care[141]. In addition, an individualized approach to affirming sexual history-taking should be employed by providers when caring for TGW. More broadly, another driver of sexual health disparities among TGW is their limited representations in research studies and clinical trials in the field. Data for TGW are often aggregated together with those of cisgender MSM and thus difficult to interpret. Study design and trial recruitment planning efforts must be made to appropriately report data on TGW.

Women in LMICs. Women living in LMICs face additional STI prevention challenges largely due to limited healthcare infrastructure, availability of sexual health resources and misogynistic cultural attitudes towards sexuality[142]. African countries have been particularly impacted, with the most recent WHO STI global prevalence estimates reporting the highest rates worldwide for gonorrhoea, trichomoniasis and syphilis among women in the region[1]. In addition, until very recently, distribution of HPV vaccines has been largely limited to European and North American nations, with LMICs receiving little support until approximately 2019. Even when HPV vaccines were introduced in many LMICs, uptake of the full series has been limited due to logistical challenges, highlighting an enormous, missed opportunity to curtail the rates of cervical cancer worldwide[32].

Affordable STI testing that can be performed at the point-of-care is an important tool that needs to be made available to women in LMICs. Concurrent availability and accessibility of appropriate treatment for STIs are also essential. Clinics or other community settings need to provide confidential diagnostics and treatment to mitigate restricted access owing to stigma and the potential for gender-based violence that sometimes occurs when male sexual partners find out about sexual health diagnoses. Vaccines against STIs such as *C. trachomatis* and HSV-2 also hold great promise for women of LMICs, offering both disease prevention and a reduction in the need for diagnosis and treatment. Continued pursuit of safe and effective STI vaccines should be prioritized.

Conclusion

Women are disproportionately affected by STIs throughout their lives compared with men. This is mainly owing to the higher efficiency of male-to-female transmission of STIs and the biology of the female reproductive tract. In addition, the social and structural barriers to women realizing full sexual health include limited availability of HPV immunization in many parts of the world, barriers to contraception access, lack of confidential evaluation and counselling services, and lack of STI diagnostics. Finally, women are generally less well-resourced, both financially and socially, than men. This restricts their access to the resources required for sexual safety such as comprehensive sexual healthcare and HIV/STI prevention services, and the financial security that is fundamental to sexual health. Ensuring access to diagnostics and therapies on its own will not address the yawning gap in sexual health between men and women but would be a good start.

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Author contributions

O.T.V.G. led efforts in the literature review and writing of this manuscript. C.A.M. and J.M.M. contributed to the final version of the manuscript. All authors conceived the main conceptual ideas for the manuscript together.

Competing interests

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