

Sexually transmitted infections: challenges ahead

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WHO estimated that nearly 1 million people become infected every day with any of four curable sexually transmitted infections (STIs): chlamydia, gonorrhoea, syphilis, and trichomoniasis. Despite their high global incidence, STIs remain a neglected area of research. In this Commission, we have prioritised five areas that represent particular challenges in STI treatment and control. Chlamydia remains the most commonly diagnosed bacterial STI in high-income countries despite widespread testing recommendations, sensitive and specific non-invasive testing techniques, and cheap effective therapy. We discuss the challenges for chlamydia control and evidence to support a shift from the current focus on infection-based screening to improved management of diagnosed cases and of chlamydial morbidity, such as pelvic inflammatory disease. The emergence and spread of antimicrobial resistance in *Neisseria gonorrhoeae* is globally recognised. We review current and potential future control and treatment strategies, with a focus on novel antimicrobials. Bacterial vaginosis is the most common vaginal disorder in women, but current treatments are associated with frequent recurrence. Recurrence after treatment might relate to evidence that suggests sexual transmission is integral to the pathogenesis of bacterial vaginosis, which has substantial implications for the development of effective management approaches. STIs disproportionately affect low-income and middle-income countries. We review strategies for case management, focusing on point-of-care tests that hold considerable potential for improving STI control. Lastly, STIs in men who have sex with men have increased since the late 1990s. We discuss the contribution of new biomedical HIV prevention strategies and risk compensation. Overall, this Commission aims to enhance the understanding of some of the key challenges facing the field of STIs, and outlines new approaches to improve the clinical management of STIs and public health.

Introduction

Sexually transmitted infections (STIs) are among the most common acute conditions worldwide.¹ WHO estimated in 2012 that there were 357·4 million new global cases of four common curable STIs: chlamydia (130·9 million cases), gonorrhoea (78·3 million cases), syphilis (5·6 million cases), and trichomoniasis (142·6 million cases; figure 1).² Additionally, there are

alarming increases in antimicrobial resistance in *Neisseria gonorrhoeae* and *Mycoplasma genitalium*.³ Although most STIs are not usually fatal, they result in a substantial burden of disease.¹ The complications of curable STIs include pelvic inflammatory disease, ectopic pregnancy, infertility, chronic pelvic pain, seronegative arthropathy, and neurological and cardiovascular diseases.⁴ STIs in pregnancy can cause fetal or neonatal

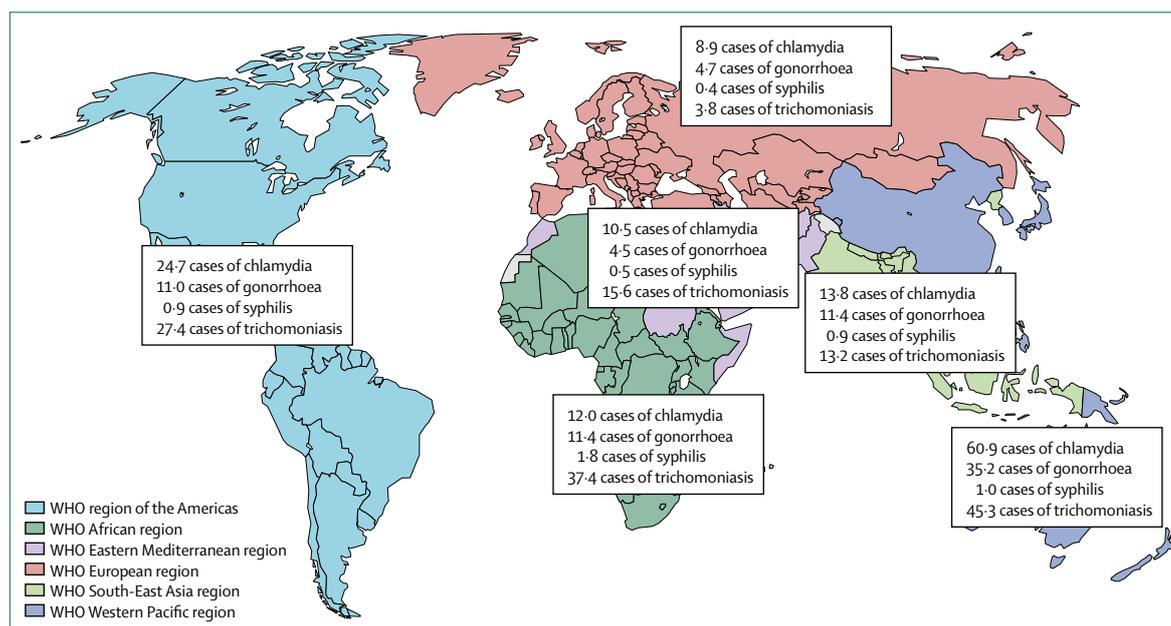


Figure 1: WHO regional estimates of new cases of four curable sexually transmitted infections
Data are estimated numbers of incident cases in millions for chlamydia, gonorrhoea, syphilis, and trichomoniasis in 2012, by WHO region.² Global totals differ slightly from those in the text because of rounding. Disputed territories are shaded in grey.

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death, premature delivery, and neonatal encephalitis, eye infections, and pneumonia.⁴ STIs can also increase the infectiousness of and susceptibility to HIV.⁵ Despite these complications, STIs remain a neglected field for clinical and public health practice and for research.⁶ People with STIs experience stigma, STIs disproportionately affect marginalised groups such as sex workers and men who have sex with men (MSM), and condemnatory moral attitudes toward STIs result in unwillingness to prioritise STI control policies.^{6–8} In this Commission of *The Lancet Infectious Diseases*, we have selected five key issues for STI control that face major challenges globally and for which action is imperative.

This Commission addresses current challenges for research, practice, and policy that we selected because they are common and important global health priorities, or because new evidence is emerging in the area. Partner notification is an essential part of the management of most STIs and is mentioned in several parts of the Commission. We use this term to include all processes involved in informing the sex partners or needle-sharing contacts of people with STIs of their potential exposure to an infectious disease and ensuring their evaluation or treatment, or both.⁴ We consider partner management, partner services, and partner information to be synonymous.

Part 1 of the Commission addresses *Chlamydia trachomatis*, commonly known as chlamydia. Chlamydia is the most common bacterial STI globally¹ and causes serious reproductive tract complications in women.⁹ Despite 20 years having passed since the first randomised controlled trial (RCT)¹⁰ of an intervention to reduce its complications, the scientific and public health communities remain unsure of how to reduce chlamydia prevalence and impact on society. The most recent RCT¹¹ of a screening and intervention did not find a marked effect on prevalence despite a substantial increase in the proportion of the target population that received screening. In this part of the Commission, Hocking and Low assess the latest research about screening, treatment, and management of chlamydia, and suggest a way forward to define chlamydia control priorities for the future.

In part 2 of the Commission, Unemo addresses the globally recognised threat of the emergence and spread of antimicrobial resistance in *N gonorrhoeae*. This organism has become resistant to virtually all antibiotics that have been available to treat it since sulphonamides were first used in the 1930s. The first clinical failure from the use of dual therapy with ceftriaxone and azithromycin was reported in 2016.¹² For this reason, we focus on current and future treatment strategies, including three novel antimicrobials that are being evaluated in phase 2 or phase 3 RCTs. We also report on novel strategies that aim to reduce the incidence and prevalence of gonorrhoea, particularly in MSM, which should also reduce the probability of antimicrobial resistance developing. Ultimately, the development of vaccines

against both *N gonorrhoeae* and *C trachomatis* are likely to be the only sustainable solutions to control these infections.¹³

We chose to include bacterial vaginosis in this Commission for three main reasons despite it not being considered a traditional STI. First, an accumulating body of epidemiological and microbiological evidence suggests that sexual transmission is integral to its pathogenesis.^{14,15} Second, bacterial vaginosis has been neglected although it is the most prevalent urogenital disorder in women of reproductive age worldwide and is associated with serious reproductive and obstetric sequelae, including preterm delivery and increased risk of STI and HIV acquisition and transmission of HIV.^{16,17} Third, treatment failure is unacceptably high: more than half of women have a recurrence after recommended therapy but neither bacterial vaginosis treatment efficacy nor outcomes have improved for decades.¹⁸ In part 3 of the Commission, Bradshaw and colleagues summarise the research implicating sexual transmission and propose combination approaches to management that include antimicrobials, biofilm-disrupting agents, and partner treatment.

Part 4 of the Commission addresses STIs in low-income and middle-income countries where more than 90% of curable STIs and almost all of the global burden of STIs occur.¹² Francis and colleagues review key strategies for STI case management and control, including syndromic management, presumptive periodic treatment, and partner notification. But they focus on rapid diagnostic tests and point-of-care tests within a published framework—ie, being affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and delivered to end-users (ASSURED).¹⁹ Point-of-care tests have considerable implications for STI control in high-income countries too, but their potential benefits are greatest in resource-constrained countries where health-care infrastructure is most limited.

Part 5 of the Commission discusses epidemics of STIs in MSM in high-income countries in the context of three biomedical treatment strategies that use antiretroviral therapies (ARTs) to prevent HIV infection. Two strategies are prophylactic treatments to reduce susceptibility in individuals who are not infected with HIV: post-exposure prophylaxis (PEP), given after specific high-risk exposures; and pre-exposure prophylaxis (PrEP), given to individuals who are not infected with HIV for continuous periods of high-risk exposure to prevent acquisition of HIV. The third strategy, known as treatment as prevention (TasP), reduces HIV infectiousness and involves starting ART as soon as HIV infection is diagnosed to prevent transmission to uninfected partners. These interventions have all been suggested to increase risky sexual behaviours through risk compensation and to result in increased transmission of STIs.²⁰ As such, de Vries and colleagues review the evidence linking PEP, TasP, and PrEP strategies to risk compensation and increasing STI prevalence.

We end the Commission with a call to action, in which we ask policy makers to rise to the public health challenge of effective STI control. Our call includes a broad suite of approaches that are often shared across infections or risk groups. They involve the optimisation of surveillance for behaviours, infections, and antimicrobial resistance; access to health services, early diagnosis, appropriate treatment, and partner notification; and intensified research into rapid point-of-care tests to detect both STIs and antimicrobial resistance, novel antimicrobials or treatment approaches (or both), and the understanding of STI transmission or pathogenesis.

Of necessity, this Commission has excluded important subjects. *M genitalium* was not included despite the rapid emergence of resistance to both first-line and second-line treatments, but *M genitalium* antimicrobial resistance and clinical management options have been reviewed in recent years elsewhere,^{3,21} and is addressed in an accompanying Comment.²² We also omitted herpes simplex virus, for which vaccine development is progressing rapidly;¹³ human papillomavirus (HPV), for which vaccination is highly effective²³ but for which implementation is now the key challenge; and infections caused by *Trichomonas vaginalis*, because there are no new strategies for treatment or control.

Part 1: chlamydia control—what should we do?

20 years after the publication of the first RCT¹⁰ of an intervention to reduce the incidence of pelvic inflammatory disease in young women, policy makers, practitioners, and researchers still need to ask, what should we do about chlamydia control? Three linked factors make this question important. First, *C trachomatis* remains the most commonly diagnosed bacterial STI despite chlamydia testing recommendations that have been in place for years in several high-income countries.^{24–28} Second, although infection might be asymptomatic in more than 80% of cases,^{29,30} chlamydia can cause tissue damage, particularly in the female reproductive tract in which ascending infection can cause pelvic inflammatory disease, which contributes to chronic pelvic pain, ectopic pregnancy, and tubal factor infertility (figure 2).⁹ Third, technological advances make chlamydia diagnosis ever easier (if not cheaper): nucleic acid amplification tests using self-collected specimens, test kits available online, mobile phones for receiving results, and rapid tests.³¹ However, the diagnosis of pelvic inflammatory disease still relies on insensitive and non-specific clinical signs.²⁸

Chlamydia control requires “a broad range of deliberate, sustained activities that aim to reduce...the incidence and prevalence of chlamydia and the incidence of reproductive tract complications”.³² The general definition of infectious disease control involves agreement on locally acceptable levels,³³ and makes a distinction between the infection and the disease that it causes. But an acceptable level of genital chlamydia infection or chlamydia-associated

pelvic inflammatory disease, ectopic pregnancy, or tubal factor infertility has not been defined in any setting. The range of chlamydia control activities is broad (figure 3), and countries should have a chlamydia control strategy that defines primary and secondary prevention activities and have systems for monitoring and evaluation.³² Secondary prevention starts with case detection and case management to prevent complications. Case management includes history taking and clinical examination, diagnostic tests, treatment, partner notifications, health promotion advice, follow-ups, and surveillance.³² Over time, particularly in high-income countries, discussions about chlamydia control have come to focus more on screening for asymptomatic infections in young sexually active adults, rather than clinical case management of infection or pelvic inflammatory disease.

WHO’s Global Health Sector Strategy on STIs 2016–21 states that, “because the best strategies to control and

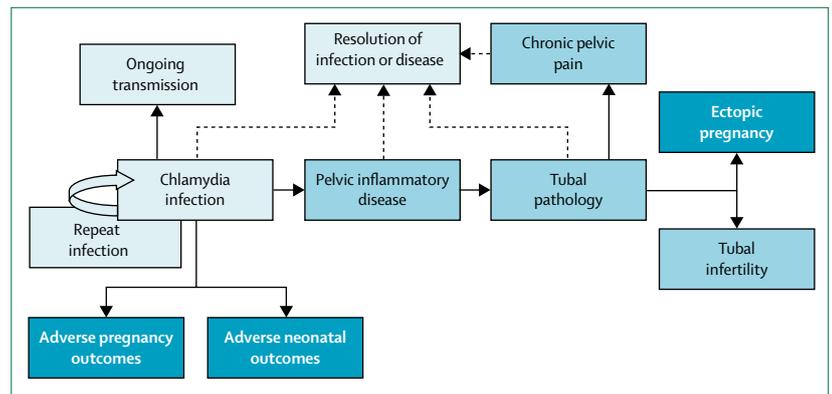


Figure 2: Natural history and sequelae of *Chlamydia trachomatis* infection in women
Light blue boxes are possible infection states, including resolution of infection or disease states. Mid-blue boxes are complications of *C trachomatis* in the upper genital tract. Dark blue boxes are pregnancy-related consequences of *C trachomatis* infection. Straight solid lines are possible transitions to consequences or complications. Curved solid line is repeated chlamydia infection, which can cause reproductive tract consequences and complications again. Dotted lines are transitions from conditions that can resolve. Length of arrows is not proportional to time.

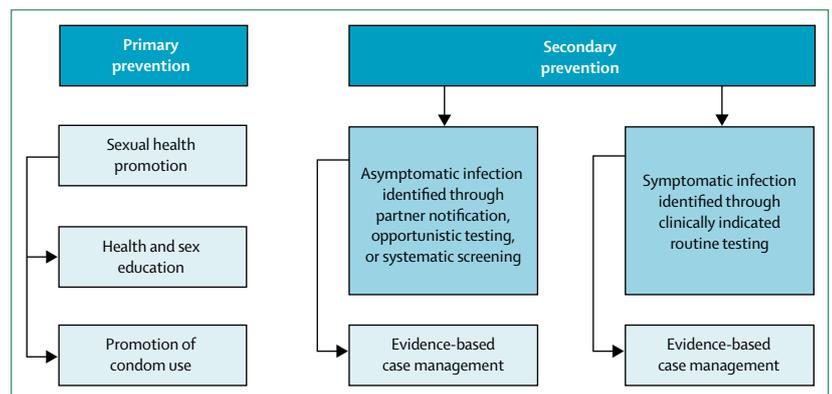


Figure 3: Interventions for the control of chlamydia in a population
Evidence-based case management includes partner notification, prevention of re-infection (advice on sexual behaviour and condom use), and re-testing within a recommended time period after treatment. Adapted from the European Centre for Disease Prevention and Control’s guidance on chlamydia control in Europe,³³ by permission of the European Centre for Disease Prevention and Control.

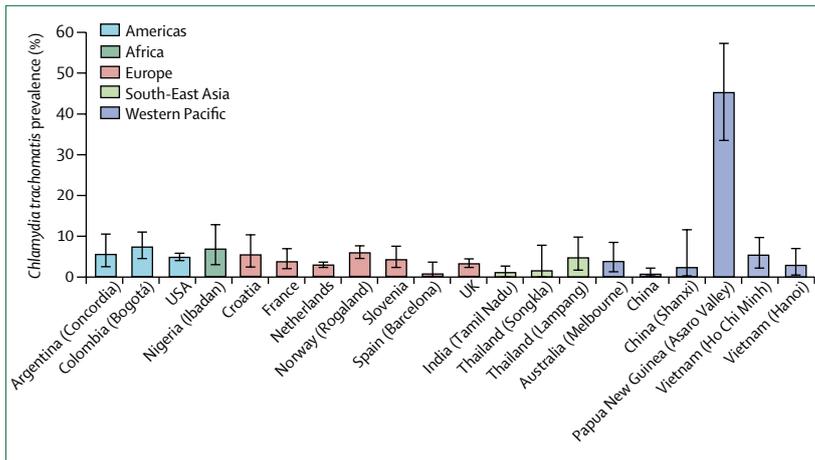


Figure 4: Prevalence estimates of chlamydia in sexually experienced women aged 25 years or younger, by WHO region

Data are estimated in a non-systematic selection of cross-sectional surveys of randomly sampled individuals from the general population to obtain samples representative of a whole country or a region of a country. Each bar represents a single cross-sectional study, error bars are 95% CIs, and n is the number of individuals sampled. *Europe*: Croatia, national (n=151);⁴⁷ France, national (n=106);³⁹ Netherlands, national (n=2626);⁴¹ Norway, Rogaland (n=930);⁴² Slovenia, national (n=265);⁴¹ Spain, Barcelona (n=157);⁴⁸ and the UK, island of Great Britain (n=992).⁴⁵ *Americas*: Argentina, Concordia (n=148);⁴⁸ Colombia, Bogotá (n=278);⁴⁸ and the USA, national (n=unavailable).⁴⁶ *Africa*: Nigeria, Ibadan (n=120).⁴⁸ *South east Asia*: India, Tamil Nadu (n=282);⁴⁹ Thailand, Songkla (n=69);⁴⁸ and Thailand, Lampang (n=129).⁴⁸ *Western Pacific*: Australia, Melbourne (n=135);⁴⁰ China, national (n=194);⁵⁰ China, Shanxi Province (n=46);⁴⁸ Papua New Guinea, Asaro Valley (n=73);⁵¹ Vietnam, Ho Chi Minh (n=158);⁴⁸ and Vietnam, Hanoi (n=123).⁴⁸

measure chlamydia infections are still to be defined, further research and cost-effectiveness analyses are [to be] encouraged.⁷³⁴ With this statement in mind, in this section of the Commission we first outline the global epidemiology of genital chlamydia and its complications. We review evidence about current chlamydia control activities and the effects of screening interventions on chlamydia prevalence and pelvic inflammatory disease. We then discuss the challenges ahead for chlamydia control and question whether we should shift from an infection-based focus on screening uptake to a health outcomes-based focus with improved case management and investment in research to further the understanding about the epidemiology of pelvic inflammatory disease and other chlamydia-associated morbidity.

Global epidemiology of chlamydia infections

WHO estimated that in 2012 about 130·9 million people worldwide became newly infected with chlamydia (figure 1) and that 4·2% of women and 2·7% of men aged 15–49 years had a prevalent infection.² In high-income countries, chlamydia is most common in young heterosexual adults with estimates for adults aged 26 years or younger from a meta-analysis³⁵ of population-based surveys of 4·3% (95% CI 3·6–5·0) in women and 3·6% (2·8–4·4) in men. Chlamydia is also common in MSM attending sexual health clinics, in whom chlamydia positivity ranges from 2% to 5% for urethral infection and 6% to 9% for rectal infection.^{36–38} Few countries have nationally representative surveys of chlamydia prevalence

(ie, random samples of the general population aimed at providing unbiased estimates) but, in those that do,^{39–47} prevalence is similar in women and men aged 25 years or younger, and appears similar in countries that promote widespread chlamydia testing (eg, USA and England)^{45,46} and those without recommendations (eg, Croatia and Slovenia; figure 4).^{41,47} Within countries, higher chlamydia prevalence is associated with social disadvantage⁵² and being in a minority ethnic group.^{44,53}

In low-income and middle-income countries, population-based surveys^{48–51} of chlamydia prevalence are also very uncommon. Estimates of chlamydia prevalence in the general population in the few countries that have done such surveys are mostly similar to those in high-income countries (figure 4).² In a non-systematic collection of studies, the lowest estimate was in women in Tamil Nadu, India, (<1%)⁴⁹ and the highest in Asaro Valley, Papua New Guinea, which estimated a prevalence of 45% (95% CI 33·5–57·3) in women 25 years or younger.⁵¹ Data from unselected 15-year-old to 24-year-old women attending antenatal clinics in the south Pacific islands also found that about 20% of pregnant women have chlamydia.^{54,55} Although we found no nationally representative surveys in South Africa, chlamydia prevalence in pregnant women was as high⁵⁶ as that found in the south Pacific islands. Reasons for regional variations have not been examined in detail. In addition to study design issues, social, cultural, and economic conditions, differences in sexual practices, gender inequality, and circumcision practices might have a role.^{2,54,57}

Global epidemiology of pelvic inflammatory disease and reproductive tract morbidity

Compared with international data about chlamydia infection, little is known about international variations in the incidence and prevalence of pelvic inflammatory disease and other reproductive tract morbidity caused by chlamydia. WHO estimated that chlamydial infections caused a total of 1·43 million disability-adjusted life-years in 2012, most in low-income and middle-income countries (36% in WHO African Region and 25% in WHO South-East Asia Region).⁵⁸

The rate of diagnosis of pelvic inflammatory disease from any cause on discharge from hospital varies from around 37 to 194 cases per 100 000 women aged 15–39 years in different countries.⁵⁹ Chlamydia infection is found in association with about 20% of cases of pelvic inflammatory disease; one study⁶⁰ at a large sexual health clinic in Australia found no causative organism in more than 60% of cases of pelvic inflammatory disease. A major challenge is that there is no consensus about the criteria for the diagnosis of upper genital tract chlamydial disease and there are no accurate non-invasive diagnostic tests, such as radiological imaging or biomarkers. Pelvic inflammatory disease is usually diagnosed on the basis of lower abdominal and cervical signs and symptoms, and diagnostic criteria have poor sensitivity and specificity.²⁸

Natural history of *C trachomatis* and reproductive complications

The host immune response to chlamydia strongly influences susceptibility, clearance, the probability of upper genital tract pathogenesis, and, ultimately, the effectiveness of interventions.^{61,62} Untreated infection that resolves spontaneously might confer some immunity against further infection,⁶³ but the duration of immunity is unclear. Antimicrobial treatment, however, might reduce the immune response and, once treated, people become susceptible to infection again, increasing their risk of repeat chlamydia infection, the so-called arrested immunity hypothesis.^{64,65} Repeat chlamydia infections after treatment are common. In cohort studies,^{66,67} more than 20% of young women enrolled from general practice acquired a repeat infection within 12 months of treatment.

Several reviews^{9,68-71} have examined the risk of sequelae following infection, but estimates are limited by diagnostic challenges. Mathematical syntheses of evidence from different types of studies estimate that the probability of clinical pelvic inflammatory disease following infection with chlamydia is about 16% (95% credible interval 6–25)⁷² and the probability of tubal factor infertility in women who have had at least one chlamydia infection is about 1% (varies depending on age).⁷³ These models also estimate that the proportion of pelvic inflammatory disease attributable to chlamydia is 20%, ectopic pregnancy attributable to chlamydia is 5%, and tubal factor infertility attributable to chlamydia is 29–45%.⁷⁴ The risk of reproductive tract morbidity in women might increase with repeated infection.⁷⁵⁻⁷⁷ It is unclear, however, whether the increase in risk is due to an increase in the cumulative infection time or a higher probability of progression with each subsequent infection.⁹ Ascertainment bias in diagnosis might also explain the observations if physicians are more likely to test for chlamydia in previously infected women who attend with lower abdominal pain, or to assign the diagnosis of pelvic inflammatory disease to a woman diagnosed with chlamydia.

It is not known how or when chlamydia ascends to the upper genital tract, but there are two key hypotheses.⁶² The cellular paradigm assumes that actively infected epithelial cells have a key role and that chemokines secreted by these cells damage the tissues directly. The immunological paradigm assumes that tissue damage occurs because of T-cell responses involved in clearing infection after repeat or persistent infection. If the cellular paradigm is the main driver of chlamydia pathogenesis, then identifying and treating infections before they ascend should be the main focus of control programmes. If the immunological paradigm is more important, then prevention of repeat infections should be prioritised.⁶¹

The timing of ascending infection will also affect the effect of a screening intervention. If chlamydia ascends the canal shortly after infection causing immediate tubal inflammation, annual screening and treatment will not

stop tubal pathology.⁷⁸ A mathematical model⁷⁹ using data from an RCT,⁸⁰ found that the trial results of the effect of a single chlamydia screen on the cumulative incidence of pelvic inflammatory disease up to 1 year later, could only be achieved if progression to pelvic inflammatory disease occurred at a constant rate or at the end of infection.

Pregnant women infected with chlamydia have an increased risk of preterm delivery,⁸¹ and vaginally delivered babies of untreated mothers are at risk of conjunctivitis and pneumonia.⁸² In men, chlamydia can cause epididymo-orchitis,⁸³ but effects on male fertility are disputed; some investigators have found no effect, whereas some investigators suggest decreased semen quality or impaired sperm fertilisation capacity and DNA integrity.^{84,85}

Current chlamydia control activities

Case detection and case management are central to chlamydia control strategy in addition to primary prevention of STIs. Clinical guidelines can include recommendations for opportunistic chlamydia testing to detect asymptomatic infection in people with specified risk factors for infection (figure 3). Opportunistic testing can also be implemented at a population level as a screening programme. Screening programmes require infrastructure not only for chlamydia testing, but for treatment, partner notification, repeat testing, monitoring, and quality control.³² Several high-income countries, including Australia, Canada, UK, and the USA, recommend yearly opportunistic chlamydia screening for all sexually active women or both women and men in the age groups at highest risk of infection.²⁴⁻²⁸ The coverage of chlamydia testing has been used to monitor performance,⁸⁶⁻⁸⁸ but none of these countries sets targets for chlamydia prevalence or pelvic inflammatory disease incidence.

Surveys in Europe show that the number of countries with any chlamydia control activities increased between 2007 and 2012.²⁷ The number of countries reporting the use of chlamydia case management guidelines and opportunistic testing increased, but fewer countries reported that they had an ongoing or planned chlamydia screening programme.²⁷ Of note, the Netherlands and Ireland have elected not to implement screening programmes, and Sweden and Denmark, both of which have had widespread opportunistic chlamydia screening, reported that their STI control strategies have partly shifted from promoting testing to intensifying primary prevention activities.²⁷ Ongoing debate about the evidence to support chlamydia screening⁸⁹⁻⁹¹ and its cost-effectiveness⁸⁹ might have influenced these decisions.

Effectiveness of chlamydia screening in clinical trials

The rationale for chlamydia screening is that testing should detect asymptomatic infections in women before they cause pelvic inflammatory disease or other reproductive complications. If a large enough proportion

of the population can be screened, reduced incidence and prevalence of infection ought to further prevent reproductive complications indirectly by reducing exposure to infection.⁹²

A systematic review⁹⁰ of chlamydia screening interventions found four RCTs^{10,80,93,94} that looked at the effects on the incidence of pelvic inflammatory disease after a single offer of a chlamydia screening test. Overall, the trial results suggest that incidence of pelvic inflammatory disease was lower in the intervention groups than in the control groups (risk ratio [RR] 0.68, 95% CI 0.49–0.94, $P=8\%$).⁹⁰ However, when stratified by risk of bias, the summary effect was smaller in the two trials at low risk of bias (RR 0.80, 95% CI 0.55–1.17)^{80,93} than in those at high risk or unclear risk of bias (0.42, 0.22–0.83),^{10,94} suggesting the overall result might overestimate the protective effects of a screening test. Another completed cluster RCT⁹⁵ will report on the association of up to four rounds of chlamydia testing on the incidence of pelvic inflammatory disease measured in hospitals and primary care clinics.

Two cluster RCTs^{11,96} have looked at the effects of repeated rounds of chlamydia testing targeting men and women aged 16–29 years in the general population. These trials did not find a reduction in estimated prevalence. The trial in the Netherlands invited people each year by post (register-based screening), and the trial in Australia offered opportunistic testing in general practice. In both trials, fewer than 20% of those eligible had a chlamydia test, even with individual patient reminders in the Dutch trial or further support for clinicians in the Australian trial. In Peru, a cluster RCT⁹⁷ in female sex workers found that after 4 years of a multifaceted intervention, estimated prevalence was 28% lower in women in the intervention areas than in areas without an intervention (RR 0.72, 95% CI 0.54–0.98).

Only one trial⁹³ reported on the effect of screening on ectopic pregnancy, female infertility, and epididymitis in men. The intervention involved a single offer of screening, uptake was low, and outcomes did not differ between intervention and control groups. No RCT to date has reported the effects of an intervention that offers chlamydia screening during pregnancy on pregnancy or neonatal outcomes. One RCT⁹⁸ in the USA that compared antibiotic treatment with placebo in women with chlamydia detected at 23–29 weeks of gestation, found no reduction in low birthweight, preterm birth, or neonatal death in intention-to-treat analysis. One cluster RCT⁹⁹ in Uganda of presumptive antibiotic treatment found reductions in low birthweight, neonatal death, and ophthalmia neonatorum; the antibiotic regimen, azithromycin, cefixime, and metronidazole, covered several genital tract infections other than chlamydia.

A review⁸⁹ of cost-effectiveness studies found that chlamydia screening might be cost-effective at nationally accepted thresholds of cost per quality-adjusted life-year in certain circumstances in high-income countries.

Incremental cost-effectiveness ratios are sensitive to assumptions about the epidemiology and natural history of chlamydia, including the probability of developing sequelae, screening uptake, the type of model used, assumptions about quality of life, and the cost of management of the sequelae.^{89,100}

Effects of chlamydia control from observational data

Although RCTs provided data for the efficacy of chlamydia screening interventions in research conditions, surveillance, ad-hoc surveys, and routine data are used to monitor the performance of STI control strategies over time. These sources of data provide valuable information but need to be interpreted carefully, taking into account selection, measurement, ecological, and response biases.

Chlamydia incidence and prevalence

There are no data available to monitor population-based chlamydia incidence over time. In the UK and the USA, population-based surveys of chlamydia prevalence have been repeated during the time when chlamydia testing has increased. In the UK, two surveys 10 years apart found similar estimates in women and men aged 18–24 years in 2010–11 (3.2% in women [95% CI 2.2–4.6], and 2.6% in men [1.7–4.0]) and in 1999–2000 (3.1% in women [1.8–5.2], and 2.9% in men [1.3–6.3]);⁴⁵ chlamydia test coverage increased from about 8% per year in 2008¹⁰¹ to about 30% in 2011.¹⁰² In the USA, chlamydia prevalence in women aged 15–24 years was 4.1% (95% CI 2.4–6.8) in 1999–2000, and 3.8% (2.4–6.0) in 2007–08 with fluctuations in the years between;⁴⁴ chlamydia testing coverage in women aged 16–24 years was reported to be 35% or more per year.^{86,103,104} More intensive chlamydia screening in a small cohort¹⁰⁵ of adolescent women in Indiana, USA, did not reduce prevalence. The women were tested every 3 months and treated if they had a positive chlamydia test result. At each interval, about 10% of women tested were positive for chlamydia.¹⁰⁵

Several factors might help explain why the estimated chlamydia prevalence in the general population does not appear to have declined during a period of increasing chlamydia testing. First, the small sample size of chlamydia prevalence surveys reduces statistical precision, and modest reductions cannot be ruled out. Second, chlamydia test uptake might not have been sufficiently high for long enough; mathematical modelling studies show that any level of a hypothetical chlamydia screening intervention will reduce prevalence over time, but that coverage of about 35% per year or more would be needed to achieve substantial reductions within a 10-year period.^{106,107} Third, suboptimal case management with low numbers of treated sexual partners, antimicrobial treatment failure, and an increasing incidence of repeated infection following antimicrobial treatment for chlamydia might sustain numbers of prevalent infections. Fourth, it is possible that testing and treatment is reducing immunity against chlamydia in the population, leading to increased

susceptibility to infection.⁶⁵ Fifth, autoinoculation in women of cervical chlamydia infection from the rectal site has been suggested as a factor that could contribute to repeated detection of chlamydia in genital samples;¹⁰⁸ reports of rectal chlamydial infection in women have increased.^{109,110} Finally, persistent forms of *C trachomatis* might contribute to sustained prevalence. Chlamydia under the selective pressure of β -lactam antibiotics,¹¹¹ interferon γ , or deprivation of nutrients such as iron and aminoacids can enter a persistent and metabolically inactive state^{112,113} in which they are viable but semi-refractory to treatment.^{111,114,115}

Pelvic inflammatory disease and other reproductive tract complications

Routine data for diagnoses on discharge from hospital have shown declining trends in pelvic inflammatory disease and ectopic pregnancy during periods of increasing chlamydia testing and diagnosis in several countries.¹¹⁶⁻¹²² Ecological associations between chlamydia testing and pelvic inflammatory disease need careful interpretation.⁶¹ Comparisons across larger numbers of countries and longer time periods show that the degree to

which chlamydia control efforts account for the declining trend in pelvic inflammatory disease incidence is not so clear. The Organisation for Economic Co-operation and Development collates data about diagnoses on discharge from hospital, by diagnostic categories, for its member countries.¹²³ Figure 5 shows data for inflammatory diseases of female pelvic organs, which includes pelvic inflammatory disease from any cause (appendix). There are limitations in comparing the absolute rates between countries because of differences in how the conditions are diagnosed, investigated, and coded. However, trends over time show a general decrease in the rate of discharge from hospital for inflammatory diseases of the pelvis in the past two decades in countries that have different chlamydia control activity. For example, in Belgium, Ireland, and Slovenia, countries with little chlamydia testing,²⁷ hospital discharge diagnoses of inflammatory disease in female pelvic organs have decreased by about 30% in the past 15 years. In countries with data from the early 1990s, the biggest declines in hospital discharges coincide with sudden sexual behaviour changes and with decreases in the rates of other STIs, which are attributed to responses to the HIV pandemic.^{20,91,124} A cross-country analysis⁵⁹ that

See Online for appendix

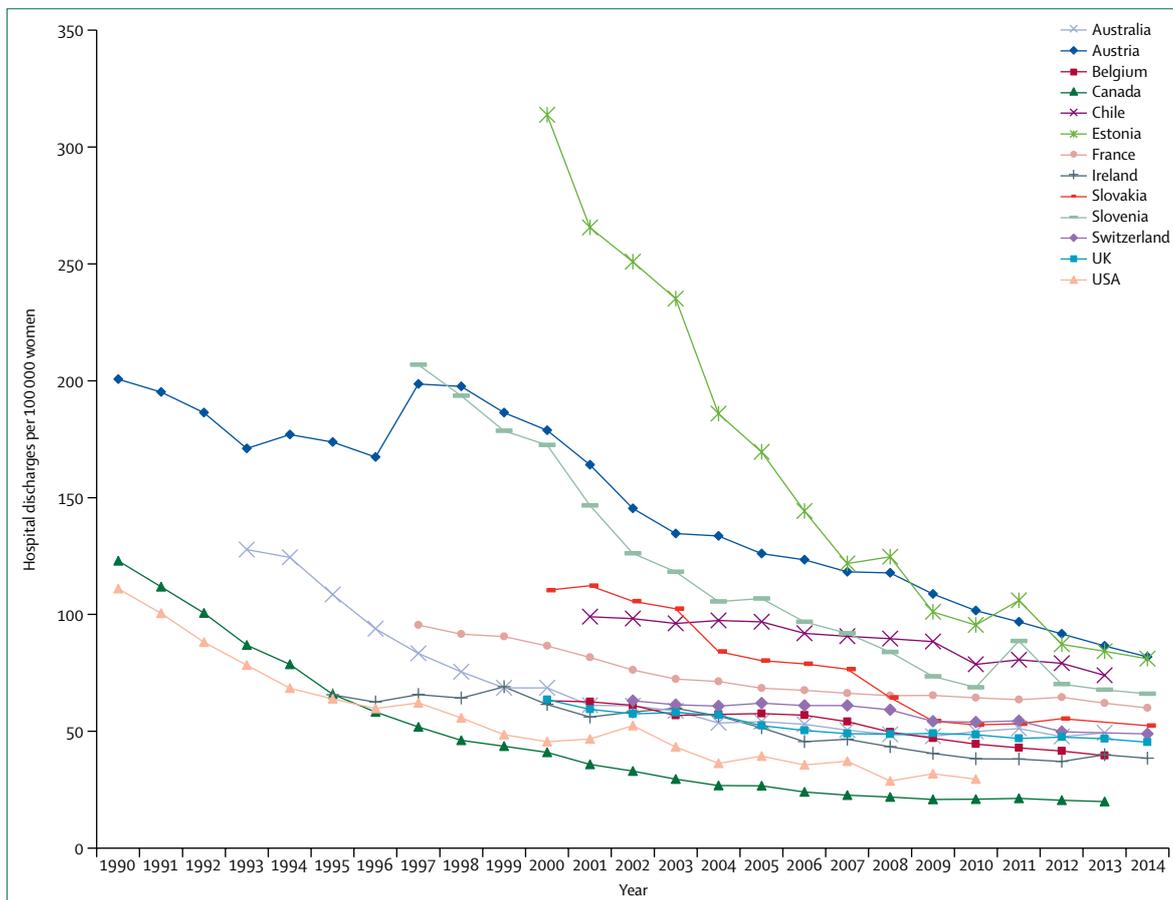


Figure 5: Hospital discharge rates for inflammatory disease in female pelvic organs. Data are from the Organisation for Economic Co-operation and Development.¹²³ See the appendix for further details.

compared hospital discharge data for pelvic inflammatory disease, ectopic pregnancy, and infertility also found similar trends in high chlamydia testing countries (Denmark, New Zealand, and Sweden)^{27,125} and low testing countries (Australia, Netherlands, and Switzerland)^{27,126} from 1999 to 2008. While inpatient admissions for these conditions have become less common, in countries that collect data from ambulatory and primary care settings, pelvic inflammatory disease diagnoses have also fallen.

Future challenges for the control of chlamydia

Shift of focus from monitoring test uptake to measuring pelvic inflammatory disease incidence

To date, chlamydia control strategies in several high-income countries promote screening for asymptomatic infection with a focus on monitoring chlamydia test uptake and chlamydia prevalence. It is surprising therefore, that pelvic inflammatory disease incidence and its complications are not routinely monitored, given that prevention of this disease and its associated complications is a key goal of chlamydia control. There has also been inadequate attention on research to further understand the natural history and immunopathology of *C trachomatis* infection, including the development of non-invasive measures of clinical and subclinical tubal infection, inflammation and damage, and biomarkers to predict upper genital tract pathology.⁶¹ **Urgent investment is needed in research to further the understanding of chlamydia natural history and develop non-invasive tools to detect upper genital tract disease, and to establish surveillance systems to record and monitor trends in pelvic inflammatory disease and other chlamydia-related complications over time.**

Realistic targets for chlamydia prevalence and incidence

Strategies for chlamydia control should be appropriate to chlamydia prevalence and incidence in the general population and key populations, such as pregnant women, sex workers, and MSM. In countries with longstanding case detection activities, including opportunistic testing and screening (mostly high-income countries), it is conceivable that chlamydia prevalence has reached an equilibrium and that further investments to increase the overall coverage of chlamydia testing might not achieve additional gains in reducing the burden of infection in the population. Within these countries, however, chlamydia control efforts should focus on the reduction of social and ethnic inequalities in chlamydia infection and pelvic inflammatory disease, improvement of health outcomes through better case management of those diagnosed with chlamydia, and implementation of surveillance systems to more reliably and accurately monitor pelvic inflammatory disease, ectopic pregnancy, and infertility incidence in primary care and ambulatory and hospital settings.

In low-income and middle-income countries, efforts should be directed towards strengthening of primary

prevention and case management for people presenting with symptomatic chlamydia infection, and of research to better define the prevalence of infection and burden of chlamydial disease. In some countries, such as among the south Pacific islands, chlamydia prevalence in the general population appears to be very high. Here, intensive research is needed to understand the reasons for high chlamydia prevalence and to plan for evidence-based sustainable interventions. Mass drug administration of azithromycin for trachoma control has been associated with a reduction in the prevalence of genital chlamydia.¹²⁷ Given the high probability of re-infection, possible increase in susceptibility to pelvic inflammatory disease after treatment, and selection pressure for antimicrobial resistance, mass treatment should not be introduced to control genital chlamydia infections in the absence of a sustainable comprehensive chlamydia control strategy and health service infrastructure. Nevertheless, in all countries, there are opportunities to improve case management of diagnosed cases to reduce the risk of chlamydia-associated complications.

Improved case management

Antimicrobial resistance has not been detected in *C trachomatis*, but the widespread use of a single-dose azithromycin for uncomplicated chlamydia infections is being questioned.^{128–131} Two meta-analyses comparing a single 1 g dose of azithromycin with 7 days of doxycycline (100 mg twice per day) found that azithromycin efficacy was slightly lower for urogenital chlamydia (94% vs 97%)¹³² and substantially lower for rectal chlamydia infection (83% vs 99%).¹³³ For men, the efficacy of azithromycin for urogenital and rectal infections was below WHO's threshold of 95% recommended for a first-line treatment.¹³⁴ Furthermore, the widespread use of single-dose azithromycin to treat chlamydial infections is likely to have contributed to macrolide resistance in *Treponema pallidum*,^{135,136} *N gonorrhoeae*,¹³⁷ and *M genitalium*.¹³⁸

Partner notification has been recommended as a part of most STI management strategies, including syndromic management, to help interrupt transmission of infections, prevent potential re-infection, and prevent complications. Improvements in partner notification are vital for chlamydia control. In addition to preventing re-infection and halting ongoing transmission, testing and treating of sexual partners of people with chlamydia is efficient for case finding because they are likely to also be infected.¹³⁹ From a health economic perspective, doubling the efficacy of partner notification (from 0.4 to 0.8 partners per index case) would cost less than increasing the screening coverage of men to the same level as women.¹⁴⁰ Expedited partner therapy and accelerated partner therapy are partner notification approaches that allow partners to receive treatment without a face-to-face consultation in a health-service setting. A Cochrane review¹³⁹ has found that expedited partner therapy was more successful than simple patient referral in reducing

repeated infection in patients with gonorrhoea and chlamydia. Accelerated partner therapy, its equivalent in the UK, is acceptable to health-care providers and patients,¹⁴¹ and an RCT to evaluate its effectiveness in reducing repeated infection (LUSTRUM is scheduled to start in 2018). Further work is needed to resolve medico-legal issues that limit wider implementation of these partner notification approaches¹⁴² and to ensure that opportunities to test for HIV infection and other STIs are not missed.¹⁴⁰

Because no RCTs have evaluated the effect on reducing chlamydia transmission in the population of repeated testing for chlamydia after treatment, there is an absence of evidence for this effect, but re-testing can detect repeat infections early. Guidelines about re-testing intervals vary between countries: some countries recommend a test of cure within 3–6 weeks after diagnosis,²⁷ whereas others recommend testing to find repeated infections within 3–6 months.^{27,28,143,144} A mathematical modelling study¹⁴⁵ suggests that an interval of 2–5 months after treatment optimises the detection of repeat infection. Mailed specimen collection kits and mobile phone text messages are effective interventions for increasing re-testing uptake, and their effect on reducing chlamydia transmission and pelvic inflammatory disease should be evaluated.^{146,147}

Rapid and point-of-care tests

Rapid diagnostic tests and point-of-care tests allow diagnosis and treatment decisions to be made at the same visit, reducing time to treatment and losses to follow-up.^{148,149} We discuss the status of point-of-care tests for chlamydia and other STIs in part 4 of this Commission.

Chlamydia vaccine

In all countries, an effective vaccine would overcome many of the problems of chlamydia control. The profile of a chlamydia vaccine remains to be determined. It is unclear whether the priority is to generate high levels of immunity against chlamydial infection or strong protection against upper genital tract disease, with limited protection against infection.¹⁵⁰ However, the prospects for a chlamydia vaccine are now considered promising.¹⁵¹ WHO and the US National Institutes of Health have developed an STI vaccine roadmap that identifies priority actions for chlamydia vaccine development.¹⁵¹ Several candidate chlamydia vaccines could enter phase 1 clinical trials in the next few years.¹³

Conclusion

In the past 20 years, awareness about chlamydia as a common STI worldwide has increased.^{2,34} Over the same period, research to increase knowledge about the natural history of chlamydia or its disease burden has not kept up. The focus of chlamydia control efforts in high-income countries has been on increased coverage of testing for asymptomatic chlamydia infection, while

fewer advances have been made in research to improve primary prevention and case management. Chlamydia control priorities could be set in future on the basis of infectious disease principles, to define acceptable prevalence and incidence of chlamydia, and disease that match the epidemiology in different geographical regions and within different population groups. Priorities for improving case management include effective partner notification strategies and re-testing to detect repeat infections early and reduce the risk of chlamydia association complications. Surveillance systems could improve the recording and monitoring of trends in pelvic inflammatory disease and other chlamydia-related complications over time. The investment and research agendas called for by international experts^{61,151,152} to further the understanding about the natural history of chlamydia and develop non-invasive measures to predict upper genital tract disease should be implemented.

Part 2: Gonorrhoea—what are current and future treatment options?

Of the 78·3 million estimated new gonorrhoea cases in adults globally in 2012, the highest number was in the WHO Western Pacific Region (35·2 million cases, figure 1). Accordingly, the vast majority of the gonorrhoea burden globally is in low-income and middle-income countries.² There is no vaccine against *N gonorrhoeae*, so effective, accessible, and inexpensive antimicrobial treatment is an essential part of gonorrhoea control measures together with primary prevention, diagnostics, partner notification, and epidemiological surveillance. If *N gonorrhoeae* infections become untreatable, people that have complications of infection, such as pelvic inflammatory disease, ectopic pregnancy, and infertility, and the facilitation of HIV transmission and acquisition, will substantially increase.^{2,153–155} *N gonorrhoeae* has developed antimicrobial resistance to all drugs previously or currently recommended for treatment. We review and discuss in this section of the Commission the emergence and spread of antimicrobial resistance in *N gonorrhoeae*, current and future treatment options with a focus on novel antimicrobials, and additional actions to control gonorrhoea and antimicrobial resistance.

Emergence and spread of antimicrobial resistance in *N gonorrhoeae*

Since the first antimicrobials, sulphonamides, were introduced for the treatment of gonorrhoea in the mid-1930s, gonococci have repeatedly shown an extraordinary ability to develop resistance to all antimicrobials that have been introduced, using almost all known antimicrobial-resistant mechanisms.¹⁵⁴ The hypothesis is that, in modern times, antimicrobial resistance in gonococci has usually developed first in the WHO Western Pacific Region (frequently Japan) followed by international spread.^{154,156,157} For many infectious diseases, including gonorrhoea, overuse and misuse,

For more on the LUSTRUM trial see <https://www.lustrum.org.uk>

including unrestricted access and suboptimal quality and dosing, of antimicrobials have resulted in antimicrobial resistance in bacterial species that share their mechanisms of resistance through horizontal gene transfer and subsequent recombination. Horizontal gene transfer is particularly possible in the pharynx, which harbours many non-gonococcal *Neisseria* spp, and can facilitate the emergence and spread of antimicrobial resistance¹⁵⁸ particularly in high-frequency transmitting populations, such as MSM and commercial sex workers. Inadequate monitoring of in-vitro antimicrobial resistance, pharmacokinetics and pharmacodynamics, and clinical efficacy of antimicrobials facilitate the initial emergence of antimicrobial resistance and the subsequent spread of resistant strains, particularly in settings with a high incidence of gonorrhoea and ineffective control measures.^{153,154,156,157,159} It is crucial to improve the understanding of the dynamics and drivers of the emergence of antimicrobial resistance and the transmission of gonococcal strains and their mechanisms of resistance, which can provide an enhanced rationale for antimicrobial stewardship and management. Whole-genome sequencing and other new molecular technologies will be invaluable to elucidate the evolution and transmission of gonococcal strains and their antimicrobial resistance, locally, nationally, and internationally.¹⁶⁰

Many countries already have high prevalence of gonococcal resistance to all antimicrobials that have been used for treatment, including sulphonamides, penicillins, tetracyclines, fluoroquinolones, and early generation macrolides and cephalosporins.^{153–155,159} The prevalence of multidrug-resistant (MDR)¹⁵⁶ gonococcal strains substantially increased during the past decade.^{153–155,159} Resistance to extended-spectrum cephalosporins, the last remaining options for empirical first-line monotherapy, has also been detected in many countries. The first extensively drug-resistant (XDR)¹⁵⁶ gonococcal strains, displaying high-level resistance to ceftriaxone (minimum inhibitory concentration [MIC] of 2–4 mg/L) and retained resistance to previously used therapeutic antimicrobials, have also been isolated in Japan, France, and Spain.^{161–163} Fortunately, these so-called superbugs have not spread further, suggesting substantially decreased biological fitness. Some additional ceftriaxone-resistant strains isolated in Japan and Australia during recent years have also been studied in detail,^{164–166} showing that both ceftriaxone-resistant strains and ceftriaxone resistance-determining penicillin-binding protein 2 (PBP2) segments (lethal target for extended-spectrum cephalosporins) are spreading.¹⁶⁶ Additional sporadic gonococcal strains with low-level ceftriaxone resistance have been described internationally.^{159,167} Importantly, strains with non-mosaic PBP2s can also develop ceftriaxone resistance, as described particularly in Asia—eg, China, South Korea, and Vietnam—but also in Argentina.^{159,167} Many additional ceftriaxone-resistant

strains might already be circulating but are undetected because of suboptimal antimicrobial resistance surveillance in many settings. Ceftriaxone or dual antimicrobial therapy (mainly a single dose [$\times 1$] of ceftriaxone 250–500 mg plus azithromycin 1–2 g $\times 1$) are currently the only options for empirical first-line therapy in most countries.^{159,168–173}

Current treatment of gonorrhoea

Principles and definitions used in conventional antimicrobial treatment

Empirical therapy is treatment given at the first health-care visit before any laboratory results are available, following recommendations in evidence-based treatment guidelines. The ideal characteristics of a first-line therapy are that it has high efficacy (cures >95% of urogenital and extragenital infections), includes multiple targets (to increase activity and delay resistance development), has no or minimal cross-resistance with other antimicrobials, is showing slow selection or induction of resistance determinants in *N gonorrhoeae*, has different mechanisms of action for drugs included in dual therapy, is available as a single oral dose with a fixed-dose combination for dual oral therapy, is widely available and affordable in appropriate quality and dose, has an appropriate paediatric formulation (eg, suspension or syrup), is stable at high temperature and humidity, has no or minimal drug–drug interactions, is safe (including during pregnancy and lactation), is well tolerated, and is active against concurrent *C trachomatis* and *M genitalium* infections (making it useful in syndromic management).

Treatment guidelines should be informed by up-to-date, local, and quality-assured surveillance data of antimicrobial resistance. Antimicrobial resistance can emerge quickly and patterns vary geographically so large RCTs are rarely done. Changes in recommended treatments are mostly based on laboratory-based surveillance data of antimicrobial resistance (the point estimate of tested strains should show that $\geq 95\%$ are susceptible), rather than clinical surveillance of cure rates. Alternative criteria for changing a recommended first-line therapy have been suggested, for example that the lower 95% CI rather than the point estimate should be 95% or more, or that more than 99% or more than 97% of strains from high-frequency transmitting populations should be susceptible.^{174–176} Ideally, additional factors should also be taken into consideration, including prevalence, local epidemiology, diagnostics used, transmission frequency, partner notification and management strategies, treatment strategies (strategies used and antimicrobials available), and cost-effectiveness.^{154,159,177}

Antimicrobial monotherapy

Oral cefixime (400 mg $\times 1$) and especially intramuscular or intravenous ceftriaxone (125–1000 mg $\times 1$) have been the last options for empirical first-line monotherapy in many countries.^{153–157,159,171} Unfortunately, treatment failures with

cefixime have been verified in many countries worldwide, and rare failures following treatment of pharyngeal gonorrhoea with ceftriaxone (250–1000 mg×1) have also been verified in several countries.^{157,159} Verified ceftriaxone treatment failures are probably a small part of the bigger problem, because few countries do active surveillance and confirm treatment failures according to international recommendations.

To avoid treatment failures, increased doses of intramuscular or intravenous ceftriaxone (1 g×1) have been used in some countries.^{178–181} On the basis of the dosages administered for community-acquired pneumonia, 2 g or less of a single dose of ceftriaxone would possibly be tolerated. Increased doses of ceftriaxone are probably only a short-term solution based on current knowledge of gonococcal antimicrobial resistance emergence, MICs of extended-spectrum cephalosporins in gonococcal superbugs and other strains resistant to these cephalosporins, verified treatment failures of extended-spectrum cephalosporins, and pharmacokinetic and pharmacodynamic simulations of these cephalosporins. For example, 20–24 h of free extended-spectrum cephalosporins above MIC (the duration of time free drug concentrations remain above the MIC, $fT>MIC$) can be required for effective treatment with these cephalosporins.¹⁸² According to Monte Carlo simulations, reflecting the diversity inherent within patient populations of a single 1 g dose of ceftriaxone, sufficient $fT>MIC$ (20–24 h) might not be achieved in 5% or less of patients even for gonococcal strains with ceftriaxone MICs as low as 0.125 mg/L, which are relatively common in many countries. The median $fT>MIC$ is 40.3 h but the lower 95% CI of $fT>MIC$ (19.6 h) is below the required 20–24 h.¹⁸² These findings might overestimate the number of treatment failures because few failures have been identified, but they show the wide circulation of gonococcal strains that could cause ceftriaxone treatment failures.

Dual antimicrobial therapy

Several agencies, regions, and countries recommend dual antimicrobial therapy for empirical first-line gonorrhoea treatment in response to emerging resistance to extended-spectrum cephalosporins, including WHO (global recommendations), the WHO European region, Germany, UK, Australia, USA, and Canada.^{28,168–173} To summarise, all these guidelines, except those of WHO¹⁷³ and Canada,¹⁷² recommend only ceftriaxone plus azithromycin as first-line therapy for uncomplicated anogenital gonorrhoea in adults. There are no RCTs that provide optimal doses of ceftriaxone and azithromycin for currently circulating gonococcal strains, and recommendations vary: intramuscular ceftriaxone doses range from 250 mg×1 (WHO, USA, and Canada) to 1 g×1 (Germany); and doses of oral azithromycin range from 1 g×1 (WHO, USA, Canada, UK, and Australia) to 2 g×1 (Europe).^{28,168–173} WHO¹⁷³ and Canadian¹⁷² guidelines

additionally recommend as oral first-line dual therapy cefixime of 400 mg×1 (WHO) or 800 mg×1 (Canada) plus azithromycin of 1 g×1.^{172,173} Pharmacodynamic studies have shown that 800 mg of cefixime (especially 400 mg×2, given 6 h apart) increases the cefixime $fT>MIC$ compared with 400 mg×1.¹⁸² In most countries, however, only cefixime 400 mg×1 is licensed because gastrointestinal adverse events are more common with 800 mg×1.¹⁸³ Many clinical failures have been verified with cefixime at 400 mg×1,^{157,159} but also with cefixime at 800 mg×1.¹⁸³ Finally, WHO also recommends monotherapy with 250 mg×1 of ceftriaxone, 400 mg×1 of cefixime, or 2 g×1 of spectinomycin, but only if up-to-date, local, high-quality surveillance data of antimicrobial resistance support their use.¹⁷³ Owing to low proportions of cure, spectinomycin monotherapy should only be used if pharyngeal gonorrhoea has been excluded, otherwise azithromycin should also be given.¹⁵³

The recommendations for dual therapy with ceftriaxone plus azithromycin are not based on evidence from RCTs. The selection of these antimicrobials and their doses has been based on surveillance data of antimicrobial resistance, predicted trends of antimicrobial resistance, old clinical trials, case reports of clinical failures with extended-spectrum cephalosporins,^{157,159} pharmacokinetic and pharmacodynamic simulations,¹⁸² and expert opinion.¹⁷¹ Unfortunately, these recommended antimicrobials might not protect each other from the development of resistance.¹⁸⁴ However, in practice the combination of ceftriaxone and azithromycin appears to cure almost all gonorrhoea cases, concomitant resistance to ceftriaxone and azithromycin is exceedingly rare, and consequently the spread of any emerged ceftriaxone resistance appears to have been mitigated so far. Additionally, dual therapy eradicates concurrent *C trachomatis* and many *M genitalium* infections. However, susceptibility to ceftriaxone has been decreasing and azithromycin resistance is increasing in many settings internationally, and concomitant resistance to ceftriaxone and azithromycin has emerged.^{153,154,159} Gonococcal strains with high-level azithromycin resistance (MIC ≥256 mg/L) have been isolated in several countries and an outbreak of such strains is ongoing in the UK.^{137,159} All the recommended and alternative dual antimicrobial regimens include 1–2 g×1 of azithromycin. However, in practice, many gonorrhoea cases will be administered ceftriaxone monotherapy, because of azithromycin resistance. Furthermore, the first global treatment failure with dual therapy (500 mg×1 of intramuscular ceftriaxone plus 1 g×1 of oral azithromycin), due to a ceftriaxone-resistant and azithromycin-resistant gonococcal XDR strain, was verified in the UK.¹² The higher cost and inconvenience of dual therapy also render it less suitable for low-income and middle-income countries, where high-quality ceftriaxone can be scarce, which will limit the mitigation of emergence and spread of gonococcal antimicrobial resistance globally.

Future treatment of gonorrhoea

Improved dual antimicrobial therapy

Dual antimicrobial therapy^{28,168–173} is recommended for treatment where up-to-date, local, and high-quality antimicrobial resistance surveillance data do not support other therapy. Owing to the rapid emergence of azithromycin resistance in *N gonorrhoeae* and also in additional STIs such as *M genitalium* infections, at least as a temporary solution, azithromycin could be replaced by solithromycin if an ongoing phase 3 RCT (SOLITAIRE-U; NCT02210325) provides evidence of effectiveness, tolerability, and safety. Furthermore, susceptibility to spectinomycin is exceedingly high globally,^{153,154,159,171,173} and it would be valuable to have this drug widely available again. There are concerns that spectinomycin resistance would be rapidly selected if it was more frequently used, but it has been used in South Korea for decades (52–73% of treatments in 2009–12) and no resistant isolates have been found since 1993.¹⁸⁵ Nevertheless, spectinomycin only eradicates a proportion of pharyngeal gonorrhoea (52%)¹⁸⁶ and should, ideally, be used in a dual therapy combination (eg, with solithromycin), which might protect it from resistance development.

Novel accessible and cost-effective antimicrobials are essential. These antimicrobials should be used in new dual therapies, to preserve their effectiveness, and, if there are oral preparations, in fixed-dose combinations that increase activity and adherence and mitigate resistance development. One RCT¹⁸⁷ has evaluated two novel dual regimens, gentamicin (240 mg×1 intramuscularly) plus azithromycin (2 g×1 orally), and gemifloxacin (320 mg×1 orally) plus azithromycin (2 g×1 orally), for the treatment of uncomplicated urogenital gonorrhoea in men and women. Gentamicin plus azithromycin cured all 202 (100%) cases and gemifloxacin plus azithromycin cured 198 (99·5%) of 199 cases. No serious adverse events occurred, but mild-to-moderate gastrointestinal adverse events, such as nausea and diarrhoea, were frequent. Of concern, 3·3% of patients administered gentamicin plus azithromycin and 7·7% of patients administered gemifloxacin plus azithromycin vomited within 1 h and might have lost a substantial amount of the drugs.¹⁸⁷ Consequently, these two regimens should mainly be considered for treatment of ceftriaxone-resistant cases, treatment failures with recommended regimen, or allergy to extended-spectrum cephalosporins.

Repurposing old antimicrobials

Old antimicrobials, such as gentamicin, ertapenem, and fosfomycin, have been suggested for future therapy. Several shortcomings with these antimicrobials have been previously reviewed. Briefly, clinical data are absent for ertapenem or old, incomplete, mainly low-quality, and only from small geographic areas, patient populations of only men, and only urogenital anatomical sites; suboptimal cure rate is at less than 95%; and

appropriate pharmacokinetic and pharmacodynamic parameters for gonorrhoea, relationship between MIC and treatment outcome, and resistance breakpoints are missing.^{153,154,157,159,177,188–190} These limitations preclude their widespread use as empirical monotherapies, but particularly in new dual antimicrobial regimens they might be useful in case of ceftriaxone resistance or allergy to extended-spectrum cephalosporins. A multi-centre (n=eight) non-inferiority phase 3 RCT, aiming to enrol 718 participants, evaluating intramuscular gentamicin (240 mg×1) plus oral azithromycin (1 g×1) for treatment of uncomplicated anogenital and pharyngeal gonorrhoea is ongoing; the comparator is intramuscular ceftriaxone (500 mg×1) plus oral azithromycin (1 g×1). Finally, with the use of timely molecular prediction of resistance to ciprofloxacin, on the basis of targeting *gyrA* mutations, this old antimicrobial can be used as personalised treatment for patients in which ciprofloxacin susceptibility has been confirmed.^{191–194}

New antimicrobials with only in-vitro data available

Several new antimicrobials (derivatives of earlier developed antimicrobials or new antimicrobial classes) have proven relatively potent in-vitro activity against gonococcal strains, but clinical data are mainly absent. These antimicrobials include the fluoroquinolones avarofloxacin (JNJ-Q2), delafloxacin (RX-3341), sitafloxacin (DU-6859), and WQ-3810; bicyclic macrolides (bicyclicolides) modithromycin (EDP-420/EP-013420/S-013420) and EDP-322; the tetracyclines eravacycline (TP-434) a fluorocycline and tigecycline a glycolcycline; 2-acyl carbapenems SM-295291 and SM-369926; aminomethyl spectinomycin;¹⁹⁵ lipopeptide dalbavancin; pleuromutilin lefamulin (BC-3781); boron-containing inhibitor AN3365; LpxC inhibitors; FabI inhibitor (eg, MUT056399); tricyclic topoisomerase inhibitor REDX05931 (evaluated also in mice);^{196,197} and topoisomerase II inhibitor VXc-486 (VT12-008911), which have all been recently reviewed.^{153,154,157,159,177,195–197} A phase 3 RCT (NCT02015637) designed to evaluate oral delafloxacin (450 mg×2 taken simultaneously) compared with intramuscular ceftriaxone (250 mg×1) for treatment of uncomplicated gonorrhoea was recently terminated on the basis of an independent interim review that concluded that the single delafloxacin monotherapy dose might not be sufficient to treat some patients.¹⁹⁸

Novel antimicrobials in clinical trial evaluation

Solithromycin (CEM-101), zoliflodacin (AZD0914/ETX0914), and gepotidacin (GSK2140944) are novel orally administered antimicrobials in clinical evaluation for treatment of gonorrhoea.^{199–219} Table 1 summarises the main characteristics of these antimicrobials.

The first fluoroketolide, solithromycin, is structurally similar to the ketolide telithromycin but it is less toxic and has increased stability and activity.^{204,210,214} Solithromycin,

For more on the ongoing non-inferiority gentamicin plus azithromycin phase 3 trial see <http://www.research.uhb.nhs.uk/gtog>

similar to other macrolides and ketolides, inhibits protein synthesis, but solithromycin has three bacterial 23S rRNA binding sites that increase the activity and delay development of resistance.²¹⁰ Solithromycin has proven a high in-vitro activity against geographically, temporally, and genetically diverse wild type, MDR, and XDR international gonococcal reference strains and clinical isolates, with in-vitro resistance and clinical resistance to all currently and previously recommended antimicrobials.^{204,214} No major cross-resistance with other antimicrobials has been observed, but strains with high-level azithromycin resistance (MIC ≥ 256 mg/L) can be resistant to solithromycin (MICs 4–32 mg/L).²⁰⁴

In a study²¹⁶ of a single dose of solithromycin (50–1600 mg) administered to healthy adults, the time-to-peak concentration (T_{max}) was 1.5–6 h and the plasma half-life ($T_{1/2}$) was 3.2–7.4 h. A phase 1 study (NCT02348424) evaluating pharmacokinetic properties, safety, and tolerability of a 1 g oral dose of solithromycin within plasma, vaginal, cervical, seminal, rectal, and pharyngeal samples has recently finished.

A phase 2 clinical trial²⁰⁵ evaluating the efficacy of solithromycin (1 g \times 1 or 1.2 g \times 1 orally) in the treatment of men and women with uncomplicated urogenital gonorrhoea was published in 2015. 46 patients received solithromycin and were evaluable for microbiological cure (1 g \times 1 [n=22] and 1.2 g \times 1 [n=24]). All patients subsequently had negative cultures at all sites examined. Solithromycin additionally cured nine (82%) of 11 *C trachomatis* infections and seven (70%) of ten *M genitalium* infections. The adverse effects were dose-dependent, and the most prevalent adverse effects were mild diarrhoea (42%), nausea (26%), and fatigue or asthenia (10%) after administration of 1 g \times 1 of solithromycin. However, most nausea and vomiting (3%) appeared 1 h or more after ingestion and the drug was possibly already absorbed.²⁰⁵ Additional data are needed and, to further increase gastrointestinal tolerability, an extended-release formulation of solithromycin might be valuable. Solithromycin (1 g \times 1 orally) is currently in a phase 3 non-inferiority RCT (SOLITAIRE-U; NCT02210325) for treatment of uncomplicated urogenital gonorrhoea in men and women, evaluating efficacy, tolerability, and safety (table 1). Of concern, analysis of the data from the initial patient cohort of 262 patients showed that solithromycin had a high success of 80.5% in the microbiological intention-to-treat population but only 91.3% in the microbiologically evaluable population (100% success for women). Consequently, solithromycin did not show non-inferiority to standard-of-care treatment. No *N gonorrhoeae* isolates showed solithromycin resistance at baseline or test-of-cure. Thus, the solithromycin treatment failures were possibly related to the duration of solithromycin exposure at the site of infection and adjustments to the dosing regimen (or possibly formulation, or both), without substantially increasing the dose-dependent adverse

Class	Mode of action	Bacterial target (known resistance mutations)	In-vitro activity against <i>Neisseria gonorrhoeae</i>			Phase of clinical trial (aimed size)	Dose	Comparator	Adverse effects
			MIC range (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)				
Solithromycin (CEM-101)	Binds to the 50S ribosomal subunit, inhibiting protein synthesis	23S rRNA (2059A \rightarrow G in 23S rRNA alleles, overexpressed MtrCDE increases MIC ^{204,215})	0.001–32 mg/L ^{204,212}	0.064–0.125 mg/L ^{204,212}	0.125–0.25 mg/L ^{204,212}	Phase 3 (300 participants)	1 g \times 1 orally	Ceftriaxone 500 mg \times 1 intramuscularly plus azithromycin 1 g \times 1 orally	Diarrhoea, nausea, and fatigue or asthenia*
Zolliflodacin (AZD0914, ETX0914)	DNA biosynthesis inhibition and accumulation of double-strand cleavages	DNA gyrase and possibly topoisomerase IV (Asp429Asn, Asp429Ala, and Lys450Thr in GyrB, ^{199,203} overexpressed MtrCDE increases MIC ²⁰⁵)	≤ 0.002 –0.25 mg/L ^{208,213,212,218}	0.064–0.125 mg/L ^{208,213,212,218}	0.125–0.25 mg/L ^{208,213,212,218}	Phase 2 (180 participants)	2 g \times 1 orally or 3 g \times 1 orally	Ceftriaxone 500 mg \times 1 intramuscularly	Transient dysgeusia and mild headache
Gepotidacin (GSK2140944)	Inhibits DNA replication through interactions with GyrA (subunit of DNA gyrase) and ParC (subunit of topoisomerase IV)	DNA gyrase and topoisomerase IV (data not available)	≤ 0.015 –1 mg/L ²¹⁵	0.25 mg/L ²¹⁵	0.5 mg/L ²¹⁵	Phase 2 (100 participants)	1.5 g \times 1 orally or 3 g \times 1 orally	No comparator	Data not available

MIC=minimum inhibitory concentration. MIC₅₀=minimum inhibitory concentration required to inhibit the growth of 50% of organisms. MIC₉₀=minimum inhibitory concentration required to inhibit the growth of 90% of organisms. \times 1=single dose. NA=not applicable. *Adverse events observed in 10% or more of patients who had solithromycin 1 g \times 1. Most nausea and vomiting appeared 1 h or more after ingestion of solithromycin, which indicates that the drug was already absorbed.²⁰⁵

Table 1: Novel antimicrobials in different stages of clinical trial evaluation for treatment of gonorrhoea

effects observed in the phase 2 study, might need to be considered.²²¹

The first spiropyrimidinetrione (non-fluoroquinolone topoisomerase II inhibitor), zoliflodacin, targets DNA gyrase (specifically GyrB), but possibly targets also topoisomerase IV, and has novel mechanisms of action different from all other available antimicrobials.^{199,200,203} Zoliflodacin initially showed high in-vitro activity against 250 geographically, temporally, and genetically diverse wild type, MDR, and XDR international gonococcal reference strains and clinical isolates, with in-vitro and clinical resistance to all currently and previously recommended antimicrobials.²⁰⁸ Additionally, consecutive, contemporary, and clinical isolates in Europe (873 isolates from 21 European countries), USA (100 isolates), and China (187 isolates) have been examined.^{213,217,218} The main zoliflodacin target in GyrB is highly conserved in clinical isolates.²⁰⁸ No cross-resistance with other available antimicrobials, including the frequently used topoisomerase II inhibitor ciprofloxacin, has been observed, and no zoliflodacin-resistant clinical gonococcal isolate has been identified.^{208,213,217,218} The frequency of induced or selected zoliflodacin resistance mutations is very low and some of the selected *gyrB* resistance mutations appear to increase ciprofloxacin susceptibility.^{199,203}

In a phase 1 study²⁰⁹ of healthy volunteers (aged 18–55 years) who were administered doses of zoliflodacin (200–4000 mg), the investigators observed dose-proportional increases in plasma concentration up to 800 mg. Zoliflodacin doses more than 800 mg resulted in slightly smaller dose-proportional increases up to 4000 mg. The median T_{max} was 1.5–2.3 h, and the mean terminal elimination $T_{1/2}$ was reasonably consistent, ranging between 5.3 h and 6.3 h. There were no serious adverse events or drug discontinuations due to adverse events. Transient dysgeusia (60%), attributed to suspension formulation, followed by mild transient headache (38%) were the most common adverse events.^{200,209}

A phase 2 RCT²¹⁹ evaluating the efficacy, tolerability, and safety of oral zoliflodacin (2 g×1 or 3 g×1) for the treatment of uncomplicated urogenital gonorrhoea in men and women has been done. In total, 48 (98%) of 49 patients with 2 g×1 of zoliflodacin and 47 (100%) of 47 patients with 3 g×1 of zoliflodacin achieved microbiological cure. Only 12% of patients reported any adverse events—ie, mostly mild gastrointestinal adverse events.²¹⁹ Accordingly, a single oral dose of zoliflodacin was effective and safe for treatment of uncomplicated urogenital gonorrhoea. However, it is crucial to examine additional cases of extragenital gonorrhoea, particularly pharyngeal infection.

Gepotidacin is a new non-fluoroquinolone topoisomerase II inhibitor (triazacenaphthylene) targeting DNA gyrase (GyrA subunit) and topoisomerase IV (ParC subunit), but with a different binding mode compared with fluoroquinolones.^{202,215} The MICs of gepotidacin have been shown to be relatively low; however, the MIC required to inhibit the growth of 90% of organisms was 0.25 mg/L

for 108 ciprofloxacin-susceptible isolates and 1 mg/L for 37 ciprofloxacin non-susceptible isolates, indicating some level of cross-resistance to fluoroquinolones.²¹⁵ In-vitro studies examining geographically, temporally, and genetically diverse resistant, including MDR and XDR, gonococcal isolates are ongoing.

The pharmacokinetic profile of oral gepotidacin was examined in a study²⁰⁶ of healthy participants receiving 800 mg×1, 1500 mg×1, 2300 mg×1, and 3000 mg×1. There are few reported data: a reported clearance of about 84 L/h, 9.4–51% variability in clearance, zero-order absorption, and an absorption lag time. Data showed that six men who were administered 2 g×1 of oral gepotidacin had absorbed about 50% of the drug. Faecal elimination (53%) predominated, but about 20% of total dose was eliminated unchanged in urine.²¹¹

A phase 2 RCT (NCT02294682) evaluating the optimal oral dose of gepotidacin (1.5 g×1 or 3 g×1) and efficacy, safety, and tolerability in men and women with uncomplicated urogenital gonorrhoea has been finalised, but the results of this RCT are not publicly available.

Conclusion

Gonorrhoea is a major public health concern, and emergence of gonococcal antimicrobial resistance is substantially compromising the effectiveness of treatment globally. Improvements in treatment, together with clinical and public health actions (panel 1), are needed to control gonorrhoea and antimicrobial resistance in *N gonorrhoeae*. Dual antimicrobial therapy (ceftriaxone 250–500 mg×1 plus azithromycin 1–2 mg×1) is recommended for treatment in settings where up-to-date, local, and high-quality antimicrobial resistance data do not support other therapy.^{28,168–173} This antimicrobial combination appears to treat almost all gonorrhoea cases and inhibits the spread of antimicrobial-resistant gonococcal strains. Nevertheless, wider availability internationally of other effective antimicrobials, such as spectinomycin; further studies of the repurposing of old antimicrobials, particularly gentamicin and ciprofloxacin (following timely molecular prediction of ciprofloxacin resistance or susceptibility¹⁹³); and in-vitro and clinical evaluation and subsequent licensing of novel accessible and affordable antimicrobials are imperative. Ideally, these antimicrobials should be used in new dual therapies to preserve them, and, if available as oral drugs, in fixed-dose combinations providing advantages, such as increased activity, tolerance, compliance, lower cost of manufacturing, simpler distribution, and mitigated resistance development. Several new antimicrobials have proven relatively potent in-vitro activity against gonococcal strains, but clinical data for their effects in gonorrhoea treatment are inadequate.^{153,154,157,159,177} Solithromycin, gepotidacin, and particularly zoliflodacin can be promising for gonorrhoea treatment and deserve further attention.^{199–219} Ultimately, as for chlamydia, a gonococcal vaccine might be the only sustainable solution for gonorrhoea control.¹⁵¹

Part 3: Bacterial vaginosis: reconsidering the evidence for sexual transmission—implications for research and management

Bacterial vaginosis is one of the great conundrums in sexual and reproductive health. At the time of its discovery in the 1950s, non-specific bacterial vaginitis—as it was known—was considered likely to be sexually transmitted. Studies by Gardner and Dukes established the clinical and microbiological features of bacterial vaginosis in uninfected women following direct inoculation of vaginal secretions from infected women.²²⁹ Subsequent work, however, altered this belief. The apparent absence of an obvious disease counterpart in men, the failure of male partner treatment trials to consistently reduce bacterial vaginosis recurrence in women,²³⁰ and the inability to identify a sole pathogenic microorganism all contributed to this altered belief. Although the approaches used in studies that treated the male sex partners of women with bacterial vaginosis—including study designs, dosing regimens for male partners, and endpoints in female partners—have been criticised,^{231,232} the general consensus that bacterial vaginosis is not sexually transmitted has persisted.

Advances in molecular techniques, such as 16S rRNA gene sequencing, have confirmed that bacterial vaginosis involves a profound shift in the vaginal microbiota to a dysbiotic state, characterised by high diversity of bacterial species and increased loads of aerotolerant and strict anaerobes, including *Gardnerella vaginalis* and *Atopobium vaginae*, and other fastidious bacteria associated with bacterial vaginosis, such as *Megasphaera*, *Sneathia*, and Clostridiales spp.²³³ This change is accompanied by production of volatile amines, an increase in vaginal pH, and marked depletion of key *Lactobacillus* spp, such as *L. crispatus*. *L. crispatus* appears to play an important part in defence against pathogens through the production of lactic acid, bacteriocins, and other antimicrobial molecules.^{234,235} Studies^{236,237} have detected a polymicrobial biofilm in women with bacterial vaginosis that is adherent to the vaginal epithelial cells and absent in women who are healthy. But the actual event that triggers this adverse shift in the vaginal microbiota and the development of biofilm remains elusive. In this section of the Commission, we discuss the epidemiological and microbiological evidence that supports the role of sexual transmission in the pathogenesis of incident and recurrent bacterial vaginosis. We relate this evidence to the high recurrence rates following recommended antimicrobial therapy and other treatment approaches, and we discuss the need for novel approaches and combined strategies to address the burden of disease in women.

Bacterial vaginosis is associated with reproductive and obstetric sequelae

Globally, women of reproductive age bear a high burden of bacterial vaginosis. Prevalence estimates range from 12% in Australian women,²³⁸ to 29% in North

American women,^{239,240} to more than 50% in sub-Saharan African women.²⁴¹ When present, symptoms typically include an abnormal vaginal discharge and an unpleasant fishy malodour. Qualitative studies²⁴² showed that bacterial vaginosis is associated with a substantial negative impact on self-esteem, sexual relationships, and quality of life. Although women commonly seek medical assessment, many report misdiagnosis and inconsistent clinical management, compounding their distress and confusion.^{243,244} Bacterial vaginosis is considered a benign condition, but it is associated with serious reproductive and obstetric sequelae including twice the risk of acquiring other STIs, such as chlamydia, gonorrhoea, herpes simplex virus type 2, and HIV infection;^{16,245–247} increased risk of transmission of HIV to male partners;¹⁷ and increased risk of pelvic inflammatory disease, spontaneous

Panel 1: Actions to control the emergence, spread, and effect of antimicrobial resistance in *Neisseria gonorrhoeae*

- Comprehensive case management: primary prevention (eg, public health campaigns, sexual education, behavioural counselling, and condom use), screening (where feasible, effective, and cost-effective), early diagnosis and treatment (including test of cure); partner notification and treatment; and reporting and epidemiological surveillance, to reduce the global burden of urogenital and extragenital gonorrhoea
- Strict adherence to international and national evidence-based prevention and management guidelines, including introduction of dual antimicrobial therapy in settings where up-to-date, local, and high-quality antimicrobial resistance data do not support other therapy
- Enhanced focus on prevention, early diagnosis (screening of high-risk groups—eg, men who have sex with men in some settings), and appropriate treatment of pharyngeal gonorrhoea, which is more difficult to eradicate than anogenital gonorrhoea, mostly asymptomatic, and a reservoir for development of antimicrobial resistance¹⁵⁸
- Enhanced testing and appropriate use of nucleic acid amplification tests but maintain (and strengthen in some settings) capacity for culture and testing of antimicrobial resistance
- Effective drug regulations, prescription policies, and increased awareness on correct use of antimicrobials
- Monitoring, early detection, and follow-up of failures with recommended treatment; use standard case definition and protocols for verification, management of failure, and reporting
- Strengthened quality-assured surveillance of gonorrhoea, antimicrobial use and misuse, and antimicrobial resistance globally (including international rapid communication networks)
- Capacity building to establish regional networks of laboratories to do quality-assured gonococcal culture and antimicrobial resistance testing
- Research to identify novel antimicrobials or other effective compounds for treatment of urogenital and extragenital gonorrhoea (consider to include any new antimicrobials in a dual antimicrobial regimen),^{153,154,159,222} a gonococcal vaccine,¹⁵¹ rapid molecular methods for the prediction of antimicrobial resistance (for surveillance of resistance but ideally also to inform individualised treatment),^{191–193} rapid point-of-care tests for diagnosis of gonorrhoea (ideally with combined prediction of antimicrobial resistance),^{191,192} ideal phylogenomics of gonococci and their antimicrobial resistance (also in non-cultured samples);^{160,220,223–228} and appropriate models for pharmacokinetics and pharmacodynamics (urogenital and extragenital sites) and prediction of antimicrobial resistance induction and selection, evolution, and biological fitness

abortion, preterm delivery, low birthweight, and postpartum endometritis.^{248–250}

Epidemiological evidence for sexual transmission of bacterial vaginosis

Although the weight and strength of available data support that bacterial vaginosis can be acquired through sexual activity, progress in identifying the actual transmitted agent or agents has been slow. Epidemiological data have consistently linked sexual exposure to the development of bacterial vaginosis in cross-sectional and longitudinal studies. Detection of bacterial vaginosis has been associated with inconsistent condom use and increased numbers of sexual partners in meta-analyses.¹⁴ Women with bacterial vaginosis have an earlier median age of sexual debut than women without bacterial vaginosis.²⁵¹ Although several studies^{252–254} reported bacterial vaginosis in women who have not engaged in sexual intercourse, the definition was limited to women with no history of penile-vaginal sex and self-report from potentially vulnerable populations. By contrast, a study²⁵⁵ of 500 female students collected detailed data on sexual behaviours via self-completed questionnaires and employed self-sampling. Bacterial vaginosis was not detected in women without a history of sexual activity with others, was uncommon in women who had only engaged in non-coital sexual activities, and was associated with the practice of penile-vaginal sex. Incident bacterial vaginosis has been associated with exposure to a new sexual partner,^{238,251,256} whereas recurrence after treatment has been associated with sex with an ongoing male partner,^{18,257} suggesting that men might serve as a reservoir for infection and re-infection. Several studies have found inconsistent condom use increased the risk of recurrence following treatment.^{18,258,259} Although other behaviours have been associated with bacterial vaginosis, including smoking,^{260–263} douching,²⁶⁴ dietary factors,²⁶⁵ and stress,²⁶⁶ only smoking has been consistently associated with bacterial vaginosis in adjusted analyses. However, the role of these other practices as potential cofactors in the development of bacterial vaginosis should not be discounted.

Epidemiological data consistently show high concordance of bacterial vaginosis within female partnerships.^{262,267–270} Bacterial vaginosis has been associated with practices that implicate sexual transmission between women,^{262,271} with incident bacterial vaginosis associated with exposure to a new female sexual partner, a female partner with symptoms or a history of bacterial vaginosis, and receptive oral sex in two prospective cohorts.^{270,272} Marrazzo and colleagues²⁷³ showed that monogamous female couples shared *Lactobacillus* spp strain types, and Vodstrcil and colleagues²⁷⁰ found co-enrolled female couples who did not have bacterial vaginosis at enrolment remained with a stable healthy vaginal microbiota over 24 months in the absence of new partnerships. Overall, these data provide evidence to support dynamic exchange

of both protective and detrimental vaginal bacterial species between women in sexual relationships.

The elusive male factor

The apparent absence of symptoms in male partners and the fact that no single transmissible causative agent has been identified have greatly challenged progress in determining whether bacterial vaginosis is sexually transmitted. There is, however, evidence to suggest that bacteria or bacterial communities associated with bacterial vaginosis, perhaps in biofilm form, are transferred between sexual partners. Molecular sequencing analysis has shown that the sub-preputial space and distal urethra of men can harbour a broad range of bacteria associated with bacterial vaginosis.^{274,275} These bacterial species are more prevalent in the male partners of women with bacterial vaginosis than those without.¹⁵ In monogamous couples, specific species associated with bacterial vaginosis are highly concordant between women with bacterial vaginosis and their male partners.²⁷⁶ Concordance of oligotypes of *G vaginalis* has also been reported in heterosexual couples,²⁷⁷ confirming earlier culture-based studies showing concordance of biotypes of *G vaginalis* in heterosexual partners.²⁷⁸ Overall, these data indicate sexual exchange of bacterial taxa that are associated with bacterial vaginosis between heterosexual partners is common,²⁷⁶ although it is unclear whether men are actively infected or just transiently colonised. Only one small study²⁷⁹ examined male carriage prospectively, and the results suggested these organisms spontaneously cleared over time in men without ongoing sexual exposure.

The composition of the coronal sulcus microbiota is not only influenced by sexual activity but also by male circumcision.²⁸⁰ Male circumcision has been prospectively associated with a substantial reduction in bacterial vaginosis-associated genera,^{274,275} and a profound 40–60% reduction in bacterial vaginosis incidence in female partners over 12 months.²⁸¹ Although there are few studies, the biofilm that is associated with bacterial vaginosis has been detected in male urine and semen, and more commonly found in male partners of women with bacterial vaginosis than women who are healthy.^{236,282,283} Collectively, these data provide evidence for a sanctuary or reservoir of species associated with bacterial vaginosis in men from which women might either acquire disease or be re-infected after treatment. Conversely, women with bacterial vaginosis might infect or colonise men who are uninfected, who could be particularly susceptible if uncircumcised. It is plausible that the moist micro-environment of the sub-preputial space could enhance the susceptibility of men who are uncircumcised, and could support a higher organism load that might facilitate persistence and enhance transmission to women. This explanation might underpin the ecological association seen in sub-Saharan Africa, where populations with low numbers of male circumcision also exhibit a high prevalence of bacterial vaginosis in women.²⁴¹

The concept of a so-called symptomatic male disease counterpart has not received much attention. However, in two small studies in the 1980s, Keane and colleagues²⁸⁴ reported that non-gonococcal urethritis was more common in male partners of women with bacterial vaginosis than in male partners of women without bacterial vaginosis, and that men with non-gonococcal urethritis were more likely to have female partners with bacterial vaginosis than men without non-gonococcal urethritis. In an attempt to explore this finding further, Bradshaw and colleagues²⁸⁵ examined two key bacteria associated with bacterial vaginosis, *G vaginalis* and *A vaginae*, in a case-control study of non-gonococcal urethritis using quantitative PCR. They found that these bacteria are not associated with non-gonococcal urethritis and were more commonly detected in the urethra of asymptomatic controls than in men with non-gonococcal urethritis. Manhart and colleagues²⁸⁶ examined the association between non-gonococcal urethritis and a broader range of bacteria associated with bacterial vaginosis, and they confirmed there was no association with *G vaginalis* or *A vaginae* but found that *Leptotrichia spp* and *Sneathia spp* were significantly associated with non-gonococcal urethritis. Bacterial vaginosis-associated bacterium-2, bacterial vaginosis-associated bacterium-3, and *Megasphaera spp* were only detected in men with non-gonococcal urethritis, but they were uncommon and there was no statistical evidence of an association. The only other clinical presentation that has been reported in men is the syndrome of *G vaginalis*-associated balanoposthitis. In a single case report,²⁸⁷ three men presented with a fishy odour, and erythema and irritation of the glans, sulcus, and prepuce. All three men had female partners with bacterial vaginosis, and *G vaginalis* was isolated from the glans. So, although a male-equivalent syndrome of bacterial vaginosis does not appear to be common, non-gonococcal urethritis, and perhaps balanoposthitis, might be associated with some bacterial species associated with bacterial vaginosis.

Does treating sexual partners of women with bacterial vaginosis improve cure?

RCTs done in the 1980s and 1990s did not provide consistent evidence for a reduction in bacterial vaginosis recurrence in women when their male partners were concurrently treated.^{288–293} These data formed the evidence base for subsequent treatment guidelines of bacterial vaginosis, in which partner treatment is not recommended. However, these RCTs have recently been examined in two systematic reviews.^{231,232} Mehta²³² reported that none of the trials had sufficient power to detect reasonable effect sizes, randomisation methods were deficient or insufficiently reported, adherence to therapy was only reported in men in two trials, and many of the treatment regimens, including single dose therapy, would not now be considered effective. A Cochrane review by Amaya-Guio and colleagues²³¹ concluded that low to very low quality

evidence suggests that antibiotic treatment does not lead to a lower recurrence.²³² Overall, the trials are considered inconclusive by current standards. The inconsistency between trial findings and epidemiological and microbiological data could be explained by several factors. The findings were influenced by issues in trial design,²³² but these trials were also done before advances in molecular methods that have provided evidence of detection of bacteria associated with bacterial vaginosis in the sub-preputial space of men. It is possible that optimal therapy to promote clearance of such bacteria from penile and urethral sites requires a combination of topical and oral antibiotics. Alternatively, it is possible that non-bacterial agents such as viruses or bacteriophages, which have been implicated in the pathogenesis of bacterial vaginosis, are being sexually transmitted; and if this is the case, these agents will not be influenced by male partner treatment with antimicrobials.

Do bacteriophages have a role in bacterial vaginosis?

Phage-mediated lysis of lactobacilli has been postulated as a cause of bacterial vaginosis, but there have been few publications in this area. Kiliç and colleagues²⁹⁴ and Pavlova and colleagues²⁹⁵ reported that lysogeny of *Lactobacillus* species (infection with bacteriophages) in women was common, but lactobacillus phages were more often detected in women with bacterial vaginosis than in those without. In in-vitro studies, Pavlova and colleagues²⁹⁵ showed that phages could infect lactobacilli both from the host and different women. Following this work, Blackwell²⁹⁶ hypothesised that a sexually transmitted lactobacillus phage might destroy healthy lactobacilli allowing secondary overgrowth of anaerobes, which could explain why bacterial vaginosis behaves epidemiologically like an STI but recurrence of bacterial vaginosis was unaffected by male partner treatment. The phage theory can be biologically linked to the association between bacterial vaginosis and smoking,^{260–263} because tobacco by-products accumulate in cervical secretions, and the cigarette by-product benzo(a)pyrone diol epoxide promotes phage induction.^{260,296} Blackwell again hypothesised that smoking in women or their partners might be associated with bacterial vaginosis through tobacco by-product induction of endogenous bacteriophages or sexually acquired phages.²⁹⁶ Further studies to clarify whether bacteriophages have a role in the pathogenesis of bacterial vaginosis in women and their male partners are therefore needed.

Limitations of current management and the need for new approaches

Antimicrobial therapy

Figure 6 provides a schematic representation of the broad range of approaches that have been attempted for the management and prevention of bacterial vaginosis. Because the inciting event that results in the development of bacterial vaginosis is unknown, traditional treatment approaches have aimed to reduce the vaginal burden of

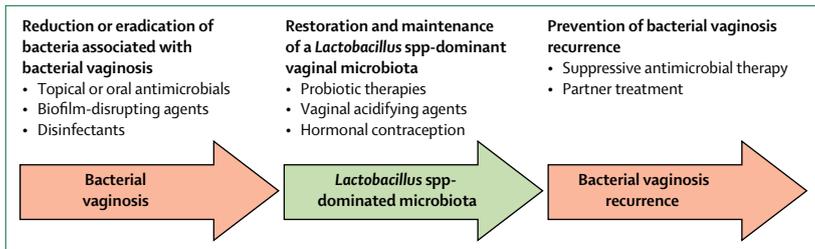


Figure 6: Interventions attempted for the management and prevention of bacterial vaginosis
Arrows show progression from bacterial vaginosis to restoration of healthy microbiota and recurrence.

anaerobes and to ameliorate concomitant symptoms. Overall, antimicrobial compounds with broad activity against most anaerobic bacteria—metronidazole and clindamycin—administered for 5–7 days appear to achieve relatively high short-term cure rates (80–90%),^{28,297,298} with use of intravaginal formulations resulting in fewer systemic side-effects.²⁹⁹ However, bacterial vaginosis recurs in 50–70% of women within 3–6 months and long-term recurrence in up to 80% of women has been reported.^{257,300–302} Possible reasons for this recurrence include re-inoculation with these organisms from an exogenous source (ie, sexual partner) or an endogenous source (ie, rectal reservoir), failure to completely suppress the growth of these bacteria (ie, located within a biofilm), persistence of host risk factors (eg, douching or smoking), failure to recolonise the vagina with desirable lactobacilli, and transmission or activation of *Lactobacillus* spp phages that destroy vaginal lactobacilli.^{294–296,303} None of these mechanisms has been conclusively shown to explain the high recurrence of bacterial vaginosis, or to identify women at increased risk for bacterial vaginosis incidence, recurrence, or sequelae. If sexual transmission is involved in the pathogenesis of bacterial vaginosis, as hypothesised, it is still not clear what is being transmitted—a single founder organism (a bacterium or virus), a bacteriophage that lyses protective *Lactobacillus* species, or a polymicrobial bacterial consortium in the form of biofilm.

Factors that determine whether a woman with bacterial vaginosis will respond to standard antimicrobial regimens are also not clear. One prospective study³⁰² indicated that detection of specific bacteria associated with bacterial vaginosis before treatment with intravaginal metronidazole predicted treatment failure at 30 days. Investigators have examined whether antimicrobial resistance has a role and, although clindamycin-resistant bacteria have been detected in women treated with vaginal clindamycin, their presence was not associated with reduced cure rates.^{304,305} Metronidazole is active against Gram-negative anaerobes and *Mobiluncus mulieris*, but it is less active against *G vaginalis*, anaerobic Gram-positive cocci, and *Mobiluncus curtisii*, and inactive against *Mycoplasma hominis* and *A vaginae*.^{304,305} Despite its spectrum of activity, many of these in-vitro non-susceptible species are eradicated following

metronidazole therapy, indicating that inhibition or elimination of metronidazole-susceptible members of the vaginal bacteria in bacterial vaginosis might result in a decline in some non-susceptible members as well. In an attempt to affect higher bacterial vaginosis cure rates, investigators have increased the dose and duration of nitroimidazoles. Metronidazole, when used as monthly presumptive therapy, was effective in preventing bacterial vaginosis over 12 months of use.³⁰⁶ Use of twice weekly vaginal metronidazole gel was also found to be effective in suppressing bacterial vaginosis, with the rationale being that suppression of overgrowth of such bacteria might offer improved symptom relief, and eventually increase the chance of restoration of a normal vaginal microbiota.³⁰⁷ Although several long-term or intermittent suppressive regimens appear effective during use, relapse on discontinuation remains common, and none of the regimens has improved long-term cure rates in women. Whether treating women with recurrent bacterial vaginosis with a longer initial course of metronidazole (10–14 days with vaginal gel or oral tablets) or a 1 week course of oral tinidazole will improve cure rates has not been established. One study²⁵⁹ that compared 14 days with 7 days of metronidazole treatment found statistical evidence of a benefit when cure was assessed 7 days after completion of therapy, but not at 21 days.

Biofilm disruption

The presence of a biofilm that is associated with bacterial vaginosis might also contribute to the high frequency of failure of antimicrobial therapy. Biofilms not only reduce antimicrobial penetration, enabling susceptible microbes to persist, but contain microbes in varying states of metabolic activity with some in more dormant inactive states.^{303,308,309} When visualised with specific fluorescent probes, *G vaginalis* has been detected in large quantities within adherent biofilms in women with bacterial vaginosis, and some studies^{310,311} indicate that these biofilms persist in women with treatment failure. Biofilm disruption might be necessary to achieve optimal efficacy of antimicrobials. Agents that display activity against biofilms include octenidine, boric acid, tobramycin, amphoteric tenside sodium cocoamphoacetate, DNases, retocyclin, and naturally occurring antimicrobials (subtilisin, poly-L-lysine, and lauramide arginine ethyl ester).^{312–318}

Octenidine and boric acid are the only agents to have been evaluated in human studies. Although the use of metronidazole after 21 days of boric acid reduced recurrence of bacterial vaginosis on treatment, late post-treatment recurrence was common.³¹² Similarly, early cure rates of bacterial vaginosis looked promising with intravaginal octenidine, but recurrence occurred in a significant proportion of women and bacterial resistance to octenidine also emerged.³¹³ An in-vitro study³¹⁸ showed that metronidazole and tobramycin were highly effective against biofilm formation but ineffective against

established biofilm. Amphoteric tenside sodium cocoamphoacetate was, however, highly effective in disrupting biofilm, reducing biomass by 51%, and augmented the effect of metronidazole, indicating that this compound might have potential as a combination approach for bacterial vaginosis. Because *G vaginalis* biofilms contain extracellular DNA, enzymatic disruption by DNase has been shown to inhibit *G vaginalis* biofilm formation and to disrupt biofilms in vitro.³¹⁴ DNase appears to be more effective in vitro when combined with metronidazole,³¹⁴ but has not been evaluated in human studies for bacterial vaginosis. RC-101, a retrocyclin and potent inhibitor of vaginolysin (a toxin produced by *G vaginalis*), also inhibits the formation of *G vaginalis* biofilms in vitro,^{316,317} and might be another potential candidate for human studies of bacterial vaginosis.

Lastly, an emerging area of research involves inhibition of quorum sensing, a strategy that some bacteria use to coordinate expression of genes involved in virulence, biofilm formation, and pathogenicity.^{309,319} Although quorum sensing inhibitors have not been evaluated in human studies, they are active in vitro against biofilms produced by *Pseudomonas aeruginosa* and *Staphylococcus* spp.^{319,320} Overall, the development of safe and effective topical agents that can disrupt the biofilm and can be combined with antimicrobials has been suggested as an important area of research.³⁰⁹

Approaches to restore a healthy vaginal microbiota

Because of the apparent ecological shift in the vaginal microflora in bacterial vaginosis, therapies that either act as vaginal disinfectants or aim to restore the vaginal ecosystem have been evaluated. Although repletion of desirable *Lactobacillus* species would seem to be key, this strategy has presented challenges, and probiotic trials to date have not shown consistent benefit.³²¹ One of the barriers to progress has been the paucity of suitable vaginal species for probiotic formulations, but a *L crispatus* vaginal capsule, first known as CTV-05 and now termed LACTIN-V, has been shown to achieve vaginal colonisation, to be safe,^{322–324} and to prevent recurrent urinary tract infections in a phase 2b RCT.³²⁵ This probiotic is now being studied for the treatment of bacterial vaginosis. The efficacy of vaginal acidifiers such as lactic acid, in the form of gels, suppositories, and acid-soaked tampons, has varied widely. Vaginal acidifiers will suppress—but not kill—vaginal anaerobes, so they might suppress without affecting a cure. A systematic review³²⁶ of these agents found they were either ineffective or not adequately tested because of a small study size, inadequate study design or data analysis, and that more data were needed.

Conclusion

The adverse impact of bacterial vaginosis is felt by the women who experience it, their partners and infants, and their health-care providers who struggle to effectively treat it. As we discussed, the available epidemiological and

microbiological data provide strong evidence of carriage of bacteria that are associated with bacterial vaginosis in male genitalia and exchange of either these species within sexual partnerships or another agent capable of inciting bacterial vaginosis. There is also compelling evidence for the effect of male circumcision and condom use on reducing the risk of bacterial vaginosis acquisition and recurrence. Overall, these data suggest that sexual transmission is an integral component of the pathogenesis of incident and recurrent bacterial vaginosis.

Earlier partner treatment trials had substantial methodologic limitations, and do not provide an adequate body of proof to discount the possibility that male partner treatment might reduce recurrence of bacterial vaginosis in women. New partner treatment trials, done in accordance with current clinical trial standards and with the use of modern microbiological tools, are needed to determine the contribution of re-infection to recurrence, and to provide an accurate evidence base for treatment guidelines. Given the data supporting an anatomical reservoir of bacteria that are associated with bacterial vaginosis in male genitalia, a logical approach might emphasise trials that study a potential role of topical antimicrobials in addition to oral agents; eradication of cutaneous carriage of these bacteria from the penile skin might reduce the risk of re-infection and optimise bacterial vaginosis cure. Female partner treatment trials could also facilitate understanding of pathogenesis and identify new approaches to management. Although the relative contribution of persistence of bacteria that are associated with bacterial vaginosis versus re-infection to recurrence of bacterial vaginosis is not clear, both mechanisms are likely to have a role. It is also possible that other factors can contribute, including failure to recolonise the vagina with desirable lactobacilli, persistence of host risk factors, or lactobacillus phages.

Ultimately, optimal treatment strategies are likely to require combination approaches, such as use of antimicrobials, biofilm-disrupting agents, and partner treatment. Efforts to optimise the therapeutic and preventive approach to this complex syndrome will, however, require allocation of the necessary resources and commitment be made to a disease that remains largely hidden from public view. Yet bacterial vaginosis is not rare or benign, it is a condition of high global burden in women of reproductive age and is associated with serious and costly sequelae, including preterm delivery and increased risk of HIV acquisition and transmission. Recognition for this neglected condition—in the form of a coherent, progressive research agenda and concomitant resource allocation—is well past due.

Part 4: STI case management and control in low-income and middle-income countries

In 2012, more than 90% of new estimated cases of trichomoniasis, chlamydia, gonorrhoea, and syphilis were from low-income and middle-income countries

(figure 1).² These curable STIs can lead to severe complications and long-term sequelae, burdening already over-stretched health-care systems. Primary prevention of STIs in low-income and middle-income countries has shown some success with vaccines against HPV and hepatitis B virus and with male circumcision, but less so with interventions to promote sustained behaviour change and condom use.³²⁷ STI case management and secondary prevention by screening or treatment to prevent complications, or both, have been hampered largely by the absence of affordable and accessible diagnostic tests. Case management of STIs in low-income and middle-income countries has relied on syndromic management for patients presenting with symptoms.^{34,134} Syndromic management, however, has poor specificity, results in overtreatment with antibiotics, and does not disrupt transmission in those with asymptomatic infection.

Most low-income and middle-income countries have policies for universal screening of syphilis during pregnancy for secondary prevention of congenital syphilis. WHO has prioritised the elimination of congenital syphilis, and Cuba became the first country to achieve the targets for elimination of mother-to-child transmission of both syphilis and HIV infection in June, 2015.³⁴ Nevertheless, implementation of policies for antenatal syphilis screening is weak in many countries. The highest estimates of syphilis prevalence were found in the WHO African Region (estimated prevalence in antenatal attendees is from 4·6% to 6·5%); the median reported proportion of antenatal attendees tested for syphilis was 58% in the WHO African Region versus 83–99% in other regions.^{2,328} The proportion of pregnant women not tested for syphilis in antenatal care decreased from 2008 to 2012 in all regions except Africa.³²⁹ The Joint United Nations Programme on HIV/AIDS published data for the global plan towards the elimination of new HIV infections, and they reported that mother-to-child transmission rates of HIV infection were reduced by 71–86% in African countries between 2009 and 2015.³³⁰ The absence of similar progress in syphilis screening in Africa illuminates the tragic reality that many babies will have avoided HIV infection but died from syphilis.^{331,332} There are few other specific policies for control of STIs in low-income and middle-income countries. Although most syndromic management guidelines include partner notification and treatment, this inclusion is often weakly implemented.³³³ Periodic presumptive treatment in targeted populations, such as commercial sex workers, has shown promise but overtreatment with antibiotics is still a concern.³³⁴

Rapid and simple point-of-care tests might provide solutions for STI case management and control. The key features of these tests are the fast turnaround times that allow completion of testing, communication of results that guide clinical decisions, and follow-up to take place at the same clinical encounter.¹⁴⁸ There are

affordable, highly sensitive, and specific point-of-care tests for syphilis. Although there are several tests in the pipeline for chlamydia and gonorrhoea, the available point-of-care tests have low accuracy or require expensive equipment.³³⁵ Even with well performing and affordable point-of-care tests, challenges will remain for the implementation of these tests into national health systems. In this section of the Commission, we review current challenges facing case management and STI control related to secondary prevention of curable STIs in low-income and middle-income countries, and we provide an update about the latest point-of-care tests.

Case management of symptomatic STIs in low-income and middle-income countries

Case management is the treatment of infections to alleviate signs and symptoms, and to prevent sequelae, and includes history-taking and clinical examination, diagnostic tests, treatment, partner notification, health promotion advice, follow-up, and surveillance.³² Case management is an integral part of an STI control strategy, because early treatment can disrupt onward transmission if treatment and partner notification are successful. The treatment of clinical syndromes, commonly called syndromic management, was developed in the late 1970s and early 1980s to address the practical difficulties of managing STIs to which diagnostic tests were not available.³³⁶ In 1985, the first WHO guidelines for STI management included four simple algorithms for the management of syndromes that are associated with common STIs: genital ulcers, urethral discharge, vaginal discharge, and pelvic inflammatory disease. Patients are treated for all the probable causes of these syndromes. These guidelines gained recognition in the growing HIV epidemic in the early 1990s, when the link between STI and HIV infection became clear, and have become the backbone of case management for STIs in many low-income and middle-income countries. The current WHO syndromic management guidelines have algorithms for six syndromes: urethral discharge, genital ulcers, scrotal swelling, vaginal discharge, low abdominal pain, and neonatal conjunctivitis.¹³⁴

The advantages of syndromic management include low cost, modest training requirements, and provision of immediate treatment. The main disadvantage is that syndromic management unnecessarily treats for infections that are not present, and misses asymptomatic infections, which are the majority of STIs globally.³³⁷ This disadvantage is especially true for vaginal discharge syndrome, which is more commonly caused by bacterial vaginosis, candidiasis, or trichomoniasis than by chlamydia and gonorrhoea.⁴⁴ Several studies have shown poor sensitivity and specificity of syndromic management for chlamydia and gonorrhoea in women.^{338–341} Efforts to increase accuracy for vaginal

discharge syndrome with a risk assessment were evaluated, but sensitivity and specificity remained poor.³⁴² This finding is because most women with vaginal discharge do not have these infections, and most women (up to 70%) with chlamydia and gonorrhoea have no symptoms.³³⁷ Unfortunately, asymptomatic infection is still likely to cause harmful sequelae. A study³⁴¹ of female sex workers in South Africa has shown that cervicovaginal inflammatory markers were elevated in women with an STI whether it was symptomatic or not. Previous studies³⁴³ have suggested that elevated inflammatory markers might facilitate HIV transmission, and thus, women with asymptomatic STIs might be as susceptible to HIV infection as those with symptoms. Additionally, it is estimated that the use of syndromic management results in the unnecessary treatment of 60–98% of women presenting with vaginal discharge for chlamydia and gonorrhoea.³⁴⁴ Any use of antibiotics encourages resistance, so it is important to restrict unnecessary use. As noted in part 2 of this Commission, increased resistance to most antibiotics used to treat gonococcal infections has been reported worldwide, raising concerns about the eventual development of untreatable gonococcal infections with serious sexual and reproductive health consequences.

Partner notification

In part 1 of this Commission, partner notification strategies for the management of diagnosed chlamydia were discussed. In the context of syndromic management in low-income and middle-income countries, partner treatment often results in over-prescription of antibiotics, especially of partners of women with vaginal discharge, most of whom do not have an STI.³⁴⁵ A systematic review³⁴⁶ of partner notification in developing countries found that partner notification for STIs was feasible in low-income and middle-income countries, and that most patients diagnosed with STIs were willing to self-notify their regular partners. There are, however, major barriers to successful partner notification, including fear of abuse and rejection resulting from partner referral, especially for women. Physical and economic vulnerability of women must be considered in the design of partner notification strategies in low-income and middle-income countries where female partners might be blamed for the infection.³⁴⁵ Development and evaluation of partner notification strategies are needed in low-income and middle-income countries with use of biological outcomes, such as re-infection.¹³⁹

Targeted presumptive treatment

Presumptive treatment is the treatment for a presumed infection in populations with a high burden of STIs without confirmation of infection by an examination or laboratory test. Presumptive treatment for STIs might be given at repeated intervals, in which case it is known as periodic presumptive treatment. Periodic presumptive

treatment is complementary to syndromic management and targets asymptomatic infection in high burden, key populations—many of whom are stigmatised and hard to reach, such as female sex workers. Most periodic presumptive treatment targets chlamydia, gonorrhoea, and syphilis, and it has been most extensively assessed in sex worker populations. In 2005, a WHO consultation reviewed experience from nine countries and recommended that periodic presumptive treatment be considered as a part of the package of services to rapidly reduce STI prevalence in sex worker settings, particularly where STI control is poor.³⁴⁷ In 2012, a review³⁴⁸ reported the results from 15 studies and showed consistent reductions of about 50% prevalence in populations with high chlamydia and gonorrhoea prevalence. There was inadequate evidence for chancroid—one study showed rapid decline of chancroid—and mixed evidence for syphilis. Modelling studies³⁴⁹ have shown that, if sufficient coverage is achieved (>30% of the target population), periodic presumptive treatment interventions can effectively reduce the STI prevalence within the target population, and that interventions with sufficient coverage (≥40%) and follow-up (≥2 years) could substantially decrease incidence of HIV infections (>20%).

Presumptive treatment can be an effective approach to the treatment of asymptomatic infection in women, at least those at high risk, and might interrupt transmission between sex workers and their clients, but needs evaluation in other populations. Presumptive treatment must be sustained; once stopped, infections recur. Additionally, a disadvantage is unnecessary treatment of people who are not infected with an STI and the contribution to the development of antimicrobial resistance.

Screening programmes

Antenatal syphilis screening and treatment is effective and cost-effective for the prevention of adverse pregnancy outcomes.^{350–352} 52 low-income and middle-income countries reported testing coverage for syphilis during antenatal care for 2012; however, only about a third reported coverage of at least 95%, whereas another third reported coverage of less than 50%.^{34,353} Of 14 countries that reported current policies for antenatal screening of *C trachomatis* and *N gonorrhoeae* infections, only Romania and Bulgaria are in the category of low income and middle income; most low-income and middle-income countries use WHO recommended syndromic management for the treatment of symptoms during antenatal care.³⁵⁴

Screening of high-risk populations, including sex workers, has shown some success in research studies and demonstration projects,^{97,355,356} but has not been widely replicated in low-income and middle-income countries because of the cost of diagnostics and laboratory capacity.³⁵⁵

Use of point-of-care testing for case management and STI control

Point-of-care tests provide prompt diagnosis for case management, provide a definite diagnosis of an STI that can further justify and facilitate partner notification, and can be used for screening antenatal care attendees and populations at high risk for STIs. There are several low-cost techniques for STI diagnosis that can be done at the point of care, including wet-mount and Gram-stain microscopy, but they require laboratory equipment and have poor sensitivity, particularly for diagnosing infections in women. Rapid plasma reagin, a nontreponemal test for syphilis, can also be done at the point of care, but it requires separation of serum, refrigeration, and equipment and has low accuracy in settings with insufficient training or facilities.^{351,357,358} Additionally, rapid plasma reagin tests are often batched or sent to a central laboratory, resulting in long turnaround times and patients not staying or returning for treatment.^{351,359,360}

To guide the development of simple and rapid point-of-care tests, WHO developed the ASSURED benchmarking in 2006. ASSURED point-of-care tests are affordable by those who are at risk for the infection; sensitive, very few false negatives; specific, very few false positives; user-friendly, very simple to do (minimal steps required with minimal training); rapid and robust, to enable treatment at visit of diagnosis and does not require refrigeration storage; equipment free, easily collected non-invasive specimens (eg, saliva and urine) and not requiring complex equipment; and delivered to end users.³⁶¹ Recent reviews and systematic reviews summarise the available information about point-of-care tests for STIs.^{362–367} These reviews evaluated available point-of-care tests and those in the pipeline. WHO's landscape analysis of point-of-care tests by Murtagh³³⁵ provides a listing of currently available tests and those in the pipeline; this analysis will be updated annually by WHO. Available point-of-care tests have been summarised in table 2.

Point-of-care tests for chlamydia and gonorrhoea

Most point-of-care tests currently available for the detection of *C trachomatis* or *N gonorrhoeae* are based on antigen detection in lateral flow format and do not meet the ASSURED criteria because of low sensitivity or specificity, or both. Although the aQcare Chlamydia TRF (Medisensor, Daegu, South Korea) and BioStar Optical ImmunoAssay (Biostar, Boulder, CO, USA) for gonorrhoea have been shown to be highly sensitive and specific, both have only been evaluated in one study each (for BioStar Optical ImmunoAssay only a pilot study including five confirmed *N gonorrhoeae* positive specimens).^{375,376} There is general agreement that most current point-of-care tests for the detection of *C trachomatis* or *N gonorrhoeae* do not perform well, and there is a need for improved assays. Nevertheless,

modelling studies have suggested that even insensitive point-of-care tests could increase the proportion of infections treated in scenarios for which it would be difficult to ensure a high proportion of patient return, and in populations for which there is potential for further STI transmission during the delay in treatment from using laboratory STI tests.^{377,378}

GeneXpert (Cepheid, Sunnyvale, CA, USA), a test based on nucleic acid amplification with high sensitivity and specificity for detection of *C trachomatis* and *N gonorrhoeae* has been termed a near-point-of-care test as it requires equipment, is expensive, and has a relatively long turnaround time (about 90 min). Several new technologies are in the pipeline (figure 7), which are likely to be highly accurate and require minimal training and processing time including the CT assay of the io System (Atlas Genetics, Trowbridge, UK), GeneXpert Omni (Cepheid), RT Cross-Priming Amplification CT Test (Ustar Biotechnologies, Hangzhou, China), Truelab Real Time quantitative micro PCR system (Molbio Diagnostics, Goa, India), Alere i platform (Alere, Waltham, MA, USA), CT/NG MAMEF-based detection (University of Maryland Baltimore County and Johns Hopkins, Baltimore, MD, USA), and MobiLab—which uses smartphones for reading results (Johns Hopkins University BioMEMS Lab, Baltimore, MD, USA).^{335,362,364}

Point-of-care tests for trichomoniasis

The OSOM Trichomonas Test (Sekisui Diagnostics, Lexington, MA, USA) for detection of *T vaginalis* infection has been shown to perform well against wet mount and culture (83·3–90·0% sensitivity and 98·8–100% specificity).^{335,364,367} This test meets the ASSURED benchmark by having few steps and a short turnaround time (10 min). GeneXpert platform also has an assay to detect *T vaginalis*, and this assay has been evaluated in two studies^{367–369} and found to be sensitive (95·0–95·6%) and specific (95·7–100%); however, the GeneXpert platform does not meet ASSURED benchmarking. In the pipeline, Atlas Genetics' io System has a test cartridge in development for the detection of *T vaginalis*, as does AmpliVue (Quidel, San Diego, CA, USA).³³⁵

Point-of-care tests for syphilis

Four treponemal point-of-care tests for syphilis have been evaluated and met the ASSURED criteria, and these tests are recommended in resource-limited settings: Determine Syphilis TP (Alere), SD Bioline Syphilis 3.0 (Alere; Standard Diagnostics, Youngin, South Korea), Syphichk-WB (The Tulip Group—Qualpro, Goa, India), and VisiTect Syphilis (Omega Diagnostics, Alva, Scotland).^{373,379} These tests are accurate, cost less than US\$1 if purchased through the WHO bulk procurement programme for low-income and middle-income countries, can provide results in 15–20 min, and are easy to use with minimal training. In addition to

these tests that have been extensively evaluated, other point-of-care tests for syphilis are on the market, including Crystal TP Syphilis Test (Span Divergent, Surat, India), OnSite Syphilis Ab Combo Rapid Test (CTK Biotech, San Diego, CA, USA), Syphilis Health Check (Diagnostics Direct, Youngstown, OH, USA), and Uni-Gold Syphilis Treponemal (Trinity Biotech, Bray, Ireland).³³⁵

Treponemal point-of-care tests have been implemented and evaluated in rural antenatal care clinics in Tanzania, Uganda, and China; in rural and urban clinics in Peru and Zambia; and in remote indigenous communities in Brazil.³⁸⁰ The introduction of these tests increased the proportion of antenatal care attendees screened for syphilis to 90%, and the proportion of pregnant women with syphilis who were treated the same day exceeded 90% in all countries. Modelling from this study has shown that point-of-care tests are more cost-effective in screening and treating syphilis than laboratory-based testing methods, such as rapid plasma reagin.³⁸¹

Treponemal point-of-care tests have also been used in hard-to-reach populations. In Brazil, health-care workers in remote communities succeeded in screening 55% of the sexually active population (defined as ≥10 years of age) for syphilis, exceeding the 30–40% target originally set.³⁸⁰ Modelling studies³⁸² have estimated the effect of using rapid point-of-care tests to screen female sex workers for syphilis, and have shown that such screening could substantially reduce syphilis prevalence in this hard-to-reach group, but strategies to reduce re-infection from regular non-commercial partners are needed to maximise effect.

Once an individual has been infected with *T pallidum*, all future treponemal tests will be positive; therefore, treponemal point-of-care tests cannot distinguish between current and past infection, resulting in over treatment for syphilis. This issue is particularly important in settings where access to confirmatory testing with use of non-treponemal tests is scarce. Therefore, combination point-of-care platform tests have been developed, which include treponemal and non-treponemal antigens. The Dual Path Platform test (Chembio Diagnostic Systems, Medford, NY, USA) is the first of these combination tests, and has good sensitivity and specificity for treponemal (90·1–98·2% and 91·8–98·0%) and non-treponemal (80·6–98·2% and 89·4%) tests.³⁷⁴

Point-of-care tests for syphilis and HIV infection

There is also a need for dual syphilis and HIV infection tests. These tests could be used in populations at high risk for HIV infection and syphilis, and accelerate programmes for the elimination of mother-to-child transmission of both infections, especially in countries in Africa that have made excellent progress towards the elimination of mother-to-child transmission of HIV infection but not syphilis.³⁸³ In 2017, WHO published an

	Manufacturer (place of manufacture)	Sample type	Sensitivity (%)	Specificity (%)
<i>Chlamydia trachomatis</i>*³⁶⁵				
BioStar OIA Chlamydia test ³⁶³	Biostar (Boulder, CO, USA)	Endocervical swabs	59·4–73·8%	98·4–100%
Clearview Chlamydial test ³⁶³	Alere (Waltham, MA, USA)	Endocervical swabs; vaginal swabs	49·7%; 32·8%	97·9%; 99·2%
QuickVue Chlamydia Test ³⁶³	Quidel (San Diego, CA, USA)	Endocervical swabs; vaginal swabs	25·0–65·0%; 83·5%	100%; 98·9%
aQcare Chlamydia TRF ^{368,369}	Medisensor (Daegu, South Korea)	Endocervical and urethral swabs; urine	93·8%; 88·2%	96·8%; 94·7%
Chlamydial Rapid Test ^{368,369}	Diagnostics for the Real World (Sunnyvale, CA, USA)	Male urine; vaginal swabs	41·4%; 39·4–74·2%	89·0%; 94·4–96·8%
ACON Chlamydia Rapid Test Device ^{368,369}	ACON Laboratories (San Diego, CA, USA)	Vaginal swabs; endocervical swabs; male urine	66·7%; 22·7–30·5%; 43·8%	91·3%; 99·8–100%; 98·3%
GeneXpert (duplex for <i>C trachomatis</i> and <i>N gonorrhoeae</i>) ³⁶³	Cepheid (Sunnyvale, CA, USA)	Endocervical swabs; vaginal swabs; female urine; male urine	97·4%; 98·7%; 97·6%; 97·8%	99·6%; 99·4%; 99·8%; 99·9%
<i>Neisseria gonorrhoeae</i>*³⁷⁰				
BioStar OIA GC Test ³⁶³	Biostar	Endocervical swabs; urine	60·0%; 100%	89·9%; 93·0–98·0%
ACON Duo (duplex for <i>C trachomatis</i> and <i>N gonorrhoeae</i>) ^{368,369}	ACON Laboratories	Endocervical swabs	12·5%	99·8%
GeneXpert (duplex for <i>C trachomatis</i> and <i>N gonorrhoeae</i>) ³⁶³	Cepheid	Endocervical swabs; vaginal swabs; female urine; male urine	100%; 100%; 95·6%; 98·9%	100%; 99·9%; 99·9%; 99·9%
<i>Trichomonas vaginalis</i>³⁶⁷				
OSOM Trichomonas Test ³⁶³	Sekisui Diagnostics (Lexington, MA, USA)	Vaginal swabs	83·3–90·0%	98·8–100%
GeneXpert (for <i>T vaginalis</i>) ³⁶⁴	Cepheid	Vaginal swabs	95·0–95·6%	95·7–100%
Affirm VPIII Microbial Identification Test* ³⁶³	Becton, Dickinson and Company (Franklin Lakes, NJ, USA)	Vaginal swabs	46·3%	100%
<i>Treponema pallidum</i> (syphilis)^{374,372}				
Determine Syphilis TP ³⁷³	Alere	Whole blood, serum, plasma	59·6–100%	95·7–100%
VisiText Syphilis ³⁷³	Omega Diagnostics (Alva, Scotland)	Whole blood, serum, plasma	72·7–98·2%	98·1–100%
Syphicheck-WB ³⁷³	The Tulip Group–Qualpro (Goa, India)	Whole blood, serum, plasma	64·0–97·6%	98·4–99·7%
SD Bioline Syphilis 3·0 ³⁷³	Alere; Standard Diagnostics (Yongin, South Korea)	Whole blood, serum, plasma	85·7–100%	95·5–99·4%
Crystal TP Syphilis Test	Span Divergent (Surat, India)	Whole blood, serum, plasma	NA	NA
OnSite Syphilis Ab Combo Rapid Test	CTK Biotech (San Diego, CA, USA)	Whole blood	NA	NA
Syphilis Health Check	Diagnostics Direct (Youngstown, OH, USA)	Whole blood, serum, plasma	NA	NA
Uni-Gold Syphilis Treponemal	Trinity Biotech (Bray, Ireland)	Whole blood, serum, plasma	NA	NA

(Table 2 continues on next page)

	Manufacturer (place of manufacture)	Sample type	Sensitivity (%)	Specificity (%)
(Continued from previous page)				
DPP Syphilis Test ³⁷⁴	Chembio Diagnostic Systems (Medford, NY, USA)	Treponemal antibody; non-treponemal	90.1–98.2%; 80.6–98.2%	91.2–98.0%; 89.4%
Dual HIV/T pallidum (syphilis)³⁶⁶				
SD BIOLINE HIV/Syphilis Duo Rapid Test ³³⁵	Alere; Standard Diagnostics	HIV: whole blood, serum, plasma; syphilis: whole blood, serum, plasma	97.9–99.0%; 93.0–99.6%	99.0–100%; 99.1–100%
DPP HIV-Syphilis Assay ³³⁵	Chembio Diagnostic Systems	HIV: whole blood, serum, plasma; syphilis: whole blood, serum, plasma	98.9%; 95.3%	97.9–99.6%; 97.0–99.6%
Multiplo Rapid TP/HIV Antibody Test ³³⁵	MedMira (Halifax, Canada)	HIV: whole blood, serum, plasma; syphilis: whole blood, serum, plasma	97.9%; 94.1%	94.2–99.5%; 94.2–99.1%
INSTI HIV/Syphilis Multiplex Test	bioLytical Laboratories (Richmond, Canada)	HIV: whole blood, serum, plasma; syphilis: whole blood, serum, plasma	NA	NA
OnSite HIV/Syphilis Ab Combo Rapid Test	CTK Biotech	HIV: whole blood, serum, plasma; syphilis: whole blood, serum, plasma	NA	NA

OIA=Optical ImmunoAssay. DPP=dual path platform. NA=not available. *Sensitivity and specificity compared with nucleic acid amplification tests.

Table 2: Point-of-care tests for sexually transmitted infections currently on the market with available sensitivities and specificities

information note to provide advice for countries using or planning to introduce dual HIV and syphilis point-of-care tests in antenatal services and other testing sites.³⁸⁴ There are currently five of this type of dual point-of-care test on the market (figure 8), of which three have published data on sensitivity and specificity: SD BIOLINE HIV/Syphilis Duo Rapid Test (Alere; Standard Diagnostics), DPP HIV-Syphilis Assay (Chembio Diagnostic Systems), and Multiplo Rapid TP/HIV Antibody Test (MedMira, Halifax, Canada).^{335,366} In addition to these tests, there is an innovative dual point-of-care test in the pipeline, mChip Assay (Junco Labs, Columbia University, New York, NY, USA; in collaboration with OPKO Health, Miami, FL, USA), which uses a microfluidic mChip and a smart phone for powering the reaction as well as reading and transmitting the results.³³⁵

Point-of-care tests for antimicrobial-resistant gonorrhoea

There are currently no commercially available diagnostic assays that detect gonococcal antimicrobial resistance.¹⁹² The development of these diagnostics with a focus towards point-of-care tests is urgently needed. Detection of *N gonorrhoeae* and its main resistance determinants at the point-of-care would improve management and help to slow the spread of antimicrobial resistance, particularly in low-income and middle-income countries.¹⁹²

Challenges for the implementation of point-of-care tests

Point-of-care tests have the potential to transform case management and STI control in low-income and middle-income countries. To be effective at the population level, however, they must be adopted by national health systems, and this implementation requires careful consideration. Decentralising testing from the laboratory can put tremendous stresses on fragile health-care systems in terms of supply chain management, training, quality assurance, and monitoring effect.

A study³⁸⁵ in Peru has shown that the use of point-of-care tests offered an opportunity to improve screening coverage for syphilis and other aspects of health systems.³⁸⁰ Widespread adoption and use depends on engagement with the authorities; dissipating of tensions between providers and identifying champions; training according to the needs identified; provision of monitoring, supervision, support, and recognition; sharing of results and discussion of actions together; consulting and obtaining of feedback from users; and integration with other services, such as with rapid HIV testing.^{380,385} As countries begin to implement point-of-care testing, adequate training and quality assurance programmes must be developed in parallel. Smit and colleagues³⁸⁶ studied the use of dry blood spots to evaluate quality of point-of-care tests for syphilis and HIV infection in Tanzania, and they found that quality varied between clinics, which helped to identify clinics that needed remedial training.

Ultimately, point-of-care tests pave the way for self-sampling and self-testing outside of a clinical setting, including community-based organisations, pharmacies, and at home. Home-based testing for HIV infection has been shown to reach wide sections of communities in a diverse range of contexts and settings, and is viewed to be the gateway to accessing early treatment and care.³⁸⁷ However, important lessons can be learned from the roll out of simple and rapid point-of-care tests for HIV infection in which the major challenges have been well recognised, including poor quality control, unreliable supply chains, non-standardised training, and inadequate numbers of health-care workers.³⁸⁸ Decentralisation of testing for curable STIs might increase access to testing and awareness of STIs, but linkage to the health-care system will be crucial for diagnostic confirmation, treatment, counselling, and follow-up.³⁶² Point-of-care tests that meet ASSURED benchmarks are likely to fill an important gap for STI control in low-income and middle-income countries; however the technological innovation of these tests needs to be mirrored by innovation in health-care delivery and careful planning for implementation.

Conclusion

Low-income and middle-income countries bear the majority of global incident cases of STIs; however, their national health systems are less resourced to manage STI

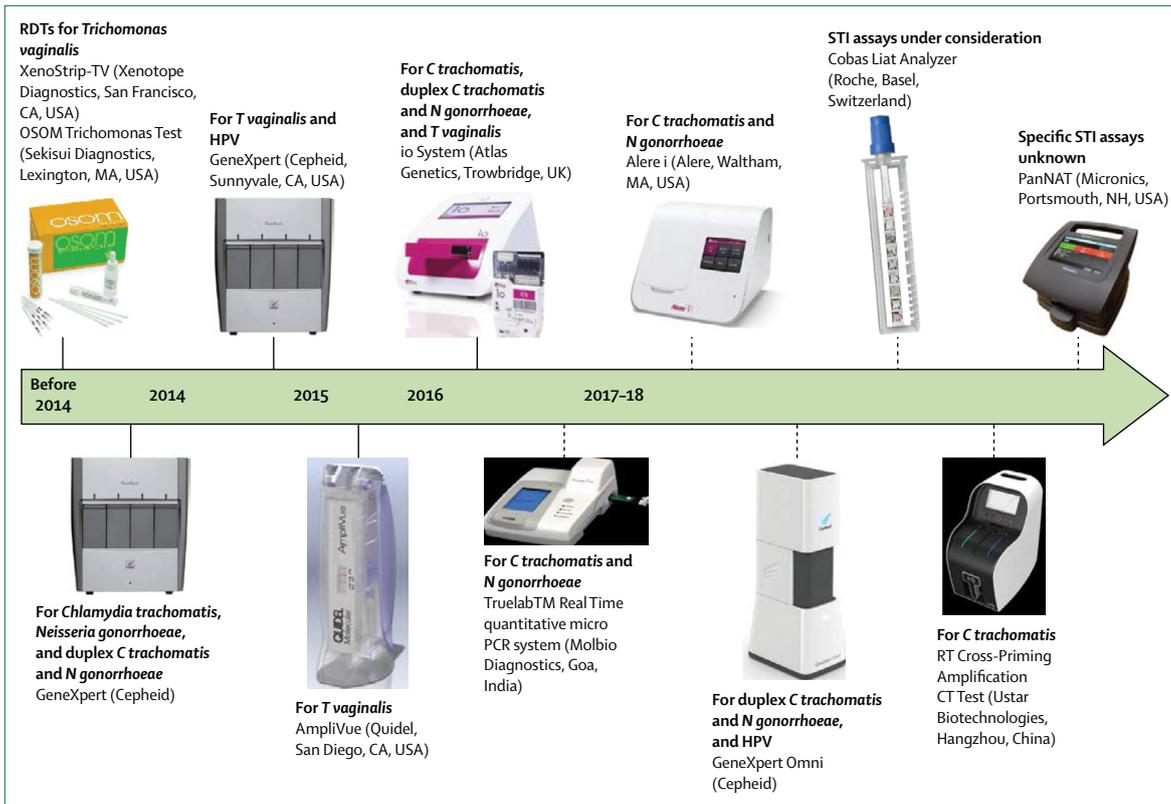


Figure 7: Point-of-care tests or near-point-of-care tests for STIs
 These tests are either available or in the pipeline. The dotted line indicates that no market launch date has been set by the manufacturer for these tests.³³⁵ RTDs=rapid diagnostic tests. HPV=human papillomavirus.

cases or implement secondary prevention. Point-of-care tests that meet the ASSURED benchmark of WHO could bridge the gap for STI case management and control in these settings. Currently, there are point-of-care tests for syphilis and trichomoniasis that meet the ASSURED benchmark. By contrast, there are no ASSURED point-of-care tests for chlamydia or gonorrhoea, and the development and evaluation of point-of-care tests for these infections are urgently needed, particularly for antimicrobial-resistant *N gonorrhoeae*. Although development of ASSURED point-of-care tests is a crucial target, the successful implementation of these tests into health-care systems for the prevention and control of STIs is the goal. The goal for the implementation of such tests into antenatal screening for syphilis is 100% screening and treatment of syphilis worldwide. Future ASSURED point-of-care tests for curable STIs will need to be integrated into syndromic management guidelines and control strategies, such as partner notification and targeted presumptive treatment. It will be essential that implementation science guides integration of point-of-care tests into current strategies for STI case management and control in low-income and middle-income countries, by addressing political, cultural, socioeconomic, and behavioural factors.³⁸⁹

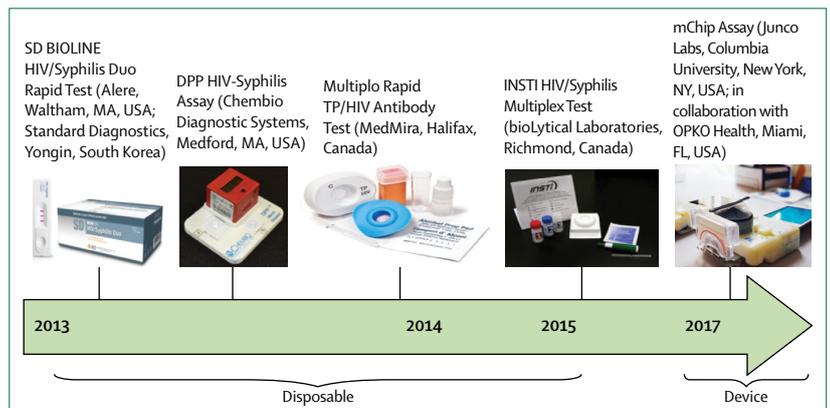


Figure 8: Available point-of-care tests for dual syphilis and HIV infection diagnosis³³⁵

Part 5: STIs in MSM in the era of biomedical interventions for HIV prevention

A historical perspective provides insights into the epidemiology of STIs in MSM in the 21st century as we enter a new era of antiretroviral-based biomedical interventions for HIV prevention in high-income countries. The first relevant trend was the increase in notification rates of gonorrhoea and syphilis in men

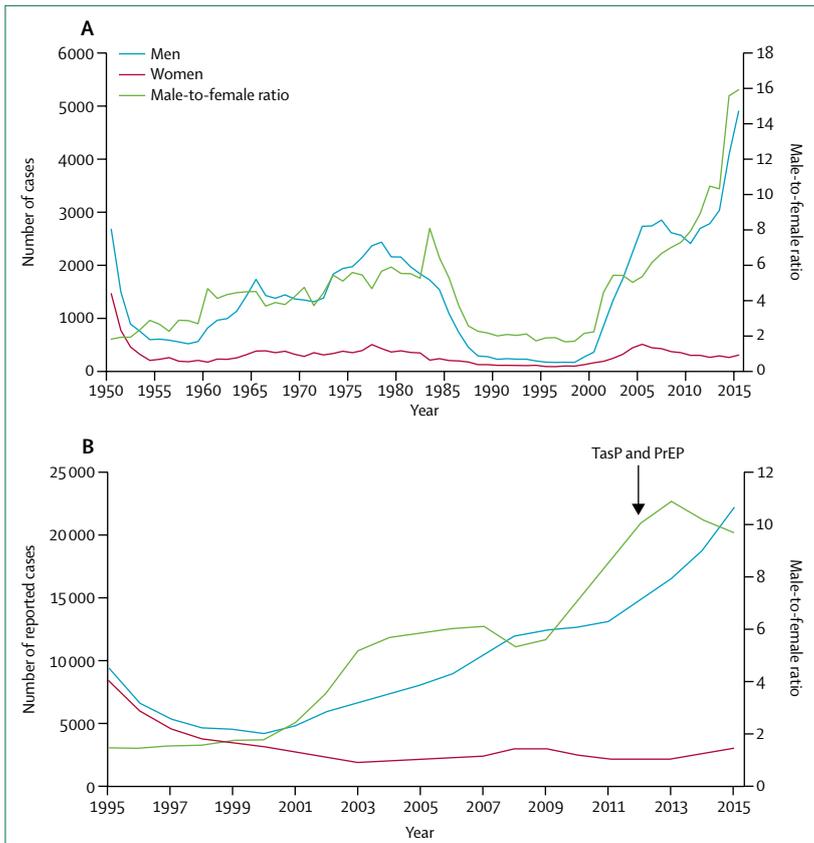


Figure 9: Number of reported cases of syphilis by sex and male-to-female ratio
 (A) Number of new diagnoses of primary, secondary, and early latent syphilis in 1950–2015 in England and Wales. Data from Public Health England, by personal communication (CKF). (B) Number of reported cases of primary and secondary syphilis in 1995–2015 in the USA.^{393,392} In England and Wales, the ratio of male-to-female syphilis notifications increased from around 1960 until 1983, suggesting that the excess male infections were in men who have sex with men. After 1983, the ratio fell steeply after the first reports of AIDS. From around 2000, the male-to-female ratio increased again both in England and Wales and in the USA, coinciding with the increasing use of combination antiretroviral therapy to treat HIV infection. In 2012 in the USA, antiretroviral treatment as prevention (TasP) was recommended nationally and pre-exposure prophylaxis (PrEP) was licensed.

from the 1960s onwards in countries such as England and Wales³⁹⁰ (figure 9A) and the USA.^{393,394} The increase in infections in MSM can be inferred from the increasing ratio of male-to-female notifications in surveillance systems that do not record the route of acquisition of STIs. Sexual acts between men were illegal in these countries in the 1960s, and levels of stigma towards both homosexuality and STIs were still extremely high.³⁹⁵ The availability of penicillin was already stated to have encouraged morally sanctioned behaviours by removing fear as a deterrent, particularly of syphilis.⁸

Feldman remarked that “to the astute venereologist AIDS is an almost inevitable consequence of the increase in sexually transmitted diseases”.³⁹³ Rates of gonorrhoea in England and Wales^{124,390} and in the USA^{393,394} and the male-to-female ratio of syphilis infections in England and Wales (figure 9A) reached a peak in the mid-to-late 1970s. Other STIs were also common; 50–70% of MSM had serological evidence of hepatitis B infection³⁹⁶ and outbreaks of infections, such as lymphogranuloma venereum, were

reported.³⁹⁷ Infections such as hepatitis A and enteric pathogens—eg, *Giardia lamblia*, *Entamoeba histolytica*, and *Shigella* spp—were common causes of gastrointestinal disease in MSM and resulted in terms (now considered inappropriate) such as gay bowel syndrome.³⁹⁸ Given what is now known about the biological effects of STIs to increase infectiousness of and susceptibility to HIV,³ these infections are likely to have facilitated the early spread of HIV before it became clinically apparent as opportunistic infections and cancers.

Links between the opportunistic conditions comprising AIDS, risky sexual practices, and a history of multiple STIs in MSM were noted in the early 1980s,³⁹⁹ well before a retrovirus was discovered as the cause of AIDS. Rates of gonorrhoea and syphilis began to decrease in the late 1970s but the rate of decline accelerated rapidly after the first deaths from AIDS were reported in the early 1980s.^{124,400,401} Campaigns that arose in the gay community advised MSM to reduce numbers of partners and to use condoms, resulting in the development of the terminology of safer sex within the context of harm reduction. Government-sponsored public health campaigns for the general population followed.¹²⁴ Figure 9A shows the large decline in syphilis notifications in England and Wales from 1983 onwards, but notifications of other STIs including lymphogranuloma venereum and other enteric pathogens also decreased.^{124,397} By the mid-1990s, notifications of syphilis and gonorrhoea were at their lowest since surveillance began (figures 9 and 10).

Trends in STIs and sexual behaviour in MSM since the mid-1990s have occurred in the context of continued developments and improvements in ARTs for HIV treatment and prevention. Notifications of syphilis, gonorrhoea, and chlamydia in MSM have all increased (figure 10).^{405,406,409–412} A review⁴¹² of syphilis in 31 high-income countries between 2000 and 2013 showed that the male-to-female ratio increased in all geographical regions from 4.1 in 2000 to 7.9 in 2013. New outbreaks of lymphogranuloma venereum,³⁹⁷ hepatitis C infection, and shigellosis have also appeared, particularly in MSM infected with HIV.⁴¹⁰ Combination ART (cART) became available in the mid-1990s and substantially improved the prognosis for people with HIV infection,⁴¹³ changing the nature and course of HIV infection from a deadly infection to a chronic disease. Further advances in the efficacy of cART with less toxic drugs and less complicated dosing schedules, together with improvements in monitoring viral load and resistance, prompted recommendations for earlier commencement of therapy for people infected with HIV.⁴¹⁴ The first use of cART to prevent, rather than to treat, HIV was PEP for short-term prophylaxis to reduce the risk of HIV acquisition after a substantial risk of exposure to infection.⁴¹⁵ Since the mid-2000s, the potential for cART to be used to prevent HIV transmission followed research showing that cART reduces HIV infectiousness, and when HIV replication is suppressed to undetectable concentrations in plasma, transmission can be virtually

eliminated.^{416,417} TasP (also known as test and treat⁴¹⁸) refers to a population-level strategy of starting cART as soon as HIV infection is diagnosed, irrespective of CD4 cell count, to suppress viral load and prevent transmission to sexual partners.⁴¹⁹ A regimen of two antiretrovirals, taken as PrEP to prevent acquisition of HIV during periods of regular high-risk exposures, overcomes the limitations of PEP and is the third and most recent way of using cART for MSM to prevent HIV infection.^{408,420,421}

All three uses of cART for HIV prevention have been accompanied by concern about their possible unintended negative consequences for sexual behaviour and STIs,⁴²² in an analogy with earlier fears about penicillin and syphilis.⁸ These concerns have been framed within the risk compensation hypothesis, which was first applied to sexual behaviour to explain why increases in condom use were not reflected in reductions in HIV infection incidence.⁴²³ Risk compensation occurs when an intervention prevents an adverse outcome, paradoxically making risk-taking behaviour more attractive; compensatory increases in risky behaviours then result in a failure to reduce the adverse outcome. The links between biomedical HIV treatment and prevention strategies and sexual risk are dynamic and complex.^{20,422} Behavioural surveillance in MSM, such as surveys done yearly in Sydney, Australia, for 20 years (figure 11)⁴²⁴ and the US National HIV Behavioral Survey (NHBS) done using venue-based sampling in 21 cities in the USA every 3 years since 2005,^{425,426} showed that a gradual decline in condom use could be a manifestation of risk compensation with several contributing factors over time. Treatment optimism about the benefits of improved cART has been associated with increased risky behaviour; MSM with stronger perceptions that cART has reduced the threat from HIV infection and reduces the need for safer sex engage more often in risky behaviours, such as non-condom receptive anal intercourse.^{427,428} Safer sex fatigue⁴²⁹ and the adverse effects of HIV infection on mental health⁴³⁰ also contribute to sexual risk taking. Serosorting (ie, choosing sexual partners with the same HIV serostatus) results in sexual networks stratified by HIV serostatus with reduced condom use⁴²⁶ and increased risk of STI transmission.⁴³¹

In this section of the Commission, we give an overview of the HIV prevention strategies of PEP, TasP, and PrEP, and examine evidence of whether their use results in risk compensation and increases in STI prevalence in MSM. Additionally, we speculate on the potential influence of biomedical interventions on future STI epidemiology in MSM once implemented more broadly, and we discuss alternative options for STI prevention other than condom use.

PEP

Guidelines for the use of PEP recommend it after both occupational and non-occupational exposures with a substantial risk of HIV acquisition and with a person

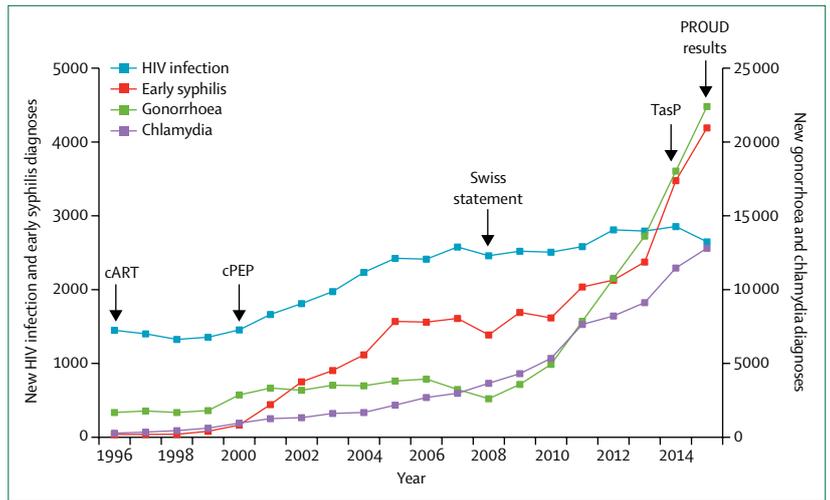


Figure 10: New diagnoses of HIV infection, early syphilis, gonorrhoea, and chlamydia
Data are new diagnoses from 1996 to 2015 in men who have sex with men (MSM) in England.⁴⁰²⁻⁴⁰⁶ Early syphilis includes primary, secondary, and early latent infections. New diagnoses of bacterial STIs and HIV were stable immediately after the introduction of cART and cPEP. Syphilis and HIV increased from 2000 onwards. Publication of the Swiss statement⁴⁰⁷—that people taking cART with suppressed viral load do not need to use condoms—coincided with increases in new diagnoses of gonorrhoea and chlamydia and further increases in syphilis, but no change in HIV infections. These trends have continued since the introduction of the TasP recommendation and the PROUD trial.⁴⁰⁸ PROUD=Pre-exposure Option for reducing HIV in the UK, immediate or Deferred trial. cART=combination antiretroviral therapy. cPEP=combination post-exposure prophylaxis. TasP=treatment as prevention.

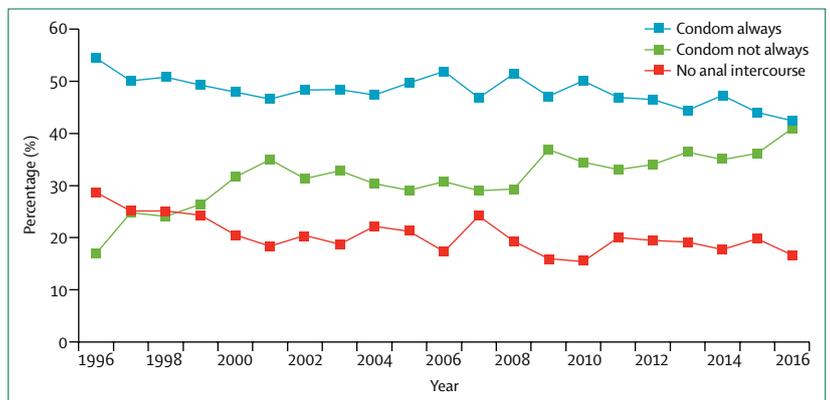


Figure 11: Condom use for anal sex in men who have sex with men
Data are for Sydney, Australia, in 1997–2016.⁴²⁴

known to have HIV infection or a person belonging to a high-risk group but with unknown HIV infection status.^{432,433} The efficacy of PEP has not been studied in RCTs, but there is a wide consensus about its effectiveness, based mainly on a case-control study⁴¹⁵ in a hospital setting, which found an 81% reduction of HIV transmission in the group that used PEP. The increased availability of PEP has led to concern that it might increase risk taking.⁴³⁴ Two studies^{435,436} found a higher risk of non-condom sexual behaviour and a higher incidence of HIV infection in the group of MSM after receipt of PEP, but these studies did not find a correlation between PEP use and changes in risky behaviour. Heuker and

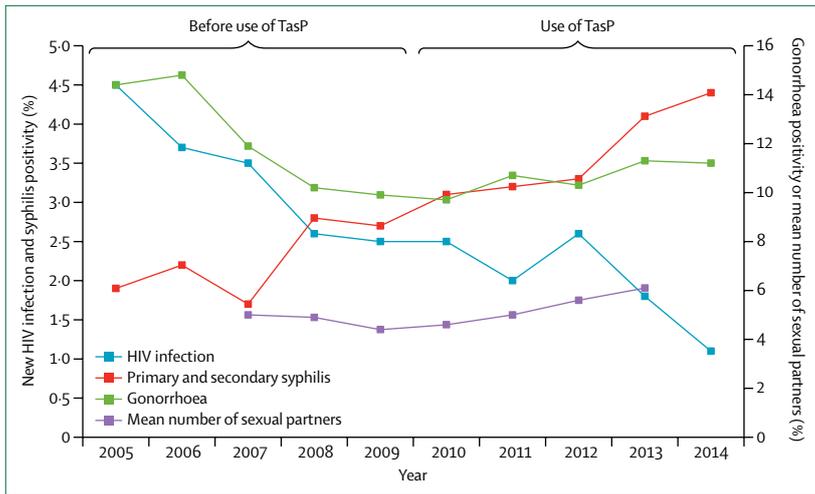


Figure 12: Percentage of tests that were positive and the mean number of sexual partners before and during the recommendation of TasP

Data are percentage of tests positive for HIV infection, primary and secondary syphilis, and gonorrhoea between 2005 and 2014, and mean number of sexual partners in the past 3 months between 2008 and 2013 in San Francisco, CA, USA.⁴⁴⁵⁻⁴³⁹ TasP=treatment as prevention.

colleagues⁴³⁶ concluded that many MSM requesting PEP already belong to a high-risk group. In high-income countries, most PEP requests come from MSM but uptake remains low: 183 requests from one large public health centre in Amsterdam, Netherlands, over a 5-year period.⁴³⁷ Successful awareness campaigns have increased uptake of PEP.⁴³⁴ The limitations associated with ascertaining exposure and eligibility, and suboptimal effectiveness, suggest that use of PEP is unlikely to have any effect on sexual risk behaviour or STIs at the population level.

TasP

The concept of using cART to prevent sexual transmission of HIV began with the finding that transmission between serodiscordant heterosexual couples was rare when the partner infected with HIV had a very low or undetectable concentration of HIV-1 RNA.^{416,417} On the basis of these observational studies, the Swiss AIDS Commission⁴⁰⁷ stated in 2008 that a serodiscordant couple could have non-condom sex if the partner infected with HIV was taking cART with sustained viral suppression and had no other STI. The Swiss statement in effect promoted widespread HIV testing and immediate treatment to reduce HIV transmission and catalysed the initiation of RCTs to examine the effect of TasP at the population level.⁴¹⁸

Mathematical modelling studies⁴³⁸ have shown how, assuming zero transmissibility with suppressed viral load, universal HIV testing and immediate cART could eliminate HIV infection within 10 years of implementation. In 2012, an individual-level RCT, HPTN 052,⁴³⁹ in nine countries (Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand,

and the USA) showed that early diagnosis and initiation of cART reduced the risk of sexual transmission within stable, mostly heterosexual, HIV-serodiscordant couples by 96% (95% CI 73–99) compared with later treatment. To extrapolate these benefits to a whole population, a sufficiently high proportion of all individuals infected with HIV would need to receive and adhere to effective cART from very early in the course of infection.⁴⁴⁰ The first of the population-level trials, a cluster RCT⁴⁴¹ in KwaZulu-Natal, South Africa, did not find a reduction in incidence of HIV infection in communities that received the TasP intervention. Suboptimal uptake of testing, particularly in young men, and delays in linkage to care are likely to have reduced the public health benefits of TasP,⁴⁴² although an earlier ecological study⁴⁴³ in the same population had suggested that HIV infection incidence was lower in people living in communities with higher cART coverage than in those with lower cART coverage.

Risk compensation, STIs, and the TasP strategy

There are few published studies about the effects of the TasP strategy on sexual behaviour and on the incidence of bacterial STIs in MSM. In most countries, ART recommendations have moved gradually towards starting treatment at high CD4 counts. At the individual level, in the HPTN 052 RCT,⁴³⁹ the frequency of new STIs (syphilis, gonorrhoea, chlamydia infections, and trichomoniasis) detected in heterosexual participants treated immediately was low and similar to that in those who received deferred treatment after a median 1.7 years of follow-up; 98% of participants were heterosexual and more than 95% in both groups reported using condoms. At the population level, the effects in the TasP trial⁴⁴¹ in KwaZulu-Natal on behavioural outcomes, including condom use, have not yet been published.

An examination of data from San Francisco, CA, USA, provided some insight at the population level because the city has biological and behavioural surveillance data spanning the introduction of TasP.⁴⁴⁴ The San Francisco Department of Public Health implemented a TasP strategy—cART for all individuals infected with HIV regardless of CD4 cell count at publicly funded HIV clinics and an expansion of HIV testing services—in 2010, 2 years before US national recommendations changed.⁴⁴⁴ We aggregated published STI surveillance data from 2005 to 2014, and we compared the positivity rates of HIV infection, syphilis, and gonorrhoea, and mean numbers of partners for self-identified gay and bisexual men before the introduction of the TasP strategy nationally (from 2005 to 2009) with the period during its implementation (from 2010 to 2014).⁴⁴⁵⁻⁴⁴⁸ Figure 12 shows that the percentage of HIV tests with a positive result was already decreasing, and declined from 4.5% in 2005 to 2.5% in 2010. HIV positivity declined further, from 2.5% in 2010 to 1.1% in 2014. By contrast, the positivity rate of early syphilis infections increased consistently from 1.9% in 2005 to 4.4% in 2014.⁴⁴⁵⁻⁴⁴⁸ The

gonorrhoea positivity rate decreased during 2005–09, but increased from 9.7% to 11.2% in 2010–14. Behavioural surveillance data show that the mean number of sex partners in the previous 3 years decreased from 5.0 in 2007 to 4.4 in 2009, and then increased from 4.6 in 2010 to 6.1 in 2013.⁴⁴⁹ The recommendation about TasP in San Francisco was thus temporally associated with increases in gonorrhoea, syphilis, and partner numbers. Risk compensation might have contributed to these trends, although the increase in syphilis began before TasP was used.

In Switzerland, the proportion of MSM who are infected with HIV in the Swiss HIV Cohort Study⁴⁵⁰ reporting non-condom sex with occasional and stable partners had increased slightly from 2000 onwards. A piecewise linear regression analysis showed a sudden change with a marked increase in non-condom sex from 2008 to 2013, after the publication of the Swiss statement that promoted TasP.^{407,450} Data from the US NHBS surveys in MSM, showed that condom use has decreased from 2005 up to 2014 over a large geographical area, and that these trends were not explained by serosorting, seropositioning, PrEP use, or cART treatment.⁴²⁶ Figures 10 and 11, which show rates of new diagnoses of bacterial STI reported in England and the decrease in condom use in Sydney, suggest that opposing trends in STI rates and in condom use have taken place in a 20 year period and cannot be attributed to any one factor, such as TasP. Nevertheless, there is a consensus that knowledge about the effects of cART on reduced infectiousness of HIV have contributed to risk compensation.²⁰ A disadvantage inherent to TasP is that its success depends on the behaviour of others.⁴⁵¹ The uninfected individual has to trust that their sexual partners infected with HIV are adherent to cART, and that the cART is sufficiently effective to mitigate transmission risk. By contrast, with PrEP and PEP, the at-risk individual takes the preventive treatment.

PrEP

Three RCTs^{408,420,421} have studied the effects of PrEP on the acquisition of HIV infection as part of an HIV prevention package for MSM that includes risk reduction counselling, condom provision, and regular HIV and STI testing. Across these trials, the use of tenofovir-emtricitabine, in combination with comprehensive sexual health care, reduced HIV incidence ranging from 44% to 86%. Two of the RCTs^{408,420} studied daily use of tenofovir-emtricitabine and one RCT⁴²¹ studied intermittent use (two tablets between 2 h and 24 h before sex, followed by one tablet two times at 24 h and 48 h after sex). The first landmark study, the Pre-exposure Prophylaxis Initiative (iPrEx),⁴²⁰ looked at the effect of daily use of tenofovir-emtricitabine in 2499 MSM from six countries (Peru, Ecuador, South Africa, Brazil, Thailand, and the USA) and was published in 2010. The Pre-exposure Option for reducing HIV in the UK,

immediate or Deferred (PROUD) trial⁴⁰⁸ enrolled 544 MSM in the UK and randomly assigned them to immediate or a 1 year delayed start of daily oral tenofovir-emtricitabine. In the Intervention Préventive de l'Exposition aux Risques avec et pour les Gays (Ipergay) trial,⁴²¹ 414 MSM were randomly assigned to either tenofovir-emtricitabine or placebo for intermittent use in France and Canada. In all PrEP trials, adherence was a strong determinant of PrEP effectiveness.⁴⁵²

These trials showed that it is feasible to identify and enrol MSM at high risk of acquiring HIV infection, with HIV infection incidences in the placebo arm of 9.0 per 100 person years in the PROUD trial and 6.6 per 100 person years in the Ipergay trial. Open-label studies, demonstration projects, and cohort studies provide additional evidence that PrEP roll out to MSM at high risk for HIV infection is feasible, safe, and prevents HIV infection.^{452–455} Eligibility criteria in most PrEP trials and demonstration projects include well known determinants for HIV acquisition in MSM, such as recent rectal or urethral STIs, a recent use of PEP, reporting anal intercourse with casual partners, and having a partner with HIV infection and a detectable viral load.⁴⁵² International guidelines for PrEP from the US Centers for Disease Control and Prevention and WHO reflect these eligibility criteria.^{456,457}

Risk compensation, STIs, and PrEP

PrEP is a powerful intervention for HIV prevention in MSM, but it has the potential to reduce commitment to primary prevention strategies, result in risk compensation,⁴²² and increase proportions of MSM with STIs. The role of PrEP in relation to sexual behaviour and STI is somewhat easier to assess than with TasP, because PrEP is an individual intervention rather than a population-based one. PrEP is, however, only in the early stages of implementation.

In the placebo-controlled trials of iPrEx⁴²⁰ and Ipergay,⁴²¹ condom use and STI incidence were similar in participants allocated to PrEP and to placebo. These findings are expected because participants were blinded and they all received the same risk-reduction advice. The PROUD RCT⁴⁰⁸ was designed as a pragmatic open-label study that would allow risk compensation to be observed. The total number of different anal sex partners was similar in the two groups, but a larger proportion of participants allocated to immediate than to deferred PrEP reported non-condom receptive anal sex with ten or more partners (21% vs 12%; $p=0.03$). However, the proportions diagnosed with STIs during the 12-month follow-up were similar in men receiving immediate and deferred PrEP. This proportion for rectal gonorrhoea or chlamydia was 36% for immediate PrEP versus 32% for deferred PrEP (odds ratio [OR] 1.00, 95% CI 0.72–1.38), and for syphilis was 11% versus 9% (1.32, 0.79–2.10).

Open-label studies should allow a more realistic assessment of the influence of PrEP on sexual behaviour.

In an open-label observational study⁴⁵³ that included MSM who had taken part in the iPrEx trial and two other studies, the proportions reporting non-condom receptive anal intercourse, non-condom insertive anal intercourse, and numbers of sexual partners all decreased to a similar extent during follow-up both in the group of PrEP recipients and the group of non-recipients, and incidence of syphilis was also similar (7.2 infections per 100 person-years in PrEP recipients and 5.4 per 100 person-years in non-recipients; hazard ratio 1.35, 95% CI 0.83–2.19). Grant and colleagues concluded that there was no evidence of risk compensation during open-label access to PrEP use, but that cohort participation and access to comprehensive prevention services might have encouraged other safer sexual behaviours. In the Demo project⁴⁵⁴ in San Francisco, Washington DC, and Miami, USA, early findings (≤ 48 weeks) in men receiving PrEP showed a stable proportion of overall reported non-condom receptive anal sex act (365 [66%] of 557) in the previous 3 months, although the mean number of condom-protected sex acts decreased. The proportions with early syphilis, gonorrhoea, and chlamydia at quarterly visits initially fell and then returned to baseline values.⁴⁵⁴ Qualitative data from participants suggest that men integrate PrEP in a dynamic way into existing risk-reduction strategies, rather than relying on it as a solitary method of HIV prevention.⁴⁵⁸

The long-term effect of PrEP for risk compensation and incidence and prevalence of STIs are not yet known. Taken together, trials of PrEP with 1–2 years of follow-up show a large reduction in HIV infection incidence in MSM who adhere to the regimen, high but similar proportions of bacterial STIs in MSM who received PrEP and those who did not, and mixed effects on sexual behaviours.⁴²⁶ Additional studies suggest that increasing the use of PrEP as a method of biomedical HIV prevention could change patterns of sexual partner seeking and condom use.^{425,459} Newcomb and colleagues⁴⁵⁹ have coined the term biomed-matching as a new strategy within MSM who meet up using geosocial networking applications and disclose their use of biomedical HIV prevention medication; they then have non-condom anal sex when the partner is also taking PrEP or has undetectable viral load on cART. MSM who receive PrEP will need to be followed up carefully over time with the use of quantitative and qualitative research methods to establish whether and how risk compensation and changing patterns of sexual partnerships and practices are affecting STIs.

STI prevention in the era of biomedical HIV prevention

The use of cART to prevent HIV acquisition and transmission, particularly TasP and PrEP, are changing the HIV prevention landscape for MSM. The continued decrease in HIV positivity in San Francisco has been attributed to TasP, and a rapid increase in the number of MSM using PrEP in London, UK, might have influenced a 40% reduction in new HIV diagnoses in 2016 compared

with 2015.⁴⁶⁰ Trends in HIV infection and other STIs seem to have been decoupled. STI rates in MSM have been increasing since the late 1990s (figure 10).^{392,402–406} The increases in notifications of bacterial STI appear to be accelerating (figures 9, 10, and 12). In England, MSM with HIV infection accounted for almost all of the increase in STI notifications in MSM; for syphilis, the proportion diagnosed in MSM with HIV infection increased from about 25% in 2009 to about 40% in 2013.⁴¹⁰ In the absence of denominator data, how much of the increase is the result of more frequent testing is not known. Widening of PrEP use, together with other behavioural changes, including an increase in the adoption of seroadaptive behaviours^{425,426} and use of geosocial networking mobile applications, such as Grindr,^{459,461} could affect sexual networks and proportions and patterns of STI. For example, if non-condom sex partnerships between MSM using PrEP who are not infected with HIV and MSM using cART who are HIV infected become more common, outbreaks of syphilis, lymphogranuloma venereum, hepatitis, and shigellosis that have occurred mostly in those infected with HIV could spread to networks of MSM without HIV infection. STIs that increase HIV infectiousness through inflammatory mechanisms⁵ could then reduce the effect of biomedical HIV prevention methods. Additional surveillance and interventions to control STIs within MSM in this new era are needed, especially if behavioural risk reduction interventions cannot reverse trends in condom use.

Treatment of curable STIs has long been considered an integral component of combination HIV prevention packages.⁴⁶² Regular STI testing to detect and treat asymptomatic infections is now widely recommended for STI control in MSM. MSM starting PrEP are advised to be tested for bacterial STIs every 3 months, and MSM in general are usually advised to be tested every year, although only about 40% of at-risk MSM in Australia were receiving annual screening in 2014.⁸⁸ One mathematical modelling study⁴⁶³ suggested that screening of MSM for chlamydia could reduce the prevalence of both chlamydia and HIV infection. These findings should be considered in light of evidence presented in parts 1 and 2 of this Commission. First, modelling studies^{106,107} also suggest that chlamydia screening in heterosexual populations will reduce chlamydia prevalence, but evidence from RCTs^{11,96} and repeated population-based cross-sectional studies^{44,45} have not found substantial reductions in chlamydia prevalence in the targeted populations. Second, as antimicrobial resistance in *N gonorrhoeae* spreads, the potential effect of increasing numbers of STI tests also needs to be considered. On the one hand, mathematical modelling studies^{464,465} of populations of MSM show that, at least for some antimicrobials, increasing gonorrhoea treatment might reduce prevalence temporarily, but that the increased selection pressure accelerates the spread of resistance,

resulting in increased prevalence over time. On the other hand, models of syphilis transmission have shown a reduction in incidence with frequent testing,⁴⁶⁶ and one ecological study⁴⁶⁷ using national surveillance data in Australia showed that when syphilis testing increased from 1.6 tests per year to 2.3 tests per year, there was a reduction in secondary syphilis cases from 45% to 26%. There was also a commensurate increase in early latent infections (from 23% to 45%) suggesting that frequent testing was detecting syphilis infection before it reached the secondary stage.⁴⁶⁷

Another possible STI intervention that has had little investigation is the daily use of doxycycline.⁴⁶⁸ A single, double-blind, RCT⁴⁶⁹ of 30 individuals followed up for 1 year showed lower proportions of STI in the doxycycline group. Interventions involving prophylactic use of antimicrobials have not been pursued further because of concern about antimicrobial resistance. One group of investigators is evaluating the use of antibacterial mouthwash for the prevention of pharyngeal gonorrhoea. The hypothesis is that saliva, used as a lubricant for both anal sex and oral sex, gives pharyngeal gonorrhoea a central role in the persistence of gonorrhoea at all anatomical sites in MSM, although relatively little is known about the transmission of STIs between anatomical sites in MSM.⁴⁷⁰ Mouthwash has been shown in laboratory experiments to inhibit *N gonorrhoeae* growth, and when used in individuals with pharyngeal gonorrhoea it reduces the chance of detecting *N gonorrhoeae* 5 min later.⁴⁷¹ Long-term prevention studies are underway using mouthwash. More research is required on STI control in MSM that does not rely on condom use, including a better understanding of infectiousness and transmission between anatomical sites in men.

Conclusion

Rates of bacterial STIs in MSM have been increasing for about 20 years and are approaching the numbers seen in the late 1970s before HIV infection first appeared. During this time, ART strategies have become powerful and important methods for HIV prevention. Evidence for a major contribution of TasP and PrEP to reductions in future HIV incidence and prevalence is accumulating. Risk compensation in response to the success of cART in reducing the infectiousness of and susceptibility to HIV, mediated through increases in non-condom sexual intercourse or increased numbers of sexual partners, has occurred.^{20,408} The contributions of behavioural responses to the biomedical HIV prevention strategies and of other factors influencing sexual behavioural change remain unknown.^{425,454,459} Quantification of the effect of biomedical HIV prevention interventions on STIs is methodologically difficult.^{401,410} On the basis of surveillance data from places with large populations of MSM,^{410,448} it is possible that the incidence and prevalence of STI in MSM will continue to increase.

STI control interventions that complement the highly effective biomedical interventions for HIV prevention are needed as part of combination prevention packages. Biomedical HIV interventions play a positive part in STI control through frequent contacts with sexual health services that allow regular continued opportunities for primary prevention and comprehensive case management of STIs, including prompt diagnosis and treatment, partner notification, promotion of condom use, and risk reduction interventions.⁴⁷²

Nevertheless, continued research is needed to investigate and understand the effects of TasP and PrEP on sexual behaviours and networks that might increase STI transmission and, through STI–HIV interactions, might drive renewed HIV transmission. Enhanced biological and behavioural surveillance activities are needed to monitor changes in STIs in MSM who are infected or not infected with HIV, antimicrobial resistance, and the emergence or re-emergence of new sexually transmissible pathogens, including enteric infections, Ebola virus, and Zika virus.⁴⁷³

Call to action

Action is required to address the substantial challenges facing STI control globally (figure 13). Antimicrobial resistance in *N gonorrhoeae* is increasing relentlessly and adverse consequences of chlamydia infection remain prevalent. STIs in MSM are increasing rapidly, new sexually transmissible infections are emerging or re-emerging, and there is evidence that bacterial vaginosis—one of the most common, but often ignored, genital conditions in women—might also be sexually transmissible. These issues are magnified in low-income and middle-income countries that bear the burden of STIs worldwide. To address these issues, policy makers need to be reached and convinced that investment in clinical and public health strategies can improve the control of STIs, on the basis of carefully considered analytical decisions founded in science. If they do not, society could suffer more than it should, and spend more than it needs to.⁴⁷⁴ In putting this case, we recognise that social, cultural, and structural conditions are major determinants of sexual behaviour, sexual risk, and STIs.³⁹⁰ Research evidence provides the scientific support for prioritising interventions, but successfully influencing health policy will require the involvement of stakeholders, including researchers, clinicians, members of civil society, and policy makers themselves.⁴⁷⁵

One of the most important messages about STI control is that good policy decisions matter much more than do poor individual ones.^{474,476,477} This message is important because effective policy interventions can put strong downward pressure on STI incidence,³⁴ whereas individual behaviour has a relatively weak effect on the population prevalence of STIs and sustained and substantial behaviour change is difficult to achieve.^{474,477,478} This case needs to be made to policy makers that STIs cost less to

Policy and programme priorities		Research priorities
Overarching	<ul style="list-style-type: none"> • Ensure accessible health care for early treatment of symptomatic STIs • Ensure health-care organisations can implement effective partner notification and treatment for STIs • Ensure funding for STI vaccine development • Ensure funding for a comprehensive STI control programme in low-income and middle-income countries, with a priority towards providing accurate surveillance programmes 	<ul style="list-style-type: none"> • Develop measures of access to health-care services and set minimum benchmarks • Robust trials to provide evidence for innovative partner notification and treatment strategies with biological outcomes (eg, re-infection rates) • Laboratory and clinical research necessary for successful vaccines • Use of implementation science to inform strategies to develop comprehensive STI control programmes in low-income and middle-income countries, including school-based sex education programmes and active targeted health promotion
Chlamydia	<ul style="list-style-type: none"> • Ensure health-care organisations have case management guidelines to improve pelvic inflammatory disease outcomes • Enhance surveillance of pelvic inflammatory disease, ectopic pregnancy, and infertility • Ensure that chlamydia control strategies state acceptable chlamydia prevalence 	<ul style="list-style-type: none"> • Robust trials to provide evidence for strategies to improve pelvic inflammatory disease outcomes and prevention, including re-testing and partner notification • Develop non-invasive tools to detect upper genital tract infection and disease • Determine prevalence, incidence, and burden of chlamydia disease
Gonorrhoea	<ul style="list-style-type: none"> • Ensure funding to develop new antimicrobials and treatments for gonorrhoea • Ensure funding to develop rapid diagnostic tests for antimicrobial resistant <i>Neisseria gonorrhoeae</i> • Reduce gonorrhoea prevalence 	<ul style="list-style-type: none"> • Laboratory and clinical research needed for new antimicrobials and other treatments for gonorrhoea • Laboratory and clinical research needed for rapid diagnostic tests, including point-of-care tests • Identify key drivers of gonorrhoea incidence and prevalence and effective interventions to reduce it
STIs in MSM	<ul style="list-style-type: none"> • Mitigate unintended consequences of PrEP • Reduce the incidence and prevalence of STIs in MSM 	<ul style="list-style-type: none"> • Identify the effects that frequent STI screening has on STI incidence and understand behavioural risk compensation • Determine the key drivers of STIs in MSM and develop combination prevention interventions
Bacterial vaginosis	<ul style="list-style-type: none"> • Develop new treatment approaches for bacterial vaginosis to improve cure • Ensure funding to establish whether bacterial vaginosis is sexually transmitted 	<ul style="list-style-type: none"> • Investigate the pathogenesis of bacterial vaginosis recurrence • Robust trials to determine if male partner treatment reduces bacterial vaginosis occurrence • Explore new agents that target the biofilm • Identify the transmissible agent(s) responsible for bacterial vaginosis
Point-of-care tests	<ul style="list-style-type: none"> • Ensure 100% of pregnant women are screened and treated for syphilis at the first prenatal visit • Develop policies for use of point-of-care tests meeting the ASSURED benchmark • Integrate point-of-care tests into STI case management guidelines 	<ul style="list-style-type: none"> • Use implementation science to effectively identify and manage syphilis using point-of-care tests • Develop and evaluate new point-of-care tests that meet the ASSURED benchmark, including antimicrobial resistance • Use implementation science to ensure effective use of point-of care tests

Figure 13: Call to action

Policy and programme priorities are shown along side with their related research priorities. This call to action assumes that in high-income countries other elements of a comprehensive STI control programme are already in place, including sound sex education programme throughout school, strong partner notification programmes that use the latest information technology systems and legislative changes for partner-delivered antibiotic treatment where appropriate, legalised frameworks for sex work, active targeted health promotion, and accurate surveillance programmes. STI=sexually transmitted infection. PrEP=pre-exposure prophylaxis. MSM=men who have sex with men.

keep under control than to treat and to manage their sequelae, when endemic proportions are high.⁴⁷⁴

The cornerstone of the health sector response to effective STI control is quality health care that is easily accessible, and is the principle behind the provision of free STI services in many countries.⁴⁷⁶ Accessible health care helps to ensure that STIs are treated early, before substantial transmission can occur.³⁴ Communities with poor access to health care have high rates of symptomatic STIs, such as gonorrhoea or trichomoniasis, and those with accessible health care have much lower rates, although the number of sexual partners in both communities might be similar.⁴⁷⁹ For example, gonorrhoea is relatively easy to control with accessible primary health care in individuals who are heterosexual and, as a result, most high-income countries' yearly notification rates of reported gonorrhoea are less than 100 per 100 000 population. Notification rates in those who are

heterosexual exceed these numbers in high-income countries in populations whose access to health care is limited, such as in uninsured Americans or Indigenous Australians living in remote communities.^{479,480} STI services are a key goal of WHO's strategy to help achieve universal health coverage, a target of the 2030 Agenda for Sustainable Development.³⁴ We call on policy makers to ensure their citizens have accessible, affordable, and quality STI care.

Largely asymptomatic STIs, such as chlamydia, provide a much greater challenge to control than do symptomatic STIs. Despite substantial proportions of the population being tested for chlamydia in some high-income countries, it has proven difficult to reduce the prevalence of chlamydia and the long-term effect of widespread testing for chlamydia on health outcomes, including pelvic inflammatory disease, ectopic pregnancy, and infertility, remains uncertain. Chlamydia control

strategies should define acceptable local targets for chlamydia prevalence, so that appropriate interventions can be prioritised. Improvement of case management of those diagnosed with chlamydia and pelvic inflammatory disease (eg, effective antimicrobial treatment, partner notification, and retesting to detect repeated infection) might achieve more than promoting widespread testing alone. Policy makers should also establish and adapt surveillance systems so that they know what effect chlamydia control activities are having on pelvic inflammatory disease and its complications. We call on policy makers to invest in the research agendas that international experts have repeatedly called for,^{61,151,152,481} to further the understanding of the natural history of chlamydia, and to develop non-invasive measures of tubal infection, inflammation and damage, and biomarkers to predict upper genital tract pathology. Furthermore, policy makers must invest in chlamydia vaccine research because without an effective vaccine, chlamydia infections are unlikely to be controlled.

The effective control of gonorrhoea is a global health priority³⁴ because of the relentless increase in antimicrobial resistance, the high incidence in low-income and middle-income countries, and increasing incidence in key populations, including MSM (figure 10).⁴¹⁰ In this context, we call on policy makers to ensure adequate and sensitive surveillance programmes are in place and on industry to support the development of effective antimicrobial agents should the current ones fail. The control of gonorrhoea in MSM presents a similar problem to chlamydia because asymptomatic pharyngeal and rectal infection are common and frequently occur in the absence of concurrent symptomatic urethral infection, so cases are only detected through testing or partner notification.⁴⁸² Some health-care professionals have advocated more frequent screening, but an increased prevalence of gonorrhoea treatment with some antimicrobials might accelerate the spread of resistance and might outweigh any gains in reducing prevalence.⁴⁶⁵ Another problem with gonorrhoea control in MSM is that it is not prevented by consistent condom use for anal sex, because the pharynx appears to have a key role in transmission of infection and antimicrobial resistance.^{158,483,484} Effective control will require understanding of how gonorrhoea is transmitted between MSM, so that evidence-based interventions can be developed just as interventions for HIV control were developed by understanding its transmission. Ideally, condoms should not be the sole part of these interventions because their use is decreasing and might decrease further.⁴²⁴ One study⁴⁷¹ has suggested a potential non-condom-based intervention. Chow and colleagues⁴⁸⁵ have found that *N gonorrhoeae* is commonly present in the saliva of men with pharyngeal infection, and that saliva is frequently used as a lubricant for anal sex. Early work⁴⁷¹ has shown that antibacterial mouthwash might inhibit *N gonorrhoeae* growth, and studies of mouthwash for gonorrhoea prevention are underway. We

call on policy makers to fund research to better understand how STIs are transmitted between MSM and to allow the development of new control programmes not based only around condoms.

Bacterial vaginosis in women is another commonly asymptomatic infection with a substantial global burden that poses similar control issues to chlamydia but has the additional problem that there is an absence of a proven transmitted pathogen. Effective control is complicated by its high-frequency relapse, which is likely to be due, at least in part, to the failure in recognising the importance of sexual transmission in its pathogenesis and the contribution of re-infection to recurrence.^{18,257} Current treatment strategies are entirely focused on the female partner, although epidemiological and microbiological data are accumulating to provide evidence for male carriage and exchange of bacteria that are associated with bacterial vaginosis within sexual partnerships.²⁷⁶ To make substantial advances in the treatment and prevention of bacterial vaginosis and its costly sequelae, a better understanding of the contribution of persistence of these bacteria versus re-infection to recurrence of bacterial vaginosis is needed. New treatment strategies are required but there is also a need to revisit male partner treatment trials with more evidence-based approaches.

Effective STI control in low-income and middle-income countries provide a particular challenge because of the high cost of diagnostic tests and insufficient laboratory capacity that accompany weak health service infrastructure. Point-of-care tests that fulfil the ASSURED benchmarking programme of WHO can play an important part in effective STI control, but understanding their limitations is important. Policy makers should fund programmes that optimise and evaluate all aspects of STI control in low-income and middle-income countries with the implementation of the validated point-of-care tests, including but not limited to screening of antenatal care attendees and high-risk populations, together with improved partner notification strategies, presumptive treatment, syndromic management, and combinations of all of these strategies.

It is important to acknowledge that STI control strategies that rely only on reducing sexual risk practices at a population level will not work well, because on their own, they afford a relatively modest effect on STI prevalence. Large multicentre studies^{477,478} of behavioural interventions for condom use have relatively modest effect sizes (about 20% effective at 1 year). By contrast, biomedical interventions, such as the HPV vaccine programme in women, have been outstandingly successful and resulted in almost complete elimination of the oncogenic HPV types included in the vaccine in vaccinated women and unvaccinated heterosexual men in Australia.^{23,474} Similarly, large effect sizes for reducing HIV acquisition are seen in RCTs^{408,420,421} of PrEP when adherence is high. Biomedical methods to prevent HIV infection have, however, contributed to increased

proportions of STIs within MSM as a result of risk compensation. No single measure will effectively control all STIs at a population level. Effective STI control will require the political will to prioritise and invest in new interventions together with the optimisation of primary and secondary prevention strategies, including integrated sex education programmes in schools, strong partner notification programmes that use the latest information technology systems and legislative changes for partner delivered antibiotic treatment where appropriate, legalised frameworks for sex work, active targeted health promotion, accurate surveillance programmes, and accessible health care for all.

Contributors

All authors take responsibility for the views expressed in their individual sections. CKF conceived the Commission and coordinated its preparation. MU, CSB, and CKF wrote the executive summary. MU and CSB wrote the introduction. JSH and NL wrote part 1. MU wrote part 2. CSB, JRS, and JMM wrote part 3. SCF, RWP, and DM wrote part 4. HJcDv, GJBS, EH, SSP, NL, and CKF wrote part 5. CKF wrote the call for action. MU, CSB, NL, and CKF were involved in editing the final version of this Commission. All authors approved the final manuscript.

Declaration of interests

We declare no competing interests.

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