Sexually Transmitted Infections: Challenges Ahead

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Word count 22164

Executive Summary

WHO estimates that nearly one million people become infected every day with any of four curable sexually transmitted infections (STIs; chlamydia, gonorrhoea, syphilis, 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, including novel antimicrobials. Bacterial vaginosis (BV) is the most common vaginal disorder in women, yet current treatments are associated with high rates of recurrence. This might relate to evidence that suggests sexual transmission is integral to the pathogenesis of BV, which has significant implications for the development of effective management approaches. STIs disproportionately affect low and middle income settings. 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 (MSM) 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 our understanding of some of the key challenges facing us in the field, and outlines new approaches to improve the clinical management of STIs and public health.

Introduction

Sexually transmitted infections (STIs) are amongst the most common acute conditions worldwide.[1] The World Health Organization (WHO) estimated that there were 357 million new cases of four common curable STIs; trichomoniasis (143 million cases), chlamydia (131 million), gonorrhoea (78 million), and syphilis (5.6 million) globally in 2012 (Figure 1).[2] In addition, there are alarming increases in antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* and *Mycoplasma genitalium*.[3] Although most STIs are not usually fatal, they result in a significant burden of disease.[1] The complications of curable STIs include pelvic inflammatory disease (PID), ectopic pregnancy, infertility, chronic pelvic pain, seronegative arthropathy, neurological and cardiovascular disease;[4] STIs in pregnancy can cause foetal or neonatal death, premature delivery, neonatal encephalitis, eye infections and pneumonia;[4] and STIs increase the infectiousness of and susceptibility to HIV.[5] Despite this burden, 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 towards STIs result in unwillingness to prioritise STI control policies.[6-8] In this *Commission of 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, are important global health priorities, or because new evidence is emerging in the area. Of necessity, this *Commission* has excluded important subjects. *M. genitalium* was not included, despite the rapid emergence of resistance to both first and second line treatments, but *M. genitalium* AMR and clinical management options have been recently reviewed elsewhere.[3,9] We also omitted herpes simplex virus, for which vaccine development is progressing rapidly,[10] human papillomavirus (HPV), for which

vaccination is highly effective,[11] but for which implementation is now the key challenge, and *Trichomonas vaginalis* infections because there are no new strategies for treatment or control. Partner notification is an essential part of the management of most STIs and is mentioned in several parts of the *Commission*. We use the term to include all processes involved in informing the sex partners or needle-sharing contacts of persons with STIs of their potential exposure to an infectious disease and ensuring their evaluation and/or treatment.[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 globally[1] and causes serious reproductive tract complications in women.[12] Yet, 20 years after the first randomised controlled clinical trial (RCT) of an intervention to reduce its complications,[13] we remain unsure how to reduce its prevalence and impact on society. Indeed, the most recent RCT of a screening intervention did not find a marked effect on prevalence despite a substantial increase in the proportion of the target population that received screening.[14] *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 AMR in *N. gonorrhoeae*. This organism has become resistant to virtually all antibiotics that have been used to treat it since sulphonamides were first used in the 1930s. The first clinical failure using dual therapy with ceftriaxone and azithromycin was verified in 2015.[15] For this reason, we focus on current and future treatment strategies, including three novel antimicrobials that are being evaluated in phase 2 or 3 RCTs. We also report on novel strategies that aim to reduce the incidence and prevalence of gonorrhoea in MSM, which should also reduce the probability of AMR 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.[10]

The *Commission* chose to include bacterial vaginosis (BV) for three main reasons, even though it is not considered a traditional STI. First, an accumulating body of epidemiological and microbiological evidence suggests that sexual transmission is integral to its pathogenesis.[16,17] Second, BV has been neglected, although it is the most prevalent urogenital disorder amongst 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 HIV transmission.[18,19] Third, treatment failure rates are unacceptably high; more than half of women have a recurrence after recommended therapy but neither BV treatment efficacy nor outcomes have improved for decades.[20] 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 and middle income settings where more than 90% of curable STIs and almost all of the global burden of STIs occur. *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 (POC) tests within a published framework; being affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free and delivered to end-users (ASSURED).[21] POC tests have considerable implications for STI control in high-income settings too, but their potential benefits are greatest in resource constrained settings where healthcare infrastructure is most limited.

Part 5 of the *Commission* discusses epidemics of STIs in MSM in high income settings in the context of three biomedical treatment strategies that use antiretroviral therapies (ART) to prevent HIV infection. Two strategies are prophylactic treatments to reduce susceptibility in HIV-uninfected individuals: post-exposure prophylaxis (PEP) given after specific high risk exposures and pre-exposure prophylaxis (PrEP), given to HIV-uninfected individuals 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.[22] *de Vries* and colleagues review the evidence linking PEP, TasP and PrEP strategies to risk compensation and increasing STI rates.

The *Commission* ends 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 AMR; access to health services, early diagnosis, appropriate treatment and partner notification, and also intensified research into: rapid POC tests to detect both STIs and AMR; novel antimicrobials and/or treatment approaches; and the understanding of STI transmission or pathogenesis.

Part 1. Chlamydia control – what should we do?

Twenty years after the publication of the first RCT of an intervention to reduce the incidence of PID by screening for asymptomatic chlamydia infection in young women,[13] we still need to ask, "what should we do?" about chlamydia control. Three linked factors make this an important question. 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.[23-27] Second, whilst infection might be asymptomatic in over 80% of cases,[28,29] chlamydia can cause tissue damage, particularly in the female reproductive tract where ascending infection can cause PID, which contributes to chronic pelvic pain, ectopic pregnancy and tubal factor infertility (Figure 2).[12] Third, technological advances make

chlamydia diagnosis ever easier (if not cheaper): nucleic acid amplification tests (NAATs) using self-collected specimens, online test kits, mobile phones for receiving results and rapid tests.[30] However, the diagnosis of PID still relies on insensitive and non-specific clinical signs.[27]

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".[31] The general definition of infectious disease control involves agreement on locally acceptable levels,[32] and makes a distinction between the infection and the disease(s) that it causes. But an acceptable level of genital chlamydia infection or chlamydia-associated PID, 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 systems for monitoring and evaluation.[31] Secondary prevention starts with case detection and management to prevent complications; case management includes history-taking and clinical examination, diagnostic tests, treatment, partner notifications, health promotion advice, follow-ups and surveillance.[31] 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 PID.

The WHO Global Health Sector Strategy on STIs 2016-2021 states that, "because best strategies to control and measure chlamydia infections are still to be defined, further research and cost-effectiveness analyses are to be encouraged"(p17).[33] With this 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 PID. 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

196 case management and investment in research to further our understanding about the
197 epidemiology of PID and other chlamydia associated morbidity.
198

199 **Global epidemiology of chlamydia infections**

200 WHO estimated that, in 2012, about 131 million people worldwide became newly infected
201 with chlamydia (Figure 1) and that 4·2% of women and 2·7% of men aged 15 to 49 years had
202 a prevalent infection.[2] In high income countries, chlamydia is most common in young
203 heterosexual adults aged ≤26 years with estimates from meta-analysis of population-based
204 surveys of 4·3% (95% confidence interval (CI) 3·6 to 5·0%) in women and 3·6% (95% CI 2·8
205 to 4·4%) in men.[34] Chlamydia is also common among MSM attending sexual health clinics
206 amongst whom chlamydia positivity ranges from 2% to 5% for urethral infection and 6% to
207 9% for rectal infection.[35-37] Few countries have nationally representative surveys of chlamydia
208 prevalence (i.e. random samples of the general population aimed at providing unbiased
209 estimates) but, amongst those that do,[38-44] prevalence is similar in women and men aged ≤26
210 years, and appears similar in countries that promote widespread chlamydia testing (e.g. USA
211 and England)[44,45] and those without recommendations (e.g. Croatia and Slovenia) (Figure
212 4).[40,46] Within countries, higher chlamydia prevalence is associated with social disadvantage[47]
213 and is higher in people from minority ethnic groups.[43,48]

214 In low and middle income countries, population-based surveys of chlamydia prevalence
215 are also very uncommon.[49-52] Estimates of chlamydia prevalence in the general population in
216 the few countries that have conducted such surveys are mostly similar to those in high income
217 countries (Figure 4).[2] The lowest estimate was in women in India (<1%)[50] and the highest in
218 Papua New Guinea, which estimated a prevalence of 45% among women ≤26 years.[51] Data
219 from unselected 15 to 24 year old women attending antenatal clinics in South Pacific Islands
220 also find that around 20% of pregnant women have chlamydia.[53,54] Whilst we found no

nationally representative surveys in South Africa, chlamydia prevalence amongst pregnant women was as high[55] 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 play a role.[2,53,56]

Global epidemiology of PID and reproductive tract morbidity

Compared with international data about chlamydia infection, very little is known about international variations in the incidence and prevalence of PID and other reproductive tract morbidity caused by chlamydia. WHO estimated that chlamydial infections caused a total of 1·43 million disability-adjusted life years (DALYs) in 2012, most in low and middle income countries (36% African Region, 25% South East Asia Region).[57]

The rate of hospitalisation for PID from any cause varies from around 37 to 194 per 100,000 women aged 15-39 years in different countries.[58] Chlamydia infection is found in association with about 20% of PID cases; one study at a large sexual health clinic in Australia found no causative organism in over 60% of PID cases.[59] A major challenge is the lack of consensus about criteria for the diagnosis of upper genital tract chlamydial disease and the lack of non-invasive tests including new radiological imaging. PID is usually diagnosed based on lower abdominal and cervical signs and symptoms and diagnostic criteria lack sensitivity and specificity.[27]

Natural history of *Chlamydia 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.[60,61] Untreated infection that resolves spontaneously might confer some immunity against further infection,[62] but the duration of immunity is unclear. Antimicrobial treatment, on the other hand, might reduce the immune response and once treated, people become susceptible to infection again, increasing their risk of repeat chlamydia infection, the "arrested immunity hypothesis".[63,64] Repeat chlamydia infections after treatment are common; in cohort studies, over 20% of young women enrolled from general practice acquired a repeat infection within 12 months of treatment.[65,66]

Several reviews have examined the risk of sequelae following infection,[12,67-70] but estimates are limited by diagnostic challenges. Mathematical syntheses of evidence from different types of studies estimate that the probability of clinical PID following infection with chlamydia is about 16% (95% credible interval 6% to 25%)[71] and the probability of tubal factor infertility in women who have ever had a chlamydia infection is about 1% (varies depending on age).[72] These models also estimate that the proportion of PID, ectopic pregnancy and tubal factor infertility attributable to chlamydia is 20%, 5% and 29% to 45%, respectively.[73] The risk of reproductive tract morbidity in women might increase with repeated infection.[74-76] 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.[12] 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 PID to a woman diagnosed with chlamydia.

We do not know how or when chlamydia ascends to the upper genital tract, but there are two key hypotheses.[61] The cellular paradigm assumes that actively infected epithelial cells play the key role and that chemokines secreted by these cells damage the tissues directly. The immunological paradigm assumes that tissue damage occurs due to 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.[60]

The timing of ascending infection will also affect the impact 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.[77] A mathematical model[78] using data from a RCT,[79] found that the trial results of the effect of a single chlamydia screen on the cumulative incidence of PID up to one year later, could only be achieved if progression to PID occurred at a constant rate or at the end of infection.

Pregnant women infected with chlamydia have an increased risk of pre-term delivery[80] and vaginally-delivered babies of untreated mothers are at risk of conjunctivitis and pneumonia.[81] Among men, chlamydia can cause epididymo-orchitis,[82] but effects on male fertility are disputed; some have found no effect, some suggest decreased semen quality, or impaired sperm fertilisation capacity and DNA integrity.[83,84]

Current chlamydia control activities

Case detection and 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.[31] Several high income countries including Australia, Canada, England 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.[23-27] The coverage of chlamydia testing has been used to monitor performance,[85-87] but none of these countries sets targets for chlamydia prevalence or PID incidence.

297 Surveys in Europe show that the number of countries with any chlamydia control activities
298 increased between 2007 and 2012.[26] The number of countries reporting the use of chlamydia
299 case management guidelines and opportunistic testing increased but fewer countries reported
300 that they had an ongoing or planned chlamydia screening programme.[26] Of note, the
301 Netherlands and Ireland have elected not to implement screening programmes and Sweden
302 and Denmark, both of which have had widespread opportunistic chlamydia screening,
303 reported that their STI control strategies have partly shifted from promoting testing to
304 intensifying primary prevention activities.[26] Ongoing debate about the evidence to support
305 chlamydia screening[88-90] and its cost effectiveness[88] might have influenced these decisions.
306
307 **Effectiveness of chlamydia screening in clinical trials**
308 The rationale for chlamydia screening is that testing should detect asymptomatic infections in
309 women before they cause PID or other reproductive complications; if a large enough
310 proportion of the population can be screened, reduced incidence and prevalence of infection
311 ought to further prevent reproductive complications indirectly by reducing exposure to
312 infection.[91]
313 A systematic review of chlamydia screening interventions[89] found four RCTs that looked
314 at the effects on PID incidence after a single offer of a chlamydia screening test.[13,79,92,93]
315 Overall, the trial results suggest that PID incidence was lower in intervention than control
316 groups (summary risk ratio, RR 0·68, 95% CI 0·49 to 0·94, I^2 8%).[89] However, when
317 stratified by risk of bias, the summary effect was smaller in the two trials at low risk of bias
318 (RR 0·80, 95% CI 0·55 to 1·17)[79,92] than in those at high or unclear risk of bias (RR 0·42,
319 95% CI 0·22 to 0·83),[13,93] suggesting the overall result might overestimate the protective
320 effects of a screening test. Another completed cluster RCT will report on the association of up
321 to four rounds of chlamydia testing on the incidence of PID measured in hospitals and
322 primary care clinics.[94]

Two cluster RCTs have looked at the effects of repeated rounds of chlamydia testing targeting 16 to 29 year old men and women in the general population.[14,95] Neither trial found 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. Chlamydia test uptake was <20% in both trials, even with individual patient reminders (Netherlands) or further support for clinicians (Australia). In Peru, a cluster RCT among female sex workers found that after four years of a multifaceted intervention, estimated prevalence was 28% lower in women in the intervention areas (RR 0·72, 95% CI 0·54 to 0·98).[96]

Only one trial reported on the impact 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.[92] No RCT to date has reported the effects of an intervention that offers chlamydia screening during pregnancy on pregnancy or neonatal outcomes. One RCT in the USA that compared antibiotic treatment with placebo in women with chlamydia detected at 23 to 29 weeks of gestation, found no reduction in low birth weight, preterm birth or neonatal death in intention to treat analysis.[97] One cluster RCT in Uganda of presumptive antibiotic treatment found reductions in low birth weight, neonatal death and ophthalmia neonatorum; the antibiotic regimen, azithromycin, cefixime and metronidazole covered several genital tract infections other than chlamydia.[98]

A review 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.[88] 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.[88,99]

Effects of chlamydia control from observational data

Whilst RCTs provide data about the efficacy of chlamydia screening interventions under 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 Great Britain and the USA, population-based chlamydia prevalence surveys have been repeated during the time when chlamydia testing rates have increased. In Great Britain, two surveys ten years apart found similar estimates among women and men aged 18 to 24 years in 2010-2011 (women, 3·2%, 95% CI 2·2 to 4·6%; men, 2·6%, 95% CI 1·7 to 4·0%) and in 1999-2000 (women, 3·1%, 95% CI 1·8 to 5·2%; men, 2·9%, 95% CI 1·3 to 6·3%);[44] chlamydia test coverage increased from about 8% per year in 2008[100] to about 30% in 2011.[101] In the USA, chlamydia prevalence in women aged 15-24 years was 4·1% (95% CI 2·4 to 6·8%) in 1999–2000 and 3·8% (2·4 to 6·0%) in 2007–2008 with fluctuations in the years between;[43] chlamydia testing coverage among 16 to 24 year old women was reported to be >35% per year.[85,102,103] More intensive chlamydia screening in a small cohort of adolescent women in Indiana, USA did not reduce prevalence.[104] The women were tested every three months and treated if they had a positive chlamydia test result; at each interval around 10% of women tested were chlamydia test positive.[104]

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 size of chlamydia prevalence surveys limits 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 around 35% per year or more would be needed to achieve substantial reductions within a ten-year period.[105,106] Third, suboptimal case management with low levels of partner notification, antimicrobial treatment failure and an increasing incidence of repeated infection following antimicrobial treatment for chlamydia might sustain levels of prevalent infections. Fourth, it is possible that testing and treatment is reducing levels of immunity against chlamydia in the population leading to increased susceptibility to infection.[64] Fifth, auto-inoculation 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;[107] reports of rectal chlamydial infection in women have increased.[108,109] Finally, persistent forms of *C. trachomatis* might contribute to sustained prevalence. Chlamydia under the selective pressure of beta-lactam antibiotics,[110] interferon-gamma (IFN-Y) or deprivation of nutrients such as iron and amino acids, can enter a persistent, metabolically inactive state[111,112] where they are viable but semi-refractory to treatment.[110,113,114]

PID and other reproductive tract complications

Routine data about diagnoses on discharge from hospital have shown declining trends in PID and ectopic pregnancy during periods of increasing chlamydia testing and increasing chlamydia diagnosis rates in several countries.[115-121] Ecological associations between chlamydia testing and PID need careful interpretation.[60] 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 PID incidence is not so clear. The Organisation for Economic Cooperation and Development (OECD) collates hospital discharge by diagnostic

categories for its member countries.[122] Figure 5 shows data for "inflammatory diseases of female pelvic organs", which includes PID from any cause (supplement table 1). 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 over the last two decades in countries that have very different levels of chlamydia control activity. For example, in Belgium, Ireland and Slovenia, countries with little chlamydia testing,[26] hospitalisations have dropped by about 30% over the past 15 years. In countries with data from the early 1990s, the biggest declines in hospitalisations coincide with sudden sexual behaviour changes and with falls in the rates of other STIs, which are attributed to responses to the HIV pandemic.[22,90,123] A cross-country analysis that compared PID, ectopic pregnancy and infertility hospitalisation data[58] also found similar trends in high chlamydia testing countries (Denmark, New Zealand, Sweden)[26,124] and low testing countries (Australia, Netherlands, Switzerland)[26,125] from 1999 to 2008. Whilst inpatient admissions for these conditions have become less common, in countries that collect data from ambulatory and primary care settings, PID diagnoses have also fallen.

Future challenges for the control of chlamydia

Shift of focus from monitoring test uptake to measuring PID 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 limited attention has been given to monitoring PID incidence and its complications given that prevention of PID and its associated complications is a key goal of chlamydia control. There has also been limited attention on research to further our understanding of the natural history and immunopathology of *C. trachomatis* infection

including the development of non-invasive measures of clinical and subclinical tubal infection, inflammatory and damage and biomarkers to predict upper genital tract pathology.[60] We urgently need investment in research to further our 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 PID and other chlamydia related complications over time.

Realistic targets for chlamydia prevalence and incidence should be established

Strategies for chlamydia control should be appropriate to levels of 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 reducing social and ethnic inequalities in rates of chlamydia and PID, improving health outcomes through better case management of those diagnosed with chlamydia and establishing surveillance systems to more reliably and accurately monitor PID, ectopic pregnancy and infertility incidence in both primary care, ambulatory and hospital settings.

In low and middle income countries efforts should be directed towards strengthening primary prevention and case management for people presenting with symptomatic chlamydia infection (see Part 4), as well as research to better define the prevalence of infection and burden of chlamydial disease. In a limited number of countries, such 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.[126] Given the high probability of re-infection, possible increase in susceptibility to PID after treatment, and selection pressure for antimicrobial resistance (AMR), 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

Use of the most efficacious antimicrobial treatment: AMR has not been detected in *C. trachomatis*, but the widespread use of single dose azithromycin for uncomplicated chlamydia infections is being questioned.[127-130] Two meta-analyses comparing a single 1 g azithromycin with seven days of doxycycline (100 mg twice per day) found that azithromycin efficacy was slightly lower for urogenital chlamydia (94% versus 97%)[131] and substantially lower for rectal chlamydia infection (83% versus 99%).[132] For men, the efficacy of azithromycin for both urogenital and rectal infection was below the WHO threshold of 95% recommended for a first line treatment.[133] Furthermore, the widespread use of single dose azithromycin to treat chlamydial infections is likely to have contributed to macrolide resistance in *Treponema pallidum*, *N. gonorrhoeae* (see Part 2)[134-136] and *M. genitalium*.[137]

Partner notification: Partner notification has been recommended as a part of most STI management strategies, including syndromic management (see Part 4), 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

472 re-infection and halting ongoing transmission, testing and treating sexual partners of people
473 with chlamydia is efficient for case finding because they are likely to also be infected.[138]
474 From a health economic perspective, doubling the efficacy of partner notification (from 0·4 to
475 0·8 partners per index case) would cost less than increasing the screening coverage of men to
476 the same level as women.[139] Expedited partner therapy (EPT) and accelerated partner therapy
477 (APT) are partner notification approaches that allow partners to receive treatment without a
478 face-to-face consultation in a health-service setting. A Cochrane review has found that EPT
479 was more successful than simple patient referral in reducing repeat infection in patients with
480 gonorrhoea and chlamydia.[138] APT, its equivalent in the UK, is acceptable to healthcare
481 providers and patients[140] and an RCT is underway to evaluate its effectiveness in reducing
482 repeated infection. Further work is needed to resolve medico-legal issues that limit wider
483 implementation of these partner notification approaches[141] and to ensure that opportunities to
484 test for HIV and other STIs are not missed.[139]

485

486 *Re-testing to detect repeat chlamydia infections early:* There is no evidence from RCTs that
487 repeated testing for chlamydia after treatment has an impact on reducing chlamydia
488 transmission in the population, but re-testing can detect repeat infections early. Guidelines
489 about re-testing intervals vary between countries: some countries recommend a test of cure
490 within three to six weeks after diagnosis,[26] others recommend testing to find repeated
491 infections within three to six months.[26,27,142,143] A mathematical modelling study suggests that
492 an interval of two to five months after treatment optimises the detection of repeat infection.[144]
493 Mailed specimen collection kits and mobile phone text messages are effective interventions
494 for increasing re-testing uptake and their impact on reducing chlamydia transmission and PID
495 should be evaluated.[145,146]

496

Rapid and POC tests

Rapid diagnostic tests and POC tests allow diagnosis and treatment decisions to be made at the same visit, reducing time to treatment and losses to follow up.[147,148] The status of POC tests for chlamydia and other STIs is discussed in Part 4.

Chlamydia vaccine

In all countries, an effective vaccine would overcome many of the problems of chlamydia control. While the profile of a chlamydia vaccine remains to be determined, prioritising high levels of immunity against infection or limited protection against infection but strong protection against upper genital tract disease,[149] the prospects for a chlamydia vaccine are now considered promising.[150] WHO and the US National Institutes of Health have developed a STI vaccine roadmap that identifies priority actions for chlamydia vaccine development.[150] Several candidate chlamydia vaccines could enter Phase 1 clinical trials in the next few years.[10]

Conclusion

Over the last 20 years, awareness about chlamydia as a common STI worldwide has increased.[2,33] Over the same period, research to increase knowledge about the natural history of chlamydia or its disease burden has not kept up, even though the first RCT of a chlamydia control intervention was primarily focused on the prevention of PID.[13] The focus of chlamydia control efforts in high income countries has been on increased coverage of testing for asymptomatic chlamydia infection, whilst fewer advances have been made in research to improve primary prevention and case management. Chlamydia control priorities could be set, in future, based on infectious disease principles, to define acceptable levels of chlamydia prevalence and incidence and disease that match the epidemiology in different geographical

522 regions and within different population groups. Priorities for improving case management
523 include effective partner notification strategies and re-testing to detect repeat infections early
524 and reduce the risk of chlamydia association complications. Surveillance systems could
525 improve to record and monitor trends in PID and other chlamydia related complications over
526 time. The investment and research agendas called for by international experts[60,150,151] to
527 further our understanding about the natural history of chlamydia and develop non-invasive
528 measures to predict upper genital tract disease should be implemented.

529

530 ## Part 2. Gonorrhoea – inevitable antimicrobial resistance – current and
531 ## future treatment options?

532 Of the 78 million estimated new gonorrhoea cases among adults globally in 2012, the highest
533 number was in the WHO Western Pacific Region (35.2 million, Figure 1). Accordingly, the
534 vast majority of the gonorrhoea burden globally is in low and middle income countries.[2]
535 There is no vaccine against *N. gonorrhoeae* so effective, accessible and inexpensive
536 antimicrobial treatment is an essential part of gonorrhoea control measures together with
537 primary prevention, diagnostics, partner notification and epidemiological surveillance. If *N.*
538 *gonorrhoeae* infections become untreatable, the numbers of people that experience
539 complications of infection, such as PID, ectopic pregnancy and infertility, and the facilitation
540 of HIV transmission and acquisition, will substantially increase.[2,152-154] *N. gonorrhoeae* has
541 developed antimicrobial resistance (AMR) to all drugs previously or currently recommended
542 for treatment. This section of the present *Commission* reviews and discusses the emergence
543 and spread of AMR in *N. gonorrhoeae*, current and future treatment options, with a focus on
544 novel antimicrobials, and additional actions to control gonorrhoea and AMR in *N.*
545 *gonorrhoeae*.

Emergence and spread of AMR 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 AMR mechanisms.[153] The hypothesis is that, in modern times, AMR in gonococci has usually developed first in the WHO Western Pacific Region (frequently Japan) followed by international spread.[153,155,156] For many infectious diseases including gonorrhoea, overuse and misuse (including unrestricted access, suboptimal quality and dosing) of antimicrobials has resulted in AMR in bacterial species that share their AMR determinants through horizontal gene transfer and subsequent recombination. Horizontal gene transfer is particularly likely in the pharynx, which harbours many non-gonococcal *Neisseria* species, and can facilitate the emergence and spread of AMR[157] particularly in high-frequency populations such as MSM and commercial sex workers. Inadequate monitoring of *in vitro* AMR, pharmacokinetics/pharmacodynamics, and clinical efficacy of antimicrobials facilitate both the initial emergence of AMR and the subsequent spread of resistant strains, particularly in settings with a high incidence of gonorrhoea and ineffective control measures.[152,153,155,156,158] It is crucial to improve the understanding of the dynamics and drivers of the emergence of AMR as well as transmission of gonococcal strains and their AMR, 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 AMR, locally, nationally and internationally.[159]

Many countries already have high prevalence rates of gonococcal resistance to all antimicrobials that have been used for treatment, including sulphonamides, penicillins, tetracyclines, fluoroquinolones and early generation macrolides and cephalosporins.[152-154,158]

572 The prevalence of multidrug-resistant (MDR)[155] gonococcal strains significantly increased
573 during the last decade.[152-154,158] Resistance to extended-spectrum cephalosporins (ESCs), the
574 last remaining options for empiric first-line monotherapy, has also been detected in many
575 countries. The first extensively drug-resistant (XDR)[155] gonococcal strains, displaying high-
576 level resistance to ceftriaxone (minimum inhibitory concentration (MIC)s 2-4 mg/L) and
577 retained resistance to previously used therapeutic antimicrobials, have also been verified in
578 Japan, France and Spain.[160-162] Fortunately, these "superbugs" have not spread further,
579 suggesting significantly decreased biological fitness. Some additional ceftriaxone-resistant
580 strains isolated in Japan and Australia during recent years have also been studied in detail,[163-
581 165] showing that both ceftriaxone-resistant strains and ceftriaxone resistance-determining
582 penicillin-binding protein 2 (PBP2) segments (lethal target for ESCs) are spreading.[165]
583 Additional sporadic gonococcal strains with low-level ceftriaxone resistance have been
584 described internationally.[158,166] Importantly, strains with non-mosaic PBP2s can also develop
585 ceftriaxone resistance, as described particularly in Asia, e.g. China, Korea, and Vietnam, but
586 also in Argentina.[158,166] Many additional ceftriaxone-resistant strains might already be
587 circulating but are undetected due to the suboptimal AMR surveillance in many settings.
588 Ceftriaxone or dual antimicrobial therapy (mainly ceftriaxone 250-500 mg×1 plus
589 azithromycin 1-2 g×1) are currently the only options for empirical first-line therapy in most
590 countries.[158,167-172]
591

592 **Current treatment of gonorrhoea**

593 *Principles and definitions used in conventional antimicrobial treatment*

594 Empirical therapy is treatment given at the first health care visit before any laboratory results
595 are available, following recommendations in evidence-based treatment guidelines. The ideal
596 characteristics of a first-line therapy are that it: has high efficacy (cures >95% of urogenital

597 and extragenital infections), includes multiple targets (to increase activity and delay resistance
598 development), has no or minimal cross-resistance with other antimicrobials, is showing slow
599 selection/induction of resistance determinants in *N. gonorrhoeae*, has different mechanisms of
600 action for drugs included in dual therapy, is available as a single oral dose, with a fixed-dose
601 combination (FDC) for dual oral therapy, is widely available and affordable in appropriate
602 quality and dose, has an appropriate paediatric formulation (e.g. suspension or syrup), is
603 stable (at high temperature and humidity levels), has no or minimal drug-drug interactions, is
604 safe (including during pregnancy and lactation), is well tolerated, and is also active against
605 concurrent *C. trachomatis* and *M. genitalium* infections (make it useful in syndromic
606 management).

607 Treatment guidelines should be informed by up-to-date, local and quality-assured
608 AMR surveillance data. AMR can emerge quickly and patterns vary geographically so large
609 RCTs are rarely conducted. Changes in recommended treatments are mostly based on
610 laboratory-based AMR surveillance data (the point estimate of tested strains should show that
611 ≥95% are susceptible), rather than clinical surveillance of cure rates. Alternative criteria for
612 changing a recommended first-line therapy have been suggested, for example that the lower
613 95% CI rather than the point estimate should be ≥95%, or that >99% or >97% of strains from
614 high-frequency transmitting populations should be susceptible.[173-175] Ideally, additional
615 factors should also be taken into consideration, including prevalence, local epidemiology,
616 diagnostics used, transmission frequency, partner notification and management strategies,
617 treatment strategies (strategies used and antimicrobials available), and cost-effectiveness,
618 should be considered.[153,158,176]

619

620 *Antimicrobial monotherapy*

621 Cefixime 400 mg×1 orally and especially ceftriaxone 125-1000 mg×1 intramuscularly (IM) or
622 intravenously (IV) have been the last options for empirical first-line monotherapy in many
623 countries.[152-156,158,170] Unfortunately, treatment failures with cefixime have been verified in
624 many countries worldwide, and rare failures following treatment of pharyngeal gonorrhoea
625 with ceftriaxone (250-1000 mg×1) have also been verified in several countries.[156,158] Verified
626 ceftriaxone treatment failures are probably the tip of the iceberg because few countries
627 conduct active surveillance and confirm treatment failures according to international
628 recommendations.

629 To avoid treatment failures, increased doses of ceftriaxone (1 g×1 IM/IV) have been used
630 in some countries.[177-180] Based on the dosages administered for community-acquired
631 pneumonia, up to 2 g×1 of ceftriaxone would likely be tolerated. Increased doses of
632 ceftriaxone are probably only a short-term solution based on current knowledge of gonococcal
633 AMR emergence, ESC MICs of gonococcal "superbugs" and other ESC-resistant strains,
634 verified ESC treatment failures and ESC pharmacokinetic/pharmacodynamic simulations. For
635 example, 20-24 hours of free ESC above MIC ($fT_{>MIC}$) can be required for effective treatment
636 with ESCs.[181] According to Monte Carlo simulations, reflecting the diversity inherent within
637 patient populations, of ceftriaxone 1 g×1, sufficient fT>MIC (20-24 hours) might not be
638 achieved in up to 5% of patients even for gonococcal strains with ceftriaxone MICs as low as
639 0·125 mg/L, which are relatively common in many countries. The median fT>MIC is
640 therefore 40·3 hours but the lower 95% CI of fT>MIC (19·6 hours) is below the required 20-
641 24 hours.[181] These findings might overestimate the number of treatment failures because few
642 failures have been identified, but they show the wide circulation of gonococcal strains that
643 could cause ceftriaxone treatment failures.

644

645 *Dual antimicrobial therapy*

Several agencies and countries recommend dual antimicrobial therapy for empirical first-line gonorrhoea treatment in response to emerging ESC resistance, including WHO (global recommendations), Europe, Germany, United Kingdom, Australia, USA, and Canada.[27,167-172] To summarise, all these guidelines, except those of WHO[172] and Canada,[171] recommend only ceftriaxone plus azithromycin as first-line 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: ceftriaxone doses range from 250 mg×1 IM (WHO, USA and Canada) to 1 g×1 IM (Germany); and doses of azithromycin range from 1 g×1 orally (WHO, USA, Canada, UK and Australia) to 2 g×1 orally (Europe).[27,167-172] WHO[172] and Canadian[171] guidelines additionally recommend an oral first-line dual therapy, cefixime 400 mg×1 (WHO) or 800 mg×1 (Canada) plus azithromycin 1 g×1.[171,172] Pharmacodynamic studies have shown that cefixime 800 mg (especially 400 mg×2, given 6 hours apart) increases the cefixime $fT_{>MIC}$ compared to 400 mg×1.[181] In most countries, however, only cefixime 400 mg×1 is licensed because gastrointestinal adverse events are more common with 800 mg×1.[182] Many clinical failures have been verified with cefixime 400 mg×1,[156,158] but also with cefixime 800 mg×1.[182] Finally, WHO also recommends monotherapy with ceftriaxone 250 mg×1, cefixime 400 mg×1, or spectinomycin 2 g×1, but only if up-to-date, local, high-quality AMR surveillance data support their use.[172] Owing to low cure rates, spectinomycin monotherapy should only be used if pharyngeal gonorrhoea has been excluded; otherwise, azithromycin should also be given.[152]

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 AMR surveillance data, predicted AMR trends, old clinical trials, case reports of clinical failures with ESCs,[156,158] pharmacokinetic/pharmacodynamic simulations,[181] and expert opinion.[170] Unfortunately, these recommended antimicrobials might not protect each other from the development of resistance.[183] However, in practice the combination of ceftriaxone

672 and azithromycin appears to cure almost all gonorrhoea cases, concomitant resistance to
673 ceftriaxone and azithromycin is exceedingly rare and consequently the spread of any emerged
674 ceftriaxone resistance appears to have been mitigated so far. In addition, dual therapy
675 eradicates concurrent *C. trachomatis* and many *M. genitalium* infections. However,
676 susceptibility to ceftriaxone is decreasing and azithromycin resistance is increasing in many
677 settings internationally, and concomitant resistance to both antimicrobials has
678 emerged.[152,153,158] Gonococcal strains with high-level azithromycin resistance (MIC≥256
679 mg/L) have been isolated in several countries worldwide and an outbreak of such strains is
680 ongoing in the UK.[134,158] All the recommended and alternative dual antimicrobial regimens
681 include azithromycin 1-2 g×1 and due to the azithromycin resistance, in practice many
682 gonorrhoea cases will be administered ceftriaxone monotherapy. Furthermore, the first global
683 treatment failure with dual therapy (ceftriaxone 500 mg×1 IM plus azithromycin 1 g×1
684 orally), due to a ceftriaxone- and azithromycin-resistant gonococcal XDR strain, was recently
685 verified in the UK.[15] The higher cost and inconvenience of dual therapy also render it less
686 suitable for low and middle income countries, where also high-quality ceftriaxone can be
687 lacking, which will limit the mitigation of emergence and spread of gonococcal AMR
688 globally.
689

690 **Future treatment of gonorrhoea**

691 *Improved dual antimicrobial therapy*

692 Dual antimicrobial therapy[27,167-172] is recommended for treatment where up-to-date, local, and
693 high-quality AMR surveillance data do not support other therapy. Ideally, owing to the rapid
694 emergence of azithromycin resistance in *N. gonorrhoeae* (and also additional STIs such as *M.*
695 *genitalium* infections), at least as a temporary solution azithromycin could be replaced by
696 solithromycin if the ongoing Phase 3 RCT provides evidence of effectiveness, tolerability and

safety. Furthermore, susceptibility to spectinomycin is exceedingly high globally,[152,153,158,170,172] 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 Korea for decades (52%-73% of treatments in 2009-2012) and no resistant isolates have been found since 1993.[184] Nevertheless, spectinomycin only eradicates a proportion of pharyngeal gonorrhoea (52%)[185] and should, ideally, be used in a dual therapy combination, e.g. with solithromycin, which might protect it from resistance development.

Novel accessible and cost-effective antimicrobials are essential. Ideally, these should be used in new dual therapies, to preserve their effectiveness, and, if there are oral preparations, in FDCs that increase activity and adherence and mitigate resistance development. One RCT has evaluated two novel dual regimens, gentamicin (240 mg×1 IM) 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.[186] Gentamicin plus azithromycin cured 100% of cases (202/202) and gemifloxacin plus azithromycin 99·5% of cases (198/199). No serious adverse events occurred, but mild-moderate gastrointestinal adverse events such as nausea and diarrhoea were frequent. Of concern, 3·3% and 7·7% of patients, respectively, vomited within one hour and might have lost a substantial amount of the drugs.[186] Consequently, these two regimens should mainly be considered for treatment of ceftriaxone-resistant cases, treatment failures with recommended regimen, or ESC allergy.

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 lacking (ertapenem) or old, incomplete, mainly low-quality, and only from limited geographic areas, patient populations (only males), and

anatomical sites (only urogenital); <95% cure rate; appropriate pharmacokinetic/pharmacodynamic parameters for gonorrhoea, relationship between MIC and treatment outcome, and resistance breakpoints are lacking.[152,153,156,158,176,187-189] 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 ESC allergy. A multi-centre (n=8) non-inferiority Phase 3 RCT, aiming to enrol 718 participants, evaluating gentamicin 240 mg×1 IM plus azithromycin 1 g×1 orally for treatment of uncomplicated anogenital and pharyngeal gonorrhoea is ongoing (www.research.uhb.nhs.uk/gtog); the comparator is ceftriaxone 500 mg×1 IM plus azithromycin 1 g×1 orally. Finally, using timely molecular prediction of resistance to ciprofloxacin, based on targeting *gyrA* mutation(s), this old antimicrobial can be used as personalised treatment for patients in whom ciprofloxacin susceptibility has been confirmed.[190-193]

New antimicrobials with only in vitro data available

Several new antimicrobials (derivates of earlier developed antimicrobials or new antimicrobial classes) have proven relatively potent *in vitro* activity against gonococcal strains, but clinical data are lacking. These antimicrobials include the fluoroquinolones avarofloxacin (JNJ-Q2), delafloxacin (RX-3341), sitafloxacin (DU-6859), and WQ-3810; bicyclic macrolides (bicyclolides) modithromycin (EDP-420/EP-013420/S-013420) and EDP-322; tetracyclines eravacycline (TP-434) and tigecycline (fluorocycline and glycylcycline, respectively); 2-acyl carbapenems SM-295291 and SM-369926; aminomethyl spectinomycin;[194] lipoglycopeptide dalbavancin, pleuromutilin lefamulin (BC-3781), boron-containing inhibitor AN3365, LpxC inhibitors, FabI inhibitor e.g. MUT056399, tricyclic topoisomerase inhibitor REDX05931 (evaluated also in mice),[195,196] and topoisomerase II inhibitor VXc-486 (VT12-008911), which all have been recently reviewed.[152,153,156,158,176,194-

[196] A Phase 3 RCT designed to evaluate delafloxacin (2×450 mg×1 orally) compared to ceftriaxone (250 mg×1 IM) for treatment of uncomplicated gonorrhoea was recently terminated (http://clinicaltrials.gov/show/NCT02015637).

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.[197-217] The main characteristics of these antimicrobials are summarised in table 1.

Solithromycin: The first fluoroketolide solithromycin is structurally similar to the ketolide telithromycin but it is less toxic and has increased stability and activity.[202,208,212] Solithromycin, like 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.[208] 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* and clinical resistance to all currently and previously recommended antimicrobials.[202,212] 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).[202]

Administering a single solithromycin dose (50-1600 mg) to healthy adults, the time-to-peak concentration (Tmax) was 1·5-6 hours and the plasma half-life ($T_{1/2}$) 3·2-7·4 hours.[214] A Phase 1 study evaluating pharmacokinetic properties, safety and tolerability of a 1 g oral dose within plasma, vaginal, cervical, seminal, rectal, and pharyngeal samples is ongoing (https://clinicaltrials.gov/ct2/show/NCT02348424).

A Phase 2 clinical trial evaluating the efficacy of solithromycin 1 g×1 or 1·2 g×1 orally in the treatment of males and females with uncomplicated urogenital gonorrhoea was performed

(https://clinicaltrials.gov/ct2/show/NCT01591447).[203] Forty-six patients received solithromycin and were evaluable for microbiological cure (1 g×1 (n=22) and 1·2 g×1 (n=24)). All (100%) were subsequently culture negative at all sites examined. Solithromycin additionally cured 82% of *C. trachomatis* infections (n=11) and 70% of *M. genitalium* infections (n=10). The adverse effects were dose-dependent and giving 1 g×1 the most prevalent were mild diarrhoea (42%), nausea (26%), and fatigue/asthenia (10%). However, most nausea and vomiting (3%) appeared ≥1 hour after ingestion and the drug was likely already absorbed.[203] Additional data are needed and, to further increase gastrointestinal tolerability, an extended-release formulation of solithromycin might be valuable. Solithromycin (1 g×1 orally) is currently in a Phase 3 non-inferiority RCT for treatment of uncomplicated urogenital gonorrhoea in males and females (SOLITAIRE-U; https://clinicaltrials.gov/ct2/show/NCT02210325), evaluating efficacy, tolerability and safety (table 1). Of concern, analysing the data from the initial patient cohort of 262 patients solithromycin demonstrated high success rates of 80·5 percent in the microbiological intent to treat population but only 91·3 percent in the microbiologically evaluable population (100% success rate for females). Consequently, solithromycin did not demonstrate non-inferiority to standard of care treatment. No *N. gonorrhoeae* isolates demonstrated solithromycin resistance at baseline or test-of-cure. Thus, the solithromycin treatment failures were most likely related to the duration of solithromycin exposure at the site of infection and adjustments to the dosing regimen (and/or possibly formulation), without substantially increasing the dose-dependent adverse effects observed in the Phase 2 study, might need to be considered.

(http://investor.cempra.com/releasedetail.cfm?ReleaseID=1014807; February 28, 2017).

Zoliflodacin: The first spiropyrimidinetrione (non-fluoroquinolone topoisomerase II inhibitor) zoliflodacin targets DNA gyrase (specifically GyrB), but likely also topoisomerase IV, and has novel mechanisms of action different from all other available antimicrobials.[197,198,201] 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.[206] Additionally, consecutive, contemporary and clinical isolates in Europe (873 isolates from 21 European countries), USA (100 isolates), and China (187 isolates) have been examined.[211,215,216] The main zoliflodacin target in GyrB is highly conserved in clinical isolates.[206] 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.[206,211,215,216] The frequency of induced or selected zoliflodacin resistance mutations is very low and, interestingly, some of the selected *gyrB* resistance mutations appear to increase ciprofloxacin susceptibility.[197,201]

Administering doses ranging between 200-4000 mg to healthy volunteers (18-55 years) in a Phase 1 study (https://clinicaltrials.gov/ct2/show/NCT02298920),[207] dose-proportional increases in plasma concentration up to 800 mg were observed. Doses >800 mg resulted in slightly smaller dose-proportional increases up to 4000 mg. The median Tmax was 1·5-2·3 hours, and the mean terminal elimination $T_{1/2}$ was reasonably consistent, ranging between 5·3-6·3 hours. 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.[198,207]

A Phase 2 RCT evaluating the efficacy, tolerability and safety of zoliflodacin 2 g×1 or 3 g×1 orally for treatment of uncomplicated urogenital gonorrhoea in men and women has been performed (https://clinicaltrials.gov/ct2/show/NCT02257918).[217] In total, 48/49 (98%) patients and 47/47 (100%) patients achieved microbiological cure with zoliflodacin 2 g×1 and zoliflodacin 3 g×1, respectively. Only 12% of patients reported any adverse events, i.e. mostly mild gastrointestinal adverse events.[217] Accordingly, single oral dose of zoliflodacin was effective and safe for treatment of uncomplicated urogenital gonorrhoea. However, it is

827 crucial to examine additional cases of extragenital gonorrhoea, particularly pharyngeal
828 infection.

829 Gepotidacin: Gepotidacin is a new non-fluoroquinolone topoisomerase II inhibitor
830 (triazaacenaphthylene) targeting DNA gyrase (GyrA subunit) and topoisomerase IV (ParC
831 subunit), but with a different binding mode compared to fluoroquinolones.[200,213] The
832 gepotidacin MICs have been shown relatively low, however, the MIC_{90} was 0·25 mg/L for
833 108 ciprofloxacin-susceptible isolates and 1 mg/L for 37 ciprofloxacin non-susceptible ones,
834 indicating some level of cross-resistance to fluoroquinolones.[213] *In vitro* studies examining
835 geographically, temporally and genetically diverse resistant, including MDR and XDR,
836 gonococcal isolates are ongoing.

837 The pharmacokinetic profile of gepotidacin was examined in a study including healthy
838 subjects receiving gepotidacin 800, 1500, 2300, and 3000 mg×1 orally. There are limited
839 reported data; a reported clearance of ~84 L/hour, 9·4-51% variability in clearance, zero-order
840 absorption, and an absorption lag time.[204] Administering 2 g×1 orally in six males, ~50% was
841 absorbed. Faecal elimination (53%) predominated, but ~20% of total dose was eliminated
842 unchanged in urine.[209]

843 A Phase 2 RCT evaluating the optimal oral dose of gepotidacin (1·5 g×1 or 3 g×1 orally)
844 and efficacy, safety, and tolerability in males and females with uncomplicated urogenital
845 gonorrhoea has recently been finalised (https://clinicaltrials.gov/ct2/show/NCT02294682), but
846 the results of this RCT are not publicly available.

847

848 **Conclusions**

849 Gonorrhoea is a major public health concern and emergence of gonococcal AMR is
850 significantly compromising the effectiveness of treatment globally. Improvements in

851 treatment, together with clinical and public health actions (table 2), are needed to control
852 gonorrhoea and AMR in *N. gonorrhoeae*. Dual antimicrobial therapy (ceftriaxone 250-500
853 mg×1 plus azithromycin 1-2 mg×1) is recommended for treatment where up-to-date, local,
854 and high-quality AMR data do not support other therapy.[27,167-172] This antimicrobial
855 combination appears to treat almost all gonorrhoea cases and inhibit the spread of AMR
856 gonococcal strains. Nevertheless, wider availability internationally of other effective
857 antimicrobials, such as spectinomycin, further studies of the repurposing of old
858 antimicrobials, particularly gentamicin and ciprofloxacin (following timely molecular
859 prediction of ciprofloxacin resistance/susceptibility[192]), and *in vitro* and clinical evaluation
860 and subsequent licensing of novel accessible and affordable antimicrobials are imperative.
861 Ideally, these antimicrobials should be used in new dual therapies, in order to preserve them,
862 and, if oral drugs, in FDCs providing advantages such as increased activity, tolerance,
863 compliance, lower cost of manufacturing, simpler distribution, and mitigated resistance
864 development. Several new antimicrobials have proven relatively potent *in vitro* activity
865 against gonococcal strains, but clinical data about their effects in gonorrhoea treatment are
866 lacking.[152,153,156,158,176] Solithromycin, gepotidacin and particularly zoliflodacin can be
867 promising for gonorrhoea treatment and deserve further attention.[197-217] Ultimately, as for
868 chlamydia, a gonococcal vaccine might be the only sustainable solution for gonorrhoea
869 control.[150]

870

871 Part 3. Bacterial vaginosis: reconsidering the evidence for sexual
872 transmission and implications for research and management

873 Bacterial vaginosis (BV) is one of the great conundrums in sexual and reproductive health. At
874 the time of its discovery in the 1950s, “non-specific bacterial vaginitis” was considered likely
875 to be sexually transmitted. Studies by Gardner and Dukes established the clinical and

876 microbiological features of BV in uninfected women following direct inoculation of vaginal
877 secretions from infected women.[218] Subsequent work, however, altered this belief. The
878 apparent absence of an obvious disease counterpart in males, the failure of male partner
879 treatment trials to consistently reduce BV recurrence in women,[219] and inability to identify a
880 sole pathogenic microorganism all contributed. While the approaches used in studies that
881 treated the male sex partners of women with BV—including study designs, dosing regimens
882 for male partners and endpoints in female partners—have been criticised,[220,221] the general
883 consensus that BV is not sexually transmitted has persisted.

884 Advances in molecular techniques, such as 16S rRNA gene sequencing, have confirmed
885 that BV involves a profound shift in the vaginal microbiota to a dysbiotic state, characterised
886 by high bacterial species diversity and increased loads of both aerotolerant and strict
887 anaerobes including *Gardnerella vaginalis*, *Atopobium vaginae* and other fastidious BV-
888 associated bacteria such as *Megasphaera, Sneathia* and *Clostridiales* species (spp.).[222] This
889 change is accompanied by production of volatile amines, a rise in vaginal pH and marked
890 depletion of key *Lactobacillus* spp. such as *L. crispatus. L. crispatus* appears to play an
891 important role in defence against pathogens through the production of lactic acid, bacteriocins
892 and other antimicrobial molecules.[223,224] Recent studies have detected a polymicrobial biofilm
893 in women with BV that is adherent to vaginal epithelial cells and absent in healthy
894 controls.[225,226] But the actual event that triggers this adverse shift in the vaginal microbiota
895 and the development of biofilm remains elusive. In this section of the *Commission*, we discuss
896 the epidemiological and microbiological evidence that supports the role of sexual
897 transmission in the pathogenesis of incident and recurrent BV. We relate this evidence to the
898 high recurrence rates following recommended antimicrobial therapy and other treatment
899 approaches, and discuss the need for novel approaches and combined strategies to address the
900 burden of disease in women.

BV is common and associated with serious reproductive and obstetric sequelae

Globally, women of reproductive age bear a high burden of BV. Prevalence estimates range from 12% in Australian women,[227] to 29% in North-American women,[228,229] to >50% in Sub-Saharan Africa.[230] When present, symptoms typically include an abnormal vaginal discharge and an unpleasant fishy malodour. Qualitative studies show that BV is associated with a significant negative impact on self-esteem, sexual relationships and quality of life.[231] Although women commonly seek medical evaluation, many report misdiagnosis and inconsistent clinical management, compounding their distress and confusion.[232,233] BV is considered a benign condition, but is associated with serious reproductive and obstetric sequelae including: a two-fold increased risk of acquiring other STIs; chlamydia, gonorrhoea, herpes simplex virus type 2 and HIV infection;[18,234-236] increased risk of transmission of HIV to male partners,[19] and increased risk of PID, spontaneous abortion, preterm delivery, low birthweight, and post-partum endometritis.[237-239]

Epidemiological evidence for sexual transmission of BV

While the weight and strength of available data support that BV can be acquired through sexual activity, there has been slow progress in determining the actual transmitted agent or agents. Epidemiological data have consistently linked sexual exposure to the development of BV in cross-sectional and longitudinal studies. Detection of BV has been associated with inconsistent condom use and increased numbers of sexual partners in meta-analyses.[16] Women with BV have an earlier median age of sexual debut than women without BV.[240] Although several studies reported BV in “virgins”, the definition was limited to women with no history of penile-vaginal sex and self-report from potentially vulnerable populations.[241-243] In contrast, a study of 500 female students collected detailed data on sexual behaviours via

926 self-completed questionnaire and employed self-sampling. BV was not detected in women
927 without a history of sexual activity with others, was uncommon in women who had only
928 engaged in non-coital sexual activities, and was associated with the practice of penile-vaginal
929 sex.[244] Incident BV has been associated with exposure to a new sexual partner,[227,240,245] while
930 recurrence after treatment has been associated with sex with an ongoing male partner,[20,246]
931 suggesting that men may serve as a reservoir for infection and reinfection. Several studies
932 have found inconsistent condom use increased the risk of recurrence following
933 treatment.[20,247,248] Although other behaviours have been associated with BV, including
934 smoking,[249-252] douching,[253] dietary factors,[254] and stress,[255] only smoking has been
935 consistently associated with BV in adjusted analyses. The role of these other practices as
936 potential co-factors in the development of BV should not be discounted, however.
937 Epidemiological data consistently show high rates of concordance of BV within female
938 partnerships.[251,256-259] BV has been associated with practices that implicate sexual
939 transmission between women,[251,260] with incident BV associated with exposure to a new
940 female sexual partner, a female partner with BV symptoms or a history of BV, and receptive
941 oral sex in two prospective cohorts.[259,261] Marrazzo and colleagues showed that monogamous
942 female couples share *Lactobacillus* strain types,[262] and Vodstrcil and colleagues found co-
943 enrolled female couples who did not have BV at enrolment remained with a stable healthy
944 vaginal microbiota over 24 months in the absence of new partnerships.[259] Overall, these data
945 provide evidence to support dynamic exchange of both protective and detrimental vaginal
946 bacterial species between women in sexual relationships, or transmission of other agents that
947 directly influence the composition of the vaginal microbiota.
948
949 **The elusive male factor**

950 The apparent lack of symptoms in male partners and the fact that no single transmissible
951 aetiologic agent has been identified have greatly challenged progress in determining if BV is
952 sexually transmitted. There is, however, evidence to suggest that BV-associated bacteria or
953 bacterial communities, perhaps in biofilm form, are transferred between sexual partners.
954 Molecular sequencing analysis has shown that the sub-preputial space and distal urethra of
955 men can harbour a broad range of BV-associated bacteria.[263,264] These BV-associated species
956 are more prevalent in the male partners of women with BV than without.[17] In monogamous
957 couples, specific BV-associated species are highly concordant between women with BV and
958 their male partners.[265] Concordance of oligotypes of *G. vaginalis* has also been reported
959 among heterosexual couples,[266] confirming earlier culture-based studies showing concordance
960 of biotypes of *G. vaginalis* among heterosexual partners.[267] Overall, these data indicate sexual
961 exchange of BV-associated bacterial taxa between heterosexual partners is common,[265]
962 although it is unclear whether men are actively infected or just transiently colonised. Only one
963 small study examined male carriage prospectively and the results suggested these organisms
964 spontaneously cleared over time in men without ongoing sexual exposure.[268]

965 The composition of the coronal sulcus microbiota is not only influenced by sexual activity
966 but also by male circumcision.[269] Male circumcision has been prospectively associated with a
967 significant reduction in BV-associated genera,[263,264] and a striking 40-60% reduction in BV
968 incidence in female partners over 12 months.[270] Although there are few studies, BV-
969 associated biofilm has been detected in male urine and semen, and more commonly found in
970 male partners of women with BV than healthy controls.[225,271,272] Collectively, these data
971 provide evidence for a sanctuary or reservoir of BV-associated species in men from which
972 women may either acquire disease, or be reinfected after treatment. Conversely, BV-infected
973 women may infect or colonise uninfected men, who could be particularly susceptible if
974 uncircumcised. It is quite plausible that the moist microenvironment of the sub-preputial
975 space could enhance the susceptibility of uncircumcised men, and could support a higher

976 organism load that may facilitate persistence and enhance transmission to women. This
977 explanation might underpin the ecological association seen in sub-Saharan Africa, where
978 populations with low rates of male circumcision also exhibit a high prevalence of BV in
979 women.[230]

980 The concept of a "symptomatic male disease counterpart" has not received much attention.
981 In two small studies in the 1980s, however, Keane and colleagues reported that non-
982 gonococcal urethritis (NGU) was more common in male partners of women with BV than in
983 male partners of women without BV, and that men with NGU were more likely to have
984 female partners with BV than men without NGU.[273] In an attempt to explore this further,
985 Bradshaw and colleagues examined two key BV-associated bacteria, *G. vaginalis* and *A.*
986 *vaginae* in a case control study of NGU using quantitative PCR, but found neither was
987 associated with NGU and both were more commonly detected in the urethra of asymptomatic
988 controls than in men with NGU.[274] Manhart and colleagues examined the association between
989 NGU and a broader range of BV-associated bacteria,[275] and confirmed there was no
990 association with *G. vaginalis* or *A. vaginae*, but found that Leptotrichia/Sneathia were
991 significantly associated with NGU. BVAB-2, BVAB-3 and *Megasphaera* were only detected
992 in men with NGU, but they were uncommon, and there was no statistical evidence of an
993 association. The only other clinical presentation that has been reported in men is the syndrome
994 of *G. vaginalis*-associated balanoposthitis. In a single case report,[276] three men presented with
995 a fishy odour, and erythema and irritation of the glans, sulcus and prepuce, all had female
996 partners with BV, and *G. vaginalis* isolated from the glans. So, although a "BV equivalent"
997 male syndrome does not appear to be common, NGU and perhaps balanoposthitis might be
998 associated with some BV-associated bacterial species.

999

1000 **Does treating sexual partners of women with BV improve cure?**

RCTs conducted in the 1980 and 1990s did not provide consistent evidence for a reduction in BV recurrence in women when their male partners were concurrently treated.[277-282] These data formed the evidence base for subsequent BV treatment guidelines that do not recommend partner treatment, however, these trials have recently been examined in two systematic reviews.[220,221] Mehta 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 males in two trials, and many of the treatment regimens, including single dose therapy, would not now be considered effective.[221] A Cochrane review by Amaya-Guio and colleagues concluded that low to very low quality evidence suggests that antibiotic treatment does not lead to a lower recurrence rate.[220,221] Overall the trials are considered inconclusive by current standards. The inconsistency between trial findings and epidemiological and microbiological data may be explained by a number of factors. The findings were clearly influenced by issues in trial design,[221] but these trials were also conducted prior to advances in molecular methods that have provided evidence of detection of BV-associated bacteria in the sub-preputial space of males. It is possible that optimal therapy to promote clearance of BV-associated bacteria from penile and urethral sites requires a combination of both 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 BV, are being sexually transmitted, and if this is the case these agents will not be influenced by male partner treatment with antimicrobials.

Do bacteriophages play a role in bacterial vaginosis?

Phage mediated lysis of lactobacilli has been postulated as a cause of BV, but there have been very few publications in this area. Kilic and Pavlova reported that lysogeny of *Lactobacillus* species (infection with bacteriophages) in women was common, but that the rate of

lactobacillus phage detection was higher in women with BV than without.[283,284] In *in vitro* studies they demonstrated that phages could infect lactobacilli both from the host and different women.[284] Following this work, Blackwell hypothesised that a sexually transmitted lactobacillus phage might destroy healthy lactobacilli allowing secondary overgrowth of anaerobes, which could explain why BV behaves epidemiologically like an STI but BV recurrence rates were unaffected by male partner treatment.[285] The phage theory can be biologically linked to the association between BV and smoking,[249-252] as tobacco products accumulate in cervical secretions, and the cigarette product benzol(a)pyrone diol epoxide promotes phage induction.[249,285] Blackwell again hypothesized that smoking in women or their partners might be associated with BV through tobacco product induction of endogenous bacteriophages or sexually acquired phages.[285] Further studies to clarify if bacteriophages play a role in the pathogenesis of BV in women and their male partners are clearly 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 BV. As the inciting event that results in the development of BV is unknown, traditional treatment approaches have aimed to reduce the vaginal burden of 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%),[27,286,287] with use of intravaginal formulations resulting in fewer systemic side effects.[288] Symptomatic BV persists or recurs in 50%-70% of women within 3-6 months, however, and long-term recurrence rates approach 80% in certain populations.[246,289-291] Possible reasons for this include: re-inoculation with these organisms from an exogenous

source (i.e. sexual partner) or an endogenous source (i.e. rectal reservoir); failure to completely suppress the growth of BV-associated bacteria (i.e. located within a biofilm); persistence of host risk factors (for example, douching or smoking); failure to recolonise the vagina with desirable lactobacilli; and transmission of or activation of *Lactobacillus* phages that destroy vaginal lactobacilli.[283-285,292] None of these mechanisms has been conclusively shown to explain the high rates of BV recurrence, or to identify women at increased risk for BV incidence, recurrence, or sequelae. If sexual transmission is involved in the pathogenesis of BV, 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 BV will respond to standard antimicrobial regimens are also not clear. One prospective study indicated that detection of specific BV-associated bacteria prior to treatment with intravaginal metronidazole predicted treatment failure at 30 days.[291] Investigators have examined whether AMR plays a role and, while clindamycin-resistant bacteria have been detected among women treated with vaginal clindamycin, their presence was not associated with reduced cure rates.[293,294] 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 *M. hominis* and *A. vaginae*.[293,294] Despite that, 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 BV might result in a decline in some non-susceptible members as well. In an attempt to effect higher BV cure rates, investigators have increased the dose and duration of nitroimidazoles. Metronidazole, when used as monthly presumptive therapy, was effective in preventing BV over 12 months of use.[295] Twice weekly vaginal metronidazole gel was also found to be effective in suppressing BV during use, with the rationale being that suppression of overgrowth of BV-associated

bacteria may offer greater symptom relief, and eventually increase the chance of restoration of a normal vaginal microbiota.[296] While a number of prolonged or intermittent suppressive regimens appear effective during use, relapse on discontinuation remains common, and none has improved long term cure rates in women. Whether treating women with recurrent BV with a longer initial course of metronidazole (10-14 days with vaginal gel or oral tablets) or a one week course of oral tinidazole will improve cure rates has not been established. One study that compared 14 days with seven days of metronidazole treatment found statistical evidence of a benefit when cure was assessed seven days after completion of therapy, but not at 21 days.[248]

Biofilm disruption

The presence of a BV-associated biofilm might also contribute to the high rates 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.[292,297,298] When visualised with specific fluorescent probes, *G. vaginalis* has been detected in large quantities within adherent biofilms among women with BV, and some studies indicate that these biofilms persist in women experiencing treatment failure.[299,300] Biofilm disruption might be necessary to achieve optimal efficacy of antimicrobials. Agents that display activity against biofilms include: octenidine, boric acid, DNAses, retrocycline, and naturally occurring antimicrobials (subtilosin, ploy-L-lysine, and lauramide arginine ethyl ester).[301-306] Boric acid and octenidine are currently the only agents to have been evaluated in human studies. While use of metronidazole after 21 days of boric acid reduced BV recurrence on treatment, late post-treatment recurrence was common.[301] Similarly, early BV cure rates looked promising with intravaginal octenidine, but BV recurrence occurred in a significant proportion of women and bacterial resistance to octenidine also emerged.[302] A recent *in vitro* study 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 might have potential as a combination approach for BV.[307] As *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.*[303] DNase appears to be even more effective *in vitro* when combined with metronidazole,[303] but has not yet been subject to human studies for BV. RC101, a retrocycline and potent inhibitor of vaginolysin (a toxin produced by *G. vaginalis*), also inhibits the formation of *G. vaginalis* biofilms *in vitro*,[305,306] and might be another potential candidate for human studies in BV. 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.[298,308] While quorum sensing inhibitors have not been evaluated in human studies, they are active *in vitro* against biofilms produced by *Pseudomonas aeruginosa* and *Staphylococcus spp*.[308,309] Overall, the development of safe and effective topical biofilm-disrupting agents that can be combined with antimicrobials has been suggested as an important area of current research.[298]

Approaches to restore a healthy vaginal microbiota

Because of the apparent ecological shift in the vaginal microflora in BV, 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 demonstrated consistent benefit.[310] One of the barriers to progress has been lack of suitable vaginal species for probiotic formulations, but a *L. crispatus* vaginal capsule, first known as CTV 05 and now termed

LACTIN-V, has recently been shown to achieve vaginal colonisation, to be safe[311-313] and to prevent recurrent urinary tract infections in a Phase 2B RCT;[314] it is now under study for treatment of BV. 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 may suppress without affecting a cure. A systematic review of these agents found they were either ineffective or not adequately tested due to limitations in study size, design or analysis, and that more data are needed.[315]

Conclusion

The adverse impact of BV 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 have discussed, the available epidemiological and microbiological data provide strong evidence of carriage of BV-associated bacteria in male genitalia and exchange of either these species within sexual partnerships or another agent capable of inciting BV. There is also compelling evidence for the impact of male circumcision and condom use on reducing the risk of BV acquisition and recurrence. Overall, these data strongly suggest that sexual transmission is an integral component of the pathogenesis of incident and recurrent BV. 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 may reduce BV recurrence in women. New partner treatment trials, conducted in accordance with current clinical trial standards, and employing modern microbiologic tools, are needed to determine the contribution of reinfection to recurrence, and to provide an accurate evidence base for treatment guidelines. Given the data supporting an anatomic reservoir of BV-associated bacteria 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

may reduce the risk of reinfection and optimise BV cure. Female partner treatment trials could also facilitate understanding of pathogenesis, and identify new approaches to management. While the relative contribution of persistence of BV-associated bacteria versus reinfection to BV recurrence is not clear, both mechanisms are likely to play a role. It is also possible that other factors including failure to recolonise the vagina with desirable lactobacilli, persistence of host risk factors or lactobacillus phages contribute. 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 BV 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 and middle income countries: the role of point of care tests

In 2012, over 90% of new estimated cases of gonorrhoea, chlamydia, trichomoniasis and syphilis were from low 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 and middle income countries has shown some success with vaccines against human papillomavirus (HPV) and hepatitis B and with male circumcision, but less so with interventions to promote sustained behaviour change and condom promotion.[316] STI case management and secondary prevention by screening and/or

1177 treatment to prevent complications have been hampered largely by the lack of affordable and
1178 accessible diagnostic tests. Case management of STIs in low and middle income countries has
1179 relied on syndromic management for patients presenting with symptoms;[133,317] syndromic
1180 management, however, has poor specificity, results in overtreatment with antibiotics and does
1181 not disrupt transmission among those with asymptomatic infection.

1182 Most low and middle income countries have policies for universal syphilis screening
1183 during pregnancy for secondary prevention of congenital syphilis. WHO has prioritised the
1184 elimination of congenital syphilis and Cuba became the first country to achieve the targets for
1185 elimination of mother-to-child transmission of both syphilis and HIV in June 2015.[33]
1186 Nevertheless, implementation of antenatal syphilis screening policies is weak in many
1187 countries. The highest estimates of syphilis prevalence were found in the WHO African
1188 Region (estimated prevalence amongst antenatal attendees is from 4·6 to 6·5%); the median
1189 reported proportion of antenatal attendees tested for syphilis was 58% in the African Region,
1190 versus 83-99% in other regions.[2,318] The proportion of pregnant women not tested for syphilis
1191 in antenatal care fell from 2008 to 2012 in all regions except Africa.[319] The Joint United
1192 Nations Programme on HIV/AIDS (UNAIDS) published data on the Global Plan towards the
1193 elimination of new HIV infections and reported that mother-to-child transmission rates of
1194 HIV were reduced by 71-86% in African countries between 2009 and 2015.[320] The lack of
1195 similar progress in syphilis screening in Africa illuminates the tragic reality that many babies
1196 will have avoided HIV, but died from syphilis.[321,322] There are few other specific policies for
1197 control of STIs in low and middle income countries. While most syndromic management
1198 guidelines include partner notification and treatment, this is often weakly implemented.[323]
1199 Periodic presumptive treatment in targeted populations, such as commercial sex workers, has
1200 shown promise but overtreatment with antibiotics is still a concern.[324]

1201 Rapid and simple POC tests might provide solutions for both STI case management and
1202 control. The key features of POC tests are turnaround times that are fast enough to allow

completion of testing, communication of results that guide clinical decisions and follow-up to take place at the same clinical encounter.[147] There are affordable highly sensitive and specific POC tests for syphilis. While there are several hopeful tests in the pipeline for chlamydia and gonorrhoea, the available POC tests have low accuracy or require expensive equipment.[325] Yet, even with well performing, affordable POC tests, challenges will remain for implementing POC testing into national health systems. This section of the *Commission* reviews current challenges facing case management and STI control related to secondary prevention of curable STIs in low and middle income countries, and provides an update of the state of the art of POC tests.

Case management of symptomatic STIs in low 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.[31] Case management is an integral part of an STI control strategy; 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 where diagnostic tests are not available.[326] 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 PID. 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 became clear, and have become the backbone of case management for STIs in many low 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.[133]

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.[327] This is especially true for vaginal discharge syndrome which is more commonly caused by BV, candidiasis or trichomoniasis, than by chlamydia and gonorrhoea.[43] Several studies have shown poor sensitivity and specificity of syndromic management for chlamydia and gonorrhoea in women.[328-331] Efforts to increase accuracy for the vaginal discharge syndrome with a risk assessment were evaluated, but sensitivity and specificity remained poor.[332] This 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.[17] Unfortunately, asymptomatic infection is still likely to cause harmful sequelae. A study among female sex workers in South Africa has shown that cervicovaginal inflammatory markers were elevated in women with an STI whether or not it was symptomatic.[331] Previous studies have suggested that elevated inflammatory markers may facilitate HIV transmission,[333] 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.[334] Any use of antibiotics encourages resistance, so it is important that the unnecessary use of antibiotics is limited. As noted by *Unemo* in Part 2, 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, *Low and Hocking* discuss partner notification strategies for the management of diagnosed chlamydia. In the context of syndromic management in low 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.[335] A systematic review of partner notification in developing countries found that partner notification for STIs was feasible in low and middle income countries and that most patients diagnosed with STIs were willing to self-notify their regular partners.[336] There are, however, major barriers to successful partner notification, including fear of abuse and rejection resulting from partner referral, especially for women. Economic vulnerability of women must be considered in the design of partner notification strategies in low and middle income countries in which female partners may be blamed for the infection.[335] There is a need for the development and evaluation of partner notification strategies in low and middle income countries using biological outcomes, such as reinfection.[138]

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 may 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 evaluated 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.[337] In 2012, a systematic review reported the results from 15 studies and showed consistent reductions of about 50% prevalence in populations with high chlamydia and gonorrhoea prevalence. There was limited evidence for chancroid - one study showed rapid decline of chancroid – and mixed evidence for syphilis.[338] Modelling studies have shown that, if sufficient coverage is achieved (>30% of the target population), periodic presumptive treatment interventions can effectively reduce the STI prevalence among the target population, and that interventions with sufficient coverage (≥40%) and follow-up (≥2 years) could significantly decrease HIV incidence (>20%).[339]

Presumptive treatment can be an effective approach to the treatment of asymptomatic infection among women (at least those at high risk) and may interrupt transmission between sex workers and their clients, but needs evaluation in other populations. Importantly, presumptive treatment must be sustained; once stopped, infections recur. In addition, a disadvantage is unnecessary treatment of people who are not infected with an STI and the contribution to the development of AMR, as discussed above.

Screening programmes

Antenatal syphilis screening and treatment is effective and cost-effective for the prevention of adverse pregnancy outcomes.[340] Fifty-two low 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%.[317,341] Of 14 countries that report current policies for antenatal screening of *C. trachomatis* and *N. gonorrhoeae* infections, only two (Romania and Bulgaria) are in the category of low and

middle income; most low and middle income countries use WHO recommended syndromic management for the treatment of symptoms during antenatal care.[342]

Screening of high-risk populations, including sex workers has shown some success in research studies and demonstration projects,[343,344] but has not been widely replicated in low and middle income countries due to the cost of diagnostics and laboratory capacity.[343] Evidence about chlamydia screening is discussed in detail in Part 1.

The use of POC testing for case management and STI control

POC tests provide prompt diagnosis for case management, provide a definite diagnosis of an STI which 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 POC, including wet mount and Gram stain microscopy, but they require laboratory equipment and lack sensitivity, particularly for diagnosing infections in women. Rapid plasma reagin (RPR), a non-treponemal test for syphilis, can also be done at the POC, but it requires separation of serum, refrigeration and equipment, and has low accuracy in settings with insufficient training or facilities.[345-347] In addition, RPR tests are often batched or sent to a central laboratory, resulting in patients not returning or staying for treatment.[345,348,349]

To guide the development of simple and rapid POC tests, WHO developed the ASSURED benchmarking in 2006. ASSURED POC 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 perform (minimal steps required with minimal training); Rapid and Robust, to enable treatment at visit of diagnosis (rapid) and does not require refrigeration storage (robust); Equipment free, easily collected non-invasive specimens (e.g. saliva and urine) and not requiring complex equipment; and Delivered to end users.[350] Three recent

systematic reviews summarise the available information on POC tests for STIs: Tucker and colleagues;[351] Gaydos and Hardick;[352] and Herbst de Cortina and colleagues.[353] Reviews evaluated available POC tests and those in the pipeline. The WHO landscape analysis of POC tests by Murtagh provides a listing of currently available POC tests and those in the pipeline;[325] this analysis will be updated annually by WHO. Available POC tests have been summarised in table 3.

POC tests for chlamydia and gonorrhoea

Most POC tests currently available for the detection of *C. trachomatis* or *N. gonorrhoeae* are based on antigen detection in lateral flow devices and do not meet ASSURED criteria because of low sensitivity and/or specificity. While the aQcare Chlamydia TRF and BioStar Optical Immunoassay 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).[354,355] There is general agreement that most current POC 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 POC tests may increase the proportion of infections treated in scenarios where it would be difficult to ensure a high patient return rate, and in populations where there is potential for further STI transmission during the delay in treatment from using laboratory STI tests.[356-358]

GeneXpert (Cepheid, Inc), a NAAT-based test with high sensitivity and specificity for detection of *C. trachomatis* and *N. gonorrhoeae* has been termed a *near*-POC test as it requires equipment, is expensive and has a relatively long turnaround time (approximately 90 minutes). There are many new technologies in the pipeline (Figure 7) which are likely to be highly accurate and require minimal training and processing time including the io® Platform (Atlas Genetics), GeneXpert® Omni (Cepheid), RT Cross-priming Amplification CT Test

(Ustar Biotechnologies), Truelab™ Real Time micro PCR System (Molbio Diagnostics Pvt. Ltd), Alere™-i Platform (Alere, Inc), CT/NG MAMEF-based detection, and MobiLab (Johns Hopkins University BioMEMS Lab).[325,351,353] The latter test employs smartphones for reading results.

POC tests for trichomoniasis

The OSOM® Trichomonas Test (Sekisui Diagnostics) 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).[325,353] The OSOM test for detection of *T. vaginalis* meets the ASSURED benchmark by having few steps and taking only 10 minutes to perform. GeneXpert platform also has an assay to detect *T. vaginalis* and this test has been evaluated in two studies and found to be sensitive and specific (95·0-95·6% and 95·7-100% respectively);[359,360] however, the GeneXpert platform does not meet ASSURED benchmarking as stated above. In the pipeline, Atlas io™ has an assay in development as well as AmpliVue® (Quidel Corporation).[325]

POC tests for syphilis

Four treponemal POC tests for syphilis have been evaluated and met the ASSURED criteria, and these are recommended in resource-limited settings: Determine™ Syphilis TP (Alere, Inc), SD Syphilis 3.0 (Alere SD Bioline), Syphicheck® WB (The Tulip Group/Qualpro), and Visitect® Syphilis (Omega Diagnostics).[350,361] These tests are accurate, cost less than $1 if purchased through the WHO bulk procurement programme for low and middle income countries, can provide results in 15 to 20 minutes, and are easy to use with minimal training. In addition to these tests that have been extensively evaluated, other POC tests for syphilis are on the market including Crystal TP Syphilis Test (Span Diagnostics), *OnSite*™ Syphilis Ab

Combo rapid Test (CTK Biotech Inc.), Syphilis Health Check™ (Diagnostics Direct), and Uni-Gold™ Syphilis Treponemal (trinity Biotech).[325]

Treponemal POC tests have been implemented and evaluated in rural antenatal care clinics in Tanzania, Uganda and China; both rural and urban clinics in Peru and Zambia; and in remote indigenous communities in Brazil.[362] The introduction of POC 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 POC tests are more cost-effective in screening and treating syphilis than laboratory-based testing methods such as the RPR.[363]

Treponemal POC 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.[362] Modelling studies have estimated the impact of using rapid POC tests to screen female sex workers for syphilis and shown that rapid POC test screening could dramatically reduce syphilis prevalence amongst this hard-to-reach group, but strategies to reduce re-infection from regular non-commercial partners are needed to maximise impact.[364]

Once a person has been infected with *T. pallidum,* all future treponemal tests will be positive; therefore, there is concern that treponemal POC tests cannot distinguish between current and past infection, resulting in over treatment for syphilis. This is particularly important in settings in which access to confirmatory testing using non-treponemal tests is limited. Therefore, combination POC platform tests have been developed which include both treponemal and non-treponemal antigens. The Dual Path Platform test is the first of these, and has good sensitivity and specificity for both treponemal (90·1-98·2% and 91·8-98·0%, respectively) and non-treponemal (80·6-98·2% and 89·4%, respectively) tests.[365]

POC tests for syphilis and HIV

There is also a need for dual syphilis and HIV tests. These could be used in populations at high risk for both HIV and syphilis, and accelerate programmes for the elimination of mother to child transmission of both HIV and syphilis, especially in countries in Africa that have made excellent progress towards the elimination of mother to child transmission of HIV but not syphilis. In 2017, WHO published an information note to provide advice for countries using or planning to introduce dual HIV/syphilis POC tests in antenatal services and other testing sites.[366] There are currently five combination HIV/syphilis POC tests on the market (Figure 8), of which three have published data on sensitivity and specificity: Standard Diagnostics (SD) Bioline HIV/Syphilis Duo Rapid Test; Chembio DPP® HIV-Syphilis Assay; and Medmira Multiplo Rapid TP/HIV Antibody Test.[325] In addition to these, there is an innovative dual POC test in the pipeline, mChip Assay (Junco Labs and Columbia University in collaboration with OPKO Health, Inc), which uses a microfluidic mChip and a smart phone for reading results.[325]

POC tests for AMR gonorrhoea

There are, as yet, no commercially available diagnostic assays that detect gonococcal AMR.[191] There is an urgent need for the development of these diagnostics with a focus towards POC tests. Detection of both *N. gonorrhoeae* and its main resistance determinants at the POC would improve management and help to slow the spread of AMR, particularly in low and middle income countries.[191]

Challenges for the implementation of POC tests

POC tests have the potential to transform case management and STI control in low and middle income countries. To be effective at the population level, however, they must be adopted by national health systems and this 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 impact.

A study in Peru has shown that the use of POC tests offers an opportunity to improve screening coverage for syphilis and other aspects of health systems.[362,367] Widespread adoption and use depends on engaging the authorities; dissipating tensions between providers and identifying champions; training according to the needs identified; providing monitoring, supervision, support and recognition; sharing results and discussing actions together; consulting and obtaining feedback from users; and integrating with other services such as with rapid HIV testing.[362,367] As countries begin to implement POC testing, adequate training and quality assurance programmes must be developed in parallel. Smit and colleagues evaluated the use of dry blood spots to evaluate quality of POC syphilis and HIV tests in Tanzania, and found that quality varied between clinics, which helped to identify which clinics needed remedial training.[357]

Ultimately, POC 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 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.[368] However, important lessons can be learned from the roll out of simple and rapid HIV POC tests in which the major challenges have been well recognised including poor quality control, unreliable supply chains, non-standardised training, and limited number of healthcare workers.[369] Decentralising testing for curable STIs might increase access to testing and awareness of STIs, but linkage to the health care system will be critical for diagnostic confirmation, treatment, counselling and follow-up.[351] POC tests that meet ASSURED benchmarks are likely to fill an important gap for STI control in low and middle income countries, yet the technological innovation of POC tests needs to be mirrored by innovation in health care delivery and careful planning for implementation.

Conclusion

Low and middle income countries shoulder the majority of global incident cases of STIs, yet national health systems are less resourced to manage STI cases or carry out secondary prevention. POC tests that meet the WHO ASSURED benchmark could bridge the gap for STI case management and control in these settings. Currently there are POC tests for syphilis and trichomoniasis which meet the ASSURED benchmark. In contrast, there are no ASSURED POC tests for chlamydia or gonorrhoea, and there is an urgent need for the development and evaluation of POC tests for these infections, as well as for AMR *N. gonorrhoeae*. Importantly, while development of ASSURED POC tests is a crucial target, the successful implementation of POC tests into health care systems for the prevention and control STIs is the goal. Indeed, the goal for the implementation of POC tests into antenatal screening for syphilis is 100% screening and treatment of syphilis worldwide. Future ASSURED POC tests for curable STIs will need to be integrated into syndromic management guidelines as well as control strategies such as partner notification and targeted presumptive treatment. It will be essential that implementation research guides integration of POC tests into current strategies for STI case management and control in low and middle income countries.

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 rise in notification rates

of gonorrhoea and syphilis in men from the 1960s onwards in countries such as England and Wales (Figure 9A) and the USA (Figure 9B). The increase in infections amongst MSM is reflected in the rising 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.[370] 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".[371] Rates of gonorrhoea and syphilis, and the male to female ratio of infections, reached a peak in the late 1970s (Figures 9 and 10). Other STIs were also common; 50-70% of MSM had serological evidence of hepatitis B infection[372] and outbreaks of infections, such as lymphogranuloma venereum (LGV) were reported.[373] Infections such as hepatitis A and enteric pathogens, such as *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'.[374] Given what is now known about the biological effects of STIs to increase both infectiousness of, and susceptibility to, HIV,[5] these infections are likely to have facilitated the early spread of HIV before it became clinically manifest 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 early on,[375] well before a retrovirus was discovered as the cause of AIDS. Rates of gonorrhoea and syphilis actually began to fall in the late 1970s but the rate of decline accelerated rapidly after the first deaths from AIDS were reported in the early 1980s.[123,376,377] 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

1504 public health campaigns for the general population followed.[123] Figure 9A shows the large
1505 decline in syphilis notifications in England from 1983 onwards, but notifications of other STIs
1506 including LGV and other enteric pathogens also fell.[123,373] By 1994, rates of syphilis and
1507 gonorrhoea were at their lowest levels since surveillance began (Figures 9A and 10).

1508 Trends in STIs and sexual behaviour in MSM since the mid-1990s have occurred in the
1509 context of continued developments and improvements in antiretroviral therapies (ARTs) for
1510 both HIV treatment and for prevention. Notification rates of syphilis, gonorrhoea and
1511 chlamydia in MSM have all risen (Figure 10).[378-381] A review of syphilis in 31 high income
1512 countries between 2000 and 2013 showed that the male to female ratio increased in all
1513 geographical regions from 4·1 in 2000 to 7·9 in 2013.[381] New outbreaks of LGV,[373] hepatitis
1514 C, and shigellosis have also appeared, particularly in HIV-infected MSM.[379] Combination
1515 ART (cART) became available in the mid-1990s and drastically improved the prognosis for
1516 people with HIV infection,[382] changing the nature and course of HIV from a deadly infection
1517 to a chronic disease. Further advances in the efficacy of cART with less toxic drugs and less
1518 complicated dosing schedules, together with improvements in monitoring viral load and
1519 resistance, prompted recommendations for earlier commencement of therapy for HIV-infected
1520 people.[383] The first use of cART to prevent, rather than treat, HIV was post-exposure
1521 prophylaxis (PEP), for short-term prophylaxis to reduce the risk of HIV acquisition after a
1522 substantial risk of exposure to infection.[384] Since the mid-2000s, the potential for cART to be
1523 used to prevent HIV transmission followed research showing that cART reduces HIV
1524 infectiousness and when HIV replication is suppressed to undetectable levels in plasma,
1525 transmission can be virtually eliminated.[385,386] Treatment as prevention (TasP; also known as
1526 "test and treat"[387]) refers to a population-level strategy of starting cART as soon as HIV is
1527 diagnosed, irrespective of CD4 cell count, to suppress viral load and prevent transmission to
1528 sexual partners.[388] A regimen of two antiretrovirals, taken as pre-exposure prophylaxis (PrEP)
1529 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.[389-391]

All three uses of cART for HIV prevention have been accompanied by concern about their possible unintended negative consequences for sexual behaviour and STIs,[392] 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 incidence.[393] 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.[22,392] Behavioural surveillance amongst MSM, such as surveys carried out yearly in Sydney, Australia for 20 years (Figure 11) and the US National HIV Behavioral Survey (NHBS) conducted using venue-based sampling in 21 cities in the USA every three years since 2005,[394,395] show 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 and that cART reduces the need for safer sex engage more often in risky behaviours such as non-condom receptive anal intercourse.[396,397] "Safer sex fatigue"[398] and the adverse effects of HIV on mental health[399] also contribute to sexual risk taking. Serosorting (choosing sexual partners with the same HIV serostatus) results in sexual networks stratified by HIV serostatus with reduced condom use[395] and increased risk of STI transmission.[400] 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. In the discussion, we speculate on the potential influence of biomedical interventions on future STI

epidemiology in MSM once implemented more broadly and discuss alternative options for STI prevention other than condom use.

Post-exposure prophylaxis (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 an HIV-positive index or an index with an unknown HIV status belonging to a high risk group.[401,402] The efficacy of PEP has not been studied in RCTs, but there is a wide consensus about its effectiveness, based mainly on one case-control study in a hospital setting, which found an 81% reduction of HIV transmission in the group that used PEP.[384] The increased availability of PEP led to concern that it may increase in risk taking.[403] Two studies did find a higher risk of non-condom sexual behaviour and a higher incidence of HIV in the group of MSM after receipt of PEP but these studies did not find a correlation between PEP use and changes in risk behaviour.[404,405] The authors concluded that many MSM requesting PEP simply already belong to a high-risk group.[405] In high income countries, most PEP requests come from MSM, but uptake remains low; 183 requests from one large public health centre in Amsterdam, The Netherlands, over a five-year period.[406] Successful awareness campaigns have increased uptake of PEP.[403] The limitations associated with ascertaining exposure and eligibility, and suboptimal effectiveness, mean that PEP use is unlikely to have any impact on sexual risk behaviour or STIs at the population level.

Treatment as prevention (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 HIV-infected partner had a very low or undetectable level of HIV-1 RNA.[385,386] Based on these

observational studies, the Swiss AIDS Commission stated in 2008 that a serodiscordant couple could have non-condom sex if the HIV-infected partner was taking cART with sustained viral suppression and no other STI.[407] 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 impact of TasP at the population level.[387] Mathematical modelling studies showed how, assuming zero transmissibility with suppressed viral load, universal HIV testing and immediate cART could eliminate HIV within ten years of implementation.[408] In 2012, an individual-level RCT in nine countries (HPTN 052, Botswana; Kenya; Malawi; South Africa; Zimbabwe; Brazil; India; Thailand; 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 to 99%) compared with later treatment.[409] To extrapolate these benefits to a whole population, a sufficiently high proportion of all HIV-infected individuals would need receive and adhere to effective cART from very early in the course of infection.[410] The first of the population level trials, a cluster RCT in Kwazulu-Natal, South Africa, did not find a reduction in HIV incidence in communities that received the TasP intervention.[411] Suboptimal uptake of testing, particularly in young men, and delays in linkage to care are likely to have limited the public health benefits of TasP,[412] even though an earlier ecological study in the same population had suggested that HIV-incidence was lower in people living in communities with higher cART coverage.[413]

Risk compensation, STIs and the TasP strategy

There is little published 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, the frequency of new STIs (syphilis, gonorrhoea, chlamydia infections, and

1606 trichomoniasis) detected among heterosexual participants treated immediately was low and
1607 similar to that in those who received deferred treatment after a median 1·7 years of follow up;
1608 98% of participants were heterosexual and >95% in both groups reported using condoms.[409]
1609 At the population level, the effects in the TasP trial in Kwazulu-Natal on behavioural
1610 outcomes, including condom use, have not yet been published.[411]

1611 An examination of data from San Francisco, USA provides some insight at the population
1612 level because the city has both biological and behavioural surveillance data spanning the
1613 introduction of TasP.[414] The San Francisco Department of Public Health implemented a TasP
1614 strategy; cART for all HIV-infected persons regardless of CD4 cell count at publicly funded
1615 HIV clinics and an expansion of HIV testing services, in 2010, two years before US national
1616 recommendations changed.[414] We aggregated published STI surveillance data from 2005 to
1617 2014 and compared the positivity rates of HIV, syphilis and gonorrhoea and mean numbers of
1618 partners among self-identified gay and bisexual men before the introduction of the TasP
1619 strategy nationally (from 2005 to 2009) with the period afterwards (from 2010 to 2014).[329,415-
1620 417] Figure 12 shows that the percentage of HIV tests with a positive result was already falling
1621 and declined from 4·5% in 2005 to 2·5% in 2010. HIV positivity dropped further, from 2·5%
1622 in 2010 to 1·1% in 2014. In contrast, the positivity rate of early syphilis infections rose
1623 consistently from 1·9% in 2005 to 4·4% in 2014.[329,415-417] The gonorrhoea positivity rate
1624 dropped during the period 2005-2009, but increased from 9·7% to 11·2% in the period 2010-
1625 2014. Behavioural surveillance data show that the mean number of sex partners in the prior
1626 three years decreased from 5·0 in 2007 to 4·4 in 2009 and then increased from 4·6 in 2010 to
1627 6.1 in 2013.[418] The recommendation about TasP in San Francisco was thus temporally
1628 associated with increases in gonorrhoea, syphilis and partner numbers. Risk compensation
1629 might have contributed to these trends, although the increase in syphilis began before TasP
1630 began. In Switzerland, the proportion of HIV-infected MSM in the Swiss HIV Cohort Study
1631 reporting non-condom sex with both 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.[419] Data from the US NHBS surveys amongst MSM, showed that condom use has decreased from 2005 up to 2014 over a large geographic area and that these trends were not explained by serosorting, seropositioning, PrEP use or cART treatment.[395] Figures 10 and 11, show rates in the bacterial STI notifications in England and the fall in condom use in Sydney, Australia, suggest that opposing trends in STI rates and in condom use have taken place over 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.[22] A disadvantage inherent to TasP is that its success depends on the behaviour of others.[420] The uninfected person has to trust that their HIV-infected sexual partners are adherent to cART and that the cART is sufficiently effective to mitigate transmission risk. In contrast, with PrEP and PEP, the at-risk individual takes the preventive treatment.

Pre-exposure prophylaxis (PrEP)

Three RCTs 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.[389-391] Across these trials, the use of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), in combination with comprehensive sexual health care, reduced HIV incidence ranging from 44% to 86%. Two of the RCTs studied daily use of TDF/FTC[389,390] and one studied intermittent use (two tablets between 24 and 2 hours before sex, followed by two times one tablet at 24 and 48 hours after sex).[391] The first landmark study, the Preexposure Prophylaxis Initiative (iPrEX), looked at the effect of daily TDF/FTC among 2499 MSM from six countries (Peru, Ecuador, South Africa, Brazil, Thailand and the

1657 USA) and was published in 2010.[389] The Pre-exposure option for reducing HIV in the UK,
1658 immediate or Deferred (PROUD) trial enrolled 544 MSM in the UK and randomised them to
1659 immediate or a one year delayed start of daily oral TDF/FTC.[390] In the Intervention
1660 Préventive de l'Éxposition aux Risques avec et pour les Gays (Ipergay) trial, 414 MSM were
1661 randomised to either TDF/FTC or placebo for intermittent use in France and Canada.[391] In all
1662 PrEP trials, adherence was a strong determinant of PrEP effectiveness.[421]

1663 These trials showed that it is feasible to identify and enrol MSM at high risk of acquiring
1664 HIV infection, with HIV incidence rates in the placebo arm of 9·0 per 100 person years in
1665 PROUD and 6·6 per 100 person years in Ipergay. Open label studies, demonstration projects
1666 and cohort studies provide additional evidence that PrEP roll-out to MSM at high risk for HIV
1667 infection is feasible, safe and prevents HIV.[421-424] Eligibility criteria in most PrEP trials and
1668 demonstration projects include well-known determinants for HIV acquisition in MSM such as
1669 recent rectal or urethral STIs, a recent use of PEP, reporting anal intercourse with casual
1670 partners and having an HIV-positive partner with a detectable viral load.[421] International
1671 guidelines for PrEP from the US Centers for Disease Control and Prevention and WHO
1672 reflect these eligibility criteria.[329,425]

1673

1674 *Risk compensation, STIs and PrEP*

1675 PrEP is a powerful intervention for HIV prevention among MSM, but it has the potential to
1676 reduce commitment to primary prevention strategies, result in risk compensation[392] and
1677 increase rates of STIs. The role of PrEP in relation to sexual behaviour and STI rates is
1678 somewhat easier to assess than with TasP because PrEP is an individual intervention rather
1679 than a population-based one. PrEP is, however, only in the early stages of implementation.

1680 In the placebo-controlled trials iPrEx and Ipergay, condom use and STI incidence were
1681 similar in participants allocated to PrEP and to placebo. These findings are expected because

participants were blinded and all received the same risk reduction advice. The PROUD RCT 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 deferred PrEP reported non-condom receptive anal sex with ten or more partners (21% vs. 12%, p=0·03). The proportions diagnosed with STIs during the 12 month follow-up period were similar in men receiving immediate and deferred PrEP, however; rectal gonorrhoea or chlamydia, 36% vs. 32% (odds ratio, OR 1·00, 95% CI 0·72 to 1·38), syphilis, 11% vs. 9% (OR 1·32, 95% CI 0·79 to 2·10).

Open-label studies should allow a more realistic assessment of the influence of PrEP on sexual behaviour. In an open-label observational study 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 in both groups and syphilis incidence (7·2 infections per 100 person years in PrEP recipients and 5·4 per 100 person years, hazard ratio 1·35, 95% CI 0·83 to 2·19) was also similar.[422] The authors 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 project in San Francisco, Washington DC and Miami, USA, early findings (up to 48 weeks) amongst men receiving PrEP have shown a stable proportion overall reported having had non-condom receptive anal sex in the previous three months (65·5%; 365/557), 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.[423] 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.[426]

The longer term impact of PrEP for risk compensation and STI rates are not yet known. Taken together, trials of PrEP with one to two years of follow up show a large reduction in HIV incidence in MSM who adhere to the regimen, high but similar levels of bacterial STIs in MSM who received and did not receive PrEP and mixed effects on sexual behaviours.[395] Additional studies suggest that increasing use of PrEP as a method of biomedical HIV prevention could change patterns of sexual partner seeking and condom use.[394,427] Newcomb and colleagues have coined the term "Biomed-matching" as a new strategy amongst 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.[427] MSM who receive PrEP will need to be followed carefully over time using both quantitative and qualitative research methods to determine whether and how risk compensation and changing patterns of sexual partnerships and practices are affecting STI rates.

STI prevention in the era of biomedical HIV prevention

The use of cART to prevent HIV acquisition and transmission, TasP and PrEP in particular, are changing the HIV prevention landscape for MSM. The continued fall in HIV positivity in San Francisco, USA 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.[428] Trends in HIV infection and other STIs seem to have been decoupled. STI rates in MSM have been rising since the late 1990s (Figure 10).[427,429] The increases in notifications of bacterial STI appear to be accelerating (Figures 9, 10 and 12). In England, HIV-infected MSM account for almost all of the increase in STI notifications in MSM; for syphilis, the proportion diagnosed in HIV-infected MSM increased from around 25% in 2009 to around 40% in 2013.[379] In the absence of denominator data, how much of the

increase is the result of more frequent testing is not known. Widening PrEP use, together with other behavioural changes, including an increase in the adoption of seroadaptive behaviours[394,395] and use of geosocial networking mobile applications, such as Grindr,[427,429] could affect sexual networks and influence rates and patterns of STI. For example, if non-condom sex partnerships between HIV-uninfected MSM using PrEP and HIV-infected MSM on cART become more common, outbreaks of syphilis, LGV, hepatitis, and shigellosis that have occurred mostly amongst HIV-infected MSM could spread to networks of HIV-uninfected MSM. STIs that increase HIV infectiousness through inflammatory mechanisms[5] could then reduce the impact of biomedical HIV prevention methods. Additional surveillance and interventions to control STIs amongst 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.[430] 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 three 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.[87] One mathematical modelling study suggested that screening MSM for chlamydia could reduce the prevalence of both chlamydia and HIV.[431] These findings should be considered in the light of evidence presented in two other sections of the *Commission*. First, modelling studies also suggest that chlamydia screening in heterosexual populations will reduce chlamydia prevalence,[105,106] but evidence from RCTs[14,95] and repeated population-based cross-sectional studies[43,44] have not found appreciable reductions in chlamydia prevalence in the target populations (Part 1). Second, as AMR in *N. gonorrhoeae* spreads (Part 2), the potential impact of increasing STI testing rates also needs to be considered. Mathematical modelling studies of MSM populations show that, at least for some antimicrobials, increasing the rate of gonorrhoea treatment might reduce prevalence

temporarily, but that the increased selection pressure accelerates the spread of AMR, resulting in increased prevalence over time.[432,433] On the other hand, models of syphilis transmission have shown a reduction in incidence with frequent testing and one ecological study using national surveillance data in Australia showed that when syphilis testing rose from 1·6 tests a year to 2·3 tests a year, there was a reduction in secondary syphilis cases (from 45% to 26%).[434,435] There was also a commensurate rise in early late infections (from 23% to 45%) suggesting that frequent testing was detecting syphilis infection before it reached the secondary stage.[434]

Another possible STI intervention that has undergone limited investigation is daily use of doxycycline.[436] A single small double blind randomised trial of 30 individuals followed for one year showed lower rates of STI in the doxycycline arm.[437] Interventions involving prophylactic use of antimicrobials have not been pursued further because of concern about AMR. One group is investigating 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, even though relatively little is known about the transmission of STIs between anatomical sites in MSM.[438] 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* five minutes later.[439] Longer 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.

Conclusions

Rates of bacterial STIs in MSM have been rising for about 20 years now and are approaching the levels seen in the late 1970s before HIV 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.[22,390] The contributions of behavioural responses to the biomedical HIV prevention strategies and of other factors influencing sexual behavioural change remain unknown.[394,423,427] Quantifying the effect of biomedical HIV prevention interventions on STI rates is methodologically difficult.[377,379] Based on surveillance data from places with large populations of MSM,[329,379] it is likely 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. Indeed, biomedical HIV interventions play a positive role 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, condom promotion and risk reduction interventions.[440]

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 HIV-uninfected and HIV-infected MSM, AMR, and the emergence or re-emergence of new sexually transmissible pathogens including enteric infections and Ebola and Zika viruses.[441]

Call to action

Action is required to address the substantial challenges facing STI control globally (table 4). AMR in *N. gonorrhoeae* is increasing relentlessly and adverse consequences of chlamydia infection remain prevalent. STIs in MSM are rising rapidly, new sexually transmissible infections are emerging or re-emerging and there is evidence that BV, one of the most common, but often ignored, genital conditions in women, might also be sexually transmissible. These issues are magnified in low and middle income countries that bear the burden of STIs worldwide. To address these issues we need to reach our policy makers and to convince them to invest in clinical and public health strategies to improve the control of STIs, based on carefully considered analytical decisions, founded in science. If they do not, we may suffer more than we should, and spend more than we need.[442] In putting this case, we recognise that social, cultural and structural conditions are major determinants of sexual behaviour, sexual risk and STIs.[443] Research evidence provides the scientific support for prioritising interventions, but successfully influencing health policy will require the involvement of stakeholders, including researchers, clinicians, and members of civil society as well as policy makers themselves.[444]

One of the most important messages about STI control is that good policy decisions matter much more than poor individual ones.[442,445,446] This is because effective policy interventions can put strong downward pressure on STI incidence,[33] while individual behaviour has a relatively weak effect on the population prevalence of STIs and sustained and substantial behaviour change is difficult to achieve.[442,446,447] We need to make the case to policy makers that STIs cost less to keep under control than to treat, and manage their sequelae, when endemic levels are high.[442]

The cornerstone of the health sector response to effective STI control is easily accessible quality health care, and is the principle behind the provision of free STI services in many

countries.[445] Accessible health care helps to ensure that STIs are treated early, before substantial transmission can occur.[33] 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, even though the number of sexual partners in both communities might be similar.[448] For example, gonorrhoea in heterosexuals is relatively easy to control with accessible primary health care and, as a result, most high income countries rates of reported gonorrhoea are well below 100 per 100,000 population. Rates in heterosexuals exceed these levels in high income countries in populations whose access to health care is limited, such as among uninsured Americans or Indigenous Australians living in remote communities.[448,449] STI services are a key goal of the WHO strategy to help achieve universal health coverage, a key target of the 2030 Agenda for Sustainable Development.[33] 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. Despite substantial proportions of the population being tested for chlamydia in some high income countries it has proven difficult to reduce the prevalence and we remain uncertain about the long term impact that widespread testing for chlamydia has on the key health outcomes including PID, ectopic pregnancy and infertility. Chlamydia control strategies should define acceptable local targets for chlamydia prevalence, so that appropriate interventions can be prioritised. Improving case management of those diagnosed with chlamydia and PID (e.g. effective antimicrobial treatment, partner notification and retesting to detect repeated infection) might achieve more than promoting widespread testing alone. We should also establish and adapt surveillance systems so that we know what impact our chlamydia control activities are having on PID and its complications. We call on policy makers to invest in the research agendas that has been repeatedly called for by international experts,[60,150,151,450] to further our understanding about the natural history of chlamydia and

develop non-invasive measures of tubal infection, inflammation and damage and biomarkers to predict upper genital tract pathology. Further we must invest in chlamydia vaccine research because without an effective vaccine, it is unlikely that we will be able to control it.

The effective control of gonorrhoea is a global health priority[33] because of the relentless rise in AMR, and the high incidence in low and middle income countries and increasing incidence in key populations, including MSM (Figure 10).[379] In this context we call on policy makers to ensure adequate and sensitive surveillance programmes are in place and industry to support the development of effective 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.[451] Some have advocated more frequent screening, but at least with some antimicrobials an increased rate of gonorrhoea treatment might accelerate the spread of AMR and might outweigh any gains in reducing prevalence.[433] 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 play a key role in transmission of both infection and AMR.[157,452,453] Effective control will require understanding how gonorrhoea is transmitted between MSM so evidence-based interventions can be developed just as interventions for HIV control were developed by understanding its transmission. Ideally condoms should not be a critical part of these interventions given condoms rates are falling and may fall further.[453] Recent research has suggested a potential non-condom based intervention.[439] Researchers 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.[454] Early work has shown that antibacterial mouthwash might inhibit *N. gonorrhoeae* growth and studies of mouthwash for gonorrhoea prevention are underway.[439] We call on policy makers to fund research to better understand

how STIs are transmitted between MSM to allow the development of new control programmes not based only around condoms.

BV 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 a lack of a proven transmitted pathogen. Effective control is complicated by its high relapse rate which is likely to be due, at least in part, to our failure to recognise the importance of sexual transmission in its pathogenesis and the contribution of reinfection to recurrence.[20,246] Current treatment strategies are entirely focused on the female partner, while accumulating epidemiological and microbiological data provide evidence of male carriage and exchange of BV-associated bacteria within sexual partnerships.[265,423] In order to make significant advances in the treatment and prevention of BV and its costly sequelae we need to better understand the contribution of persistence of BV-associated bacteria versus reinfection to BV recurrence. New treatment strategies are required but we also need to revisit male partner treatment trials with more evidence-based approaches.

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

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 of behavioural interventions for condom use for example have relatively modest effect sizes (~20% effective at one year).[446,447] In 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 in the vaccine in both vaccinated women and unvaccinated heterosexual men in Australia.[11,455] Similarly large effect sizes for reducing HIV acquisition are seen in RCTs of PrEP when adherence levels are high.[389-391] Biomedical methods to prevent HIV have, however, contributed to increased rates of STIs amongst 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 both primary and secondary prevention strategies including; integrated sex education programmes in schools, strong partner notification programmes that utilise 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 of course accessible health care for all.

FIGURE LEGENDS

Figure 1: **WHO estimates of the number of cases (in millions) of four curable STIs trichomoniasis (TV), chlamydia (CT), gonorrhoea (NG), and syphilis (TP) globally in 2012. Source: reference[2]**

Figure 2: **Natural history and sequelae of *Chlamydia trachomatis* infection in women. Length of arrows are not proportional to time. Dotted lines are conditions that can resolve.**

Figure 3: **Interventions for the control of chlamydia in the population. Source: reference[31]**

Evidence[31]-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)

Figure 4: **Chlamydia prevalence estimates among sexually experienced women ≤26 years estimated in cross sectional suveys of randomly sampled individuals from the general population in WHO regions.**

Source:

Europe

Croatia (N=151);[46] France (N=106);[38] The Netherlands (N=2626);[41] Norway (N=930);[42] Slovenia (N=265);[40] Spain (N=157);[49] United Kingdom (N=992)[44]

Americas

USA (N=unavailable);[45] Argentina (N=148);[49] Colombia (N=278)[49]

Africa

Nigeria (N=120)[49]

South-East Asia

China 1 (N=194);[52] China 2 (N=46);[49] India;[50] Thailand 1 (N=69);[49] Thailand 2 (N=129);[49] Vietnam 1 (N=158);[49] Vietnam 2 (N=123)[49]

Western Pacific

Australia (N=135);[39] Papua New Guinea (PNG; N=73)[51]

Figure 5: **Hospital discharge rates for inflammatory disease in female pelvic organs.**

Source: reference[122]

See supplementary table 1 for further detail.[122]

Figure 6: **Interventions attempted for the management and prevention of bacterial vaginosis**

Figure 7: **Point-of-care (POC) or near-POC tests for STIs that are available or in the pipeline. The dotted line means that no market launch date has been set by the company. Source: updated from reference[325]** XenoStrip-TV™ rapid diagnostic test for *T. vaginalis* (Xenotope Diagnostics, Inc, San Francisco, USA), OSOM® rapid diagnostic test for *T. vaginalis* (Sekisui Diagnostics, Lexington, USA); GeneXpert® for *C. trachomatis, N. gonorrhoeae,* duplex *C. trachomatis* and *N. gonorrhoeae, T. vaginalis,* HPV (Cepheid Inc.,

Sunnyvale, USA); AmpliVue® for *T. vaginalis* (Quidel Corporation, San Diego, USA); Atlas io™ for *C. trachomatis,* duplex *C. trachomatis* and *N. gonorrhoeae, T. vaginalis* (Atlas Genetics, Trowbridge, UK); Truelab™ Real Time micro PCR System for *C. trachomatis, N. gonorrhoeae* (Molbio Diagnostics Pvt. Ltd., Goa, India); Alere™-i for duplex *C. trachomatis* and *N. gonorrhoeae* (Alere Inc., Waltham USA); GeneXpert® Omni for duplex *C. trachomatis* and *N. gonorrhoeae*, HPV (Cepheid Inc., Sunnyvale, USA); Cobas® Liat Analyser (Roche, Basel, Switzerland); RT CPA *C. trachomatis* (Ustar Biotechnologies, Hangzhou, China); PanNAT® (Micronics, Inc., Portsmith, USA).

Figure 8: **Point-of-care tests for dual syphilis and HIV diagnosis that are available. Source: updated from reference[325]** Standard Diagnostics (SD) Bioline HIV/Syphilis Duo Rapid Test (Alere, Waltham USA)/(Standard Diagnostics, Republic of Korea); DDP ®HIV-Syphilis Assay (Chembio Diagnostic Systems, Inc., Medford, USA); Multiplo Rapid TP/HIV Antibody test (MedMira, Inc., Halifax, Canada); INSTI Combined HIV/Syphilis test (Biolytical Laboratories Inc., Richmond, Canada); mChip Assay (Junco Labs, Columbia University, New York, USA in collaboration with OPKO Health, Inc., Miami, USA).

Figure 9A: **Notifications of infectious syphilis 1950-2015 by sex and male:female ratio in England and Wales. Source: Public Health England.**

Figure 9B: **Primary and Secondary Syphilis in the US 1995-2015 by sex and male:female ratio in United States. Source: Centres for Disease Control and Prevention.**

Figure 10: **Notifications of HIV, syphilis (primary, secondary, early latent), gonorrhoea and chlamydia, 1996-2015 in men who have sex with men, England. Source:** 2001-2015, Public Health England (https://www.gov.uk/government/statistics/hiv-annual-data-tables), 2000 and earlier, National Archive (http://webarchive.nationalarchives.gov.uk/). cART, combination antiretroviral therapy; cPEP, combination post-exposure prophylaxis; Swiss statement; TasP, treatment as prevention; PROUD results made public.

Figure 11: **Condom use for anal sex among men who have sex with men in Sydney, Australia 1997-2016. Source: Gay Community Periodic Survey**

Figure 12: **Percentage of tests positive for HIV, primary and secondary syphilis and gonorrhoea, 2005-2014, and mean number of sexual partners in last three months, 2008-2013, San Francisco, USA. Source: San Francisco Department of Health.**

Contributors

Each group of authors takes responsibility for the text and views expressed in their individual sections. CKF conceived the *Commission* and coordinated its preparation. CSB wrote the executive summary together with MU and CKF. MU and CSB wrote the introduction; JSH and NL wrote Part 1; MU wrote Part 2; CSB, JAS and JMM wrote Part 3; SCF, RWP and DM wrote Part 4; HJCV, GJBS, EH, SSP, CKF and NL wrote Part 5; CKF wrote the call for action. NL, CSB, CKF and MU were involved in editing the final *Commission.* All authors approved the final manuscript.

Declaration of interests

We declare that we have no conflicts of interest.

Acknowledgments

We are grateful to Glenda Fehler and Susanne Jacobsson for their help in the preparation of the final document.

Antimicrobial (other names)	**Class**	**Mode of action**	**Bacterial target (known resistance mutations)**	***In vitro* activity against *Neisseria gonorrhoeae* (MIC range/MIC_{50}/MIC_{90} (mg/L))**	**Phase of clinical trial (aimed size)**	**Dose**	**Comparator**	**Adverse effects**
Solithromycin (CEM-101)	Fluoroketolide	Binds to the 50S ribosomal subunit, inhibiting protein synthesis	23S rRNA (A2059G in 23S rRNA alleles, overexpressed MtrCDE increases MIC[202,457])	0·001-32/0·064-0·125/0·125-0·25[202,210]	Phase 3 (300 participants)	1 g×1 p.o.	Ceftriaxone 500 mg×1 IM PLUS Azithromycin 1 g×1 p.o.	Diarrhoea, nausea and fatigue/asthenia[a]
Zoliflodacin (AZD0914, ETX0914)	Spiropyrimidinetrione	DNA biosynthesis inhibition and accumulation of double-strand cleavages	DNA gyrase and Topoisomerase IV? (D429N, D429A, and K450T in GyrB,[197,201] overexpressed MtrCDE increases MIC[201])	≤0·002-0·25/0·064-0·125/0·125-0·25[206,211,215,216]	Phase 2 (180 participants)	2 g×1 p.o. or 3 g×1 p.o.	Ceftriaxone 500 mg×1 IM	Transient dysgeusia, mild headache
Gepotidacin (GSK2140944)	Topoisomerase II inhibitor	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)	≤0·015-1/0·25/0·5[213]	Phase 2 (100 participants)	1·5 g×1 p.o. or 3 g×1 p.o.	-	Data not available

[a]Adverse events observed in ≥10% of patients using solithromycin 1 g×1 in published Phase 2 trial. Most nausea and vomiting appeared ≥1 hour after ingestion of solithromycin, which indicates that the drug was already absorbed.[203]

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

- Comprehensive case management: primary prevention (e.g. public health campaigns, sexual education, behavioural counselling, condom use), screening (where feasible, effective and cost-effective), early diagnosis, treatment (including test of cure); partner notification and treatment; reporting and epidemiological surveillance, to reduce the global burden of urogenital and extragenital gonorrhoea;
- Strict adherence to international/national evidence-based prevention and management guidelines: including introduction of dual antimicrobial therapy where up-to-date, local, and high-quality AMR data do not support other therapy;
- Enhanced focus on prevention, early diagnosis (screening of high-risk groups, e.g., men who have sex with men (MSM) 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 AMR;[157]
- Enhanced testing and appropriate use of nucleic acid amplification tests (NAATs) but maintain (and strengthen in some settings) capacity for culture and AMR testing;
- Effective drug regulations, prescription policies, and increased awareness on correct use of antimicrobials;
- Monitoring, early detection and follow-up of failures with recommended treatment; using standard case definition and protocols for verification, management of failure and reporting;
- Strengthened quality assured surveillance of gonorrhoea, antimicrobial use/misuse and AMR globally (including international rapid communication networks);
- Capacity building to establish regional networks of laboratories to perform quality-assured gonococcal culture and AMR 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),[152,153,158,458] a gonococcal vaccine,[150] rapid molecular methods for predicting AMR (for AMR surveillance but ideally also to inform individualized treatment),[190-192] rapid point of care tests for diagnosis of gonorrhoea (ideally with combined prediction of AMR);[190,191] ideal phylogenomics of gonococci and their AMR (also in non-cultured samples);[159,457,459-464] and appropriate models for pharmacokinetics/ pharmacodynamics (urogenital and extragenital sites) and prediction of AMR induction/selection, evolution and biological fitness.

Table 2: **Actions to control the emergence, spread and impact of antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* (public and private sectors)**

Organism, Test	Sample type	Sensitivity (%)	Specificity (%)
***Chlamydia trachomatis*[a]**			
Biostar OIA Chlamydia test[b]	Endocervical swabs	59·4-73·8	98·4-100
Clearview Chlamydial test[b]	Endocervical swabs	49·7	97·9
	Vaginal swabs	32·8	99·2
Quick Vue Chlamydia rapid test[b]	Endocervical swabs	25·0-65·0	100
	Vaginal swabs	83·5	98·9
aQcare Chlamydia TRF[c]	Endocervical and urethral swabs	93·8	96·8
	Urine	88·2	94·7
Chlamydial Rapid Test, Diagnostics for the Real World[c]	Male urine	41·4	89·0
	Vaginal swabs	39·4-74·2	94·4-96·8
ACON Chlamydia Rapid Test Device[c]	Vaginal swabs	66·7	91·3
	Endocervical swabs	22·7-30·5	99·8-100
	Male urine	43·8	98·3
GeneXpert CT/NG[b]	Endocervical swabs	97·4	99·6
	Vaginal swabs	98·7	99·4
	Female urine	97·6	99·8
	Male urine	97·8	99·9
***Neisseria gonorrhoeae*[a]**			
Biostar OIA GC Test[b]	Endocervical swabs	60·0	89·9
	Urine	100	93·0-98·0
ACON Duo CT/NG[c]	Endocervical swabs	12·5	99·8
GeneXpert CT/NG[b]	Endocervical swabs	100	100
	Vaginal swabs	100	99·9
	Female urine	95·6	99·9
	Male urine	98·9	99·9
Trichomonas vaginalis			
OSOM TV rapid test[b]	Vaginal swabs	83·3-90	98·8-100

GeneXpert TV[d]	Vaginal swabs	95·0-95·6	95·7-100
Affirm VPIII microbial identification test[a,b]	Vaginal swabs	46·3	100
***Treponema pallidum* (syphilis)**			
Alere Determine Syphilis TP[e]	Whole blood/serum/plasma	59·6-100	95·7-100
Omega VisiTect Syphilis[e]	Whole blood/serum/ plasma	72·7-98·2	98·1-100
Qualpro Syphicheck-WB[e]	Whole blood/serum/ plasma	64-97·6	98·4-99·7
SD Bioline Syphilis 3.0[e]	Whole blood/ serum/plasma	85.7-100	95.5-99.4
Span Diagnostics Crystal TP Syphilis Test	Whole blood/ serum/plasma	Not available	Not available
CTK Biotech OnSite™ Syphilis Ab combo Rapid	Whole blood	Not available	Not available
Diagnostics Direct Syphilis Health Check™	Whole blood/ serum/plasma	Not available	Not available
Uni-Gold™ syphilis Treponemal	Whole blood/ serum/plasma	Not available	Not available
Dual Path Platform (DDP®) Syphilis Test[f] (Chembio Diagnostic Systems, Inc)	Treponemal antibody	90·1-98·2	91·2-98·0
	Non-Treponemal	80·6-98·2	89·4
Dual HIV/TP Syphilis			
SD Bioline HIV/Syphilis Duo Rapid Test[g] (Alere/Standard Diagnostics, Inc)	Whole blood/ serum/plasma	97·9-99·0	99·0-100
	Whole blood/ serum/plasma	93·0-99·6	99·1-100
DPP® HIV-Syphilis Assay[g] (Chembio Diagnostic Systems, Inc)	Whole blood/ serum/plasma	98·9	97·9-99·6
	Whole blood/ serum/plasma	95·3	97·0-99·6
Multiplo Rapid TP/HIV Antibody Test[g] (MedMira, Inc)	Whole blood/ serum/plasma	97·9	94·2-99·5
	Whole blood/ serum/plasma	94·1	94·2-99·1
INSTI™ HIV/Syphilis Multiplex Test (Biolytical Laboratories, Inc)	Whole blood/ serum/plasma	Not available	Not available
	Whole blood/ serum/plasma	Not available	Not available
OnSite™ HIV/Syphilis Ab Combo Rapid Test (CTK Biotech)	Whole blood/ serum/plasma	Not available	Not available
	Whole blood/ serum/plasma	Not available	Not available

a= Sensitivity and specificity compared with nucleic acid amplification tests; b= Data taken from[352]; c= Data taken from[359,360]; d = Data taken from[353]; e= Data taken from[350]; f=Data taken from[365]; g= Data taken from[325]

Table 3: **Point-of-care tests for sexually transmitted infections currently on the market with available sensitivities and specificities**

Table 4: **Call to Action**

Policy Priorities	**Research Priorities**
Ensure accessible health care for early treatment of symptomatic STIs	Develop measures of 'access to health care services' and set minimum bench marks
Improve health outcomes from chlamydia, such as pelvic inflammatory disease by better case management	Robust trials of strategies to increase chlamydia re-testing and partner notification and treatment
Enhance surveillance of pelvic inflammatory disease, ectopic pregnancy and infertility	Develop non-invasive tools to detect upper genital tract infection and disease
Develop and implement effective partner treatment	Robust trials of innovative partner treatment strategies with biological outcomes (e.g. reinfection rates)
New antimicrobials and/or other treatments for gonorrhoea	Fund research into new antimicrobials and treatments for gonorrhoea
Reduce gonorrhoea prevalence	Identify key drivers of gonorrhoea prevalence and effective interventions to reduce it
Develop treatments for bacterial vaginosis (BV) with low relapse rates	Explore new agents that target the biofilm; re-evaluate the role of treatment of male sex partners
Evaluate partner treatment for BV	New partner treatment trials and identify the transmissible agent(s) responsible for BV
Ensure 100% of pregnant women are screened and treated for syphilis at the first prenatal visit	Increase implementation research to strengthen health systems to effectively identify and manage syphilis using simple and rapid POC tests

Point-of-care (POC) tests for STIs	Identify the key health systems required for effective use of POC tests, Develop new POC tests for STIs, Evaluate the use of POC tests for STIs
Pre-exposure prophylaxis (PrEP) and STI testing	Identify the effect that frequent STI screening has on STI incidence
Vaccines for STIs[150]	Undertake the laboratory and subsequent clinical research necessary for successful vaccines

[150]Footnote. The elements of this panel assume that other elements of an effective STI control program 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, accurate surveillance programmes.

Supplementary Table 1: **Explanatory notes on hospital discharge rates presented in Figure 5.**[122]

Country	Source	Comment
Australia	Australian Institute of Health and Welfare Hospital Morbidity Database	Reference period: 1 July to 30 June. Coverage: - Data are derived using AIHW analysis of the AIHW National Hospital Morbidity Database (NHMD). Please see http://meteor.aihw.gov.au/content/index.phtml/itemId/611030 for the data quality statement for the 2013–14 NHMD. For each reference year, these data are based on hospital separations from 1 July to 30 June. - Data are for principal diagnosis, recorded using the ICD-9-CM from 1993-94 to 1997-98, and recording using the ICD-10-AM (Australian modification) from 1998-99. For 2013-14, principal diagnoses were recorded using the ICD-10-AM 8th edition. - Data presented are based on overnight admitted patient separations. They exclude same-day separations.
Austria	Statistics Austria, Hospital discharge database; raw data: Austrian Ministry of Health	Reference period: 31 December. - *Coverage by hospital type*: The Austrian hospital discharge database covers all inpatient institutions classifiable as HP.1 according to SHA/OECD. - *Missing records*: The database includes all inpatient discharges and day cases: - Day cases are all cases admitted and discharged on the same day (before midnight). - Inpatients include discharges to home, other inpatient-institutions and deaths in hospitals. The Austrian hospital discharge database is based on the Austrian DRG system (DRG =

Country	Source	Comment
		diagnosis related group).
Belgium	The Federal Public Service of Health, Food Chain Safety and Environment, Directorate 1 -Minimal Clinical Data.	Reference period: during the year. Coverage: - The Federal Public Service of Health, DG 1 "Organisation of health institutions" is responsible for the registration of the Minimal Hospital Data. - Hospital days for inpatients concern only acute admissions in acute hospitals (with at least 1 overnight stay in the hospital). - Patient data in psychiatric hospitals are NOT included. - Long lasting stays are excluded (more than 6 months or 184 days). - Deceased patients are included.
Canada	Statistics Canada, *Hospital Morbidity Database*, 1980/81 to 1993/94. - Canadian Institute for Health Information, *Discharge Abstract Database* and *Hospital Morbidity Database* starting in 1994/95 (the Hospital Morbidity Database was transferred from Statistics Canada to the Canadian Institute for Health Information in 1994/95), *Ontario Mental Health Reporting System* starting in 2006/07 until 2012/13, and *Hospital Mental Health Database* starting in 2013/14.	Reference period: April 1 to March 31st Coverage: - Data are calculated on a fiscal year basis (April 1st to March 31st). All ten Canadian provinces are included for all years. In 1994/95, one territory is included while for 1995/96 to 2012/13 all territories are included, except in 2002/03 when the territory of Nunavut is excluded. - Separations in Canada include discharges both alive and dead for the condition most responsible for the length of stay. - Data are for acute care hospitals only, except for the data on mental and behavioural disorders which include psychiatric hospitals starting in 2013/14. - The data are reported as per ICD-9 until 2000/01. In 2001/02, five provinces and one territory provided their data for the first time, according to ICD-10-CA; in 2002/03 two

Country	Source	Comment
		more provinces and two more territories reported according to ICD-10-CA. In 2003/04, only Manitoba and Quebec did not submit their data according to ICD-10-CA. In 2004/05, Manitoba adopted the ICD-10-CA and Quebec did the same in 2006/07. - The total count of separations in provinces that still reported according to ICD-9, for each diagnostic category was added to the count for the provinces and territories that reported according to ICD-10-CA.
Chile	Ministry of Health (MINSAL), Department of Health Statistics and Information (DEIS).	Hospital discharges from 2001-2013 Coverage: - Data coverage is nationwide. Data include both public and private sectors. - Data include same-day separations and deaths. - Annual periodicity. Data are automatically collected monthly from the health establishments' information systems and validated and published by the Department of Health Statistics and Information (DEIS).
Estonia	Ministry of Social Affairs, Department of Health Information and Analysis, routinely collected aggregate hospital statistics. - Since 1st January 2008: National Institute for Health Development, Department of Health Statistics	Reference period: Calendar year. Coverage: - *Coverage by hospital type*: All hospitals (HP.1), public and private, are covered. - ICD-10 is used for data collection. - *Inpatient cases*: Data on discharges are collected in two ways: 1) Discharges according to ICD-10 main chapters by sex and age groups include deceased patients but not bed-days; 2) Hospital discharges by selected ICD-10 subgroups/single diagnoses and corresponding bed-days.

Country	Source	Comment
France	Ministère du Travail, de l'Emploi et de la Santé, Drees (Direction de la recherche, des études, de l'évaluation et des statistiques) - BESP; National databases from the "programme de médicalisation des systems d'information (PMSI)" (since 1997).	Reference period: Calendar year. Coverage: - French data cover residents of Metropolitan France and/or overseas Départements (Guadeloupe, Martinique, French Guyana and Réunion Island but not Mayotte), who were hospitalised in the public and private hospitals of the same area. They refer to hospitalisations (and not to patients) in the units delivering acute care in medicine, medical specialties, surgery, surgical specialties, gynecology and obstetrics (MCO). Database contains all inpatient hospitalisations, including iterative care, and ambulatory cases except haemodialysis, chemotherapy, radiotherapy and other iterative treatments.
Ireland	The data presented are derived from the HIPE (Hospital In-Patient Enquiry) data set, which records data on discharges from all publicly funded acute hospitals. HIPE is operated by the Healthcare Pricing Office (www.hpo.ie).	Reference period: Data are based on the year of discharge. Coverage: *Coverage by hospital type* - HIPE data covers all inpatients and day cases receiving curative and rehabilitative care in publicly funded acute hospitals in the State. Data for 1995 to 2004 were classified using ICD-9-CM. All HIPE discharges from 2005 are now coded using ICD-10-AM (The Australian Modification of ICD-10 incorporating the Australian Classification of Health Interventions). Although the ISHMT is used for categorising diagnoses, there are still some minor changes in the classification of diagnoses. The HMT shortlist is based on ICD-9 and ICD-10 codes, but the classification used for diagnoses in HIPE was changed from ICD-9-CM to ICD-10-AM including the

Country	Source	Comment
		Australian Coding Standards.
Slovenia	National Institute of Public Health, Slovenia; National Hospital Health Care Statistics Database.	Reference period: During the year. Coverage: - *Coverage by hospital type*: data include all private and public hospitals, all types (general and university - HP.1.1, psychiatric - HP.1.2, and specialty hospitals - HP.1.3). - Data include: - Inpatient discharges - Day-cases discharges - All patients (including uninsured, foreigners) - Long duration stays in hospitals - Palliative care in hospitals - Healthy newborn babies (since 2003) *Definition of main diagnosis*: the main diagnosis is defined as that which was responsible for the patient's admission at the hospital, which best reflects the main reason for admission, or that which is the main reason for treatment. If there is a multiple-episode case the main diagnosis is taken from the first episode.
Switzerland	FSO Federal Statistical Office, Neuchâtel. Medical Statistics of Hospitals, 2002 and following years.	Reference period: Annual census. Coverage: - *Coverage by hospital type*: The data cover all inpatient institutions (public and private hospitals) which are classifiable as HP.1 providers. However, military and prison hospitals are not included. - *Definition of main diagnosis*: The main diagnosis is defined as the condition

Country	Source	Comment
		diagnosed at the end of the hospitalisation period, primarily responsible for the patient's need for treatment or examination at the hospital.
United Kingdom	Data have been aggregated by the NHS Information Centre for Health and Social Care from the following sources: - *England*: Hospital Episode Statistics (HES); Inpatients, Health & Social Care Information Centre (HSCIC), England. http://www.hscic.gov.uk. - *Wales*: Patient Episode Database for Wales (PEDW), NHS Wales Informatics Service (NWIS). http://www.statswales.wales.gov.uk/index.htm. - *Scotland*: Information Services Division (ISD), National Health Service Scotland (SMR01 records). http://www.isdscotland.org/Health-Topics/Hospital-Care/Data_Sources_and_Clinical_Coding.doc. - *Northern Ireland*: Hospital Inpatient System (HIS), The Department for Health, Social Services and Public Safety in Northern Ireland (DHSSPSNI). http://www.dhsspsni.gov.uk/hospital-activity.	Reference period: - *England, Wales and Scotland*: Data is based on Financial Discharge Years 1st April to 31st March. - *Northern Ireland*: Data have been tabled by calendar year. - Includes records for discharge dates occurring in the reference year, regardless of admission date. Coverage: - *Coverage by hospital type*: □ *England*: Inpatient data cover activity in English NHS Hospitals and English NHS commissioned activity in the independent sector. □ *Scotland*: Data collected on discharges from non-obstetric and non-psychiatric hospitals (SMR01) in Scotland. Only patients treated as inpatients or day cases are included. The specialty of geriatric long stay is excluded. □ *Wales*: All NHS commissioned data carried out in private sector hospitals is included. □ *Northern Ireland*: Inpatient data cover activity in Northern Ireland HSC hospitals including independent sector activity carried out in HSC hospitals.
USA	Centers for Disease Control and Prevention/National Center for Health Statistics/National Hospital Discharge	Coverage: - National representative sample of the U.S.

Country	Source	Comment
	Survey Annual Summary, Advance Data from Vital and Health Statistics Summary (published annually). Vital and Health Statistics, Series 13, completed by unpublished tables. http://www.cdc.gov/nchs/about/major/hdasd/nhds.htm.	civilian non-institutionalised population. - The National Hospital Discharge Survey (NHDS) defines a hospital discharge as the formal release of an inpatient by a hospital, terminating of the period of hospitalisation (including stays of 0 nights) by death or by disposition to the place of residence, nursing home, or another hospital; survey of discharges from non-federal hospitals in which the Average Length of Stay is less than 30 days. - The National Hospital Discharge Survey (NHDS) is a continuing nationwide sample survey of short-stay hospitals in the United States. The scope of NHDS encompasses patients discharged from non-institutional hospitals located in the 50 States and the District of Columbia, excluding military and Department of Veteran's Affairs hospitals. - All U.S. discharges were coded to the International Classification of Diseases, Ninth Revision (ICD-9). - A hospital discharge is the completion of any continuous period of stay in a hospital as an inpatient.

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