

# 1 Sexually Transmitted Infections: Challenges Ahead

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## 44 **Executive Summary**

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

67

## 68 **Introduction**

69 Sexually transmitted infections (STIs) are amongst the most common acute conditions  
70 worldwide.<sup>1</sup> The World Health Organization (WHO) estimated that there were 357 million  
71 new cases of four common curable STIs; trichomoniasis (143 million cases), chlamydia (131  
72 million), gonorrhoea (78 million), and syphilis (5.6 million) globally in 2012 (Figure 1).<sup>2</sup> In  
73 addition, there are alarming increases in antimicrobial resistance (AMR) in *Neisseria*  
74 *gonorrhoeae* and *Mycoplasma genitalium*.<sup>3</sup> Although most STIs are not usually fatal, they  
75 result in a significant burden of disease.<sup>1</sup> The complications of curable STIs include pelvic  
76 inflammatory disease (PID), ectopic pregnancy, infertility, chronic pelvic pain, seronegative  
77 arthropathy, neurological and cardiovascular disease;<sup>4</sup> STIs in pregnancy can cause foetal or  
78 neonatal death, premature delivery, neonatal encephalitis, eye infections and pneumonia;<sup>4</sup> and  
79 STIs increase the infectiousness of and susceptibility to HIV.<sup>5</sup> Despite this burden, STIs  
80 remain a neglected field for clinical and public health practice and for research.<sup>6</sup> People with  
81 STIs experience stigma, STIs disproportionately affect marginalised groups such as sex  
82 workers and men who have sex with men (MSM) and condemnatory moral attitudes towards  
83 STIs result in unwillingness to prioritise STI control policies.<sup>6-8</sup> In this *Commission of Lancet*  
84 *Infectious Diseases*, we have selected five key issues for STI control that face major  
85 challenges globally and for which action is imperative.

86 This *Commission* addresses current challenges for research, practice and policy that we  
87 selected because they are common, are important global health priorities, or because new  
88 evidence is emerging in the area. Of necessity, this *Commission* has excluded important  
89 subjects. *M. genitalium* was not included, despite the rapid emergence of resistance to both  
90 first and second line treatments, but *M. genitalium* AMR and clinical management options  
91 have been recently reviewed elsewhere.<sup>3,9</sup> We also omitted herpes simplex virus, for which  
92 vaccine development is progressing rapidly,<sup>10</sup> human papillomavirus (HPV), for which

93 vaccination is highly effective,<sup>11</sup> but for which implementation is now the key challenge, and  
94 *Trichomonas vaginalis* infections because there are no new strategies for treatment or control.  
95 Partner notification is an essential part of the management of most STIs and is mentioned in  
96 several parts of the *Commission*. We use the term to include all processes involved in  
97 informing the sex partners or needle-sharing contacts of persons with STIs of their potential  
98 exposure to an infectious disease and ensuring their evaluation and/or treatment.<sup>4</sup> We consider  
99 partner management, partner services and partner information to be synonymous.

100 Part 1 of the *Commission* addresses *Chlamydia trachomatis*, commonly known as  
101 chlamydia. Chlamydia is the most common bacterial STI globally<sup>1</sup> and causes serious  
102 reproductive tract complications in women.<sup>12</sup> Yet, 20 years after the first randomised  
103 controlled clinical trial (RCT) of an intervention to reduce its complications,<sup>13</sup> we remain  
104 unsure how to reduce its prevalence and impact on society. Indeed, the most recent RCT of a  
105 screening intervention did not find a marked effect on prevalence despite a substantial  
106 increase in the proportion of the target population that received screening.<sup>14</sup> *Hocking and Low*  
107 assess the latest research about screening, treatment and management of chlamydia and  
108 suggest a way forward to define chlamydia control priorities for the future.

109 In Part 2 of the *Commission*, *Unemo* addresses the globally recognised threat of the  
110 emergence and spread of AMR in *N. gonorrhoeae*. This organism has become resistant to  
111 virtually all antibiotics that have been used to treat it since sulphonamides were first used in  
112 the 1930s. The first clinical failure using dual therapy with ceftriaxone and azithromycin was  
113 verified in 2015.<sup>15</sup> For this reason, we focus on current and future treatment strategies,  
114 including three novel antimicrobials that are being evaluated in phase 2 or 3 RCTs. We also  
115 report on novel strategies that aim to reduce the incidence and prevalence of gonorrhoea in  
116 MSM, which should also reduce the probability of AMR developing. Ultimately, the  
117 development of vaccines against both *N. gonorrhoeae* and *C. trachomatis* are likely to be the  
118 only sustainable solutions to control these infections.<sup>10</sup>

119 The *Commission* chose to include bacterial vaginosis (BV) for three main reasons, even  
120 though it is not considered a traditional STI. First, an accumulating body of epidemiological  
121 and microbiological evidence suggests that sexual transmission is integral to its  
122 pathogenesis.<sup>16,17</sup> Second, BV has been neglected, although it is the most prevalent urogenital  
123 disorder amongst women of reproductive age worldwide and is associated with serious  
124 reproductive and obstetric sequelae, including preterm delivery and increased risk of STI and  
125 HIV acquisition and HIV transmission.<sup>18,19</sup> Third, treatment failure rates are unacceptably  
126 high; more than half of women have a recurrence after recommended therapy but neither BV  
127 treatment efficacy nor outcomes have improved for decades.<sup>20</sup> In Part 3 of the *Commission*,  
128 *Bradshaw* and colleagues summarise the research implicating sexual transmission and  
129 propose combination approaches to management that include antimicrobials, biofilm-  
130 disrupting agents and partner treatment.

131 Part 4 of the *Commission* addresses STIs in low and middle income settings where more  
132 than 90% of curable STIs and almost all of the global burden of STIs occur. *Francis* and  
133 colleagues review key strategies for STI case management and control, including syndromic  
134 management, presumptive periodic treatment and partner notification. But they focus on rapid  
135 diagnostic tests and point of care (POC) tests within a published framework; being affordable,  
136 sensitive, specific, user-friendly, rapid and robust, equipment-free and delivered to end-users  
137 (ASSURED).<sup>21</sup> POC tests have considerable implications for STI control in high-income  
138 settings too, but their potential benefits are greatest in resource constrained settings where  
139 healthcare infrastructure is most limited.

140 Part 5 of the *Commission* discusses epidemics of STIs in MSM in high income settings in  
141 the context of three biomedical treatment strategies that use antiretroviral therapies (ART) to  
142 prevent HIV infection. Two strategies are prophylactic treatments to reduce susceptibility in  
143 HIV-uninfected individuals: post-exposure prophylaxis (PEP) given after specific high risk  
144 exposures and pre-exposure prophylaxis (PrEP), given to HIV-uninfected individuals for

145 continuous periods of high risk exposure to prevent acquisition of HIV. The third strategy,  
146 known as treatment as prevention (TasP), reduces HIV infectiousness and involves starting  
147 ART as soon as HIV infection is diagnosed to prevent transmission to uninfected partners.  
148 These interventions have all been suggested to increase risky sexual behaviours through risk  
149 compensation and to result in increased transmission of STIs.<sup>22</sup> *de Vries* and colleagues  
150 review the evidence linking PEP, TasP and PrEP strategies to risk compensation and  
151 increasing STI rates.

152 The *Commission* ends with a ‘call to action’, in which we ask policy makers to rise to the  
153 public health challenge of effective STI control. Our call includes a broad suite of approaches  
154 that are often shared across infections or risk groups. They involve the optimisation of:  
155 surveillance for behaviours, infections and AMR; access to health services, early diagnosis,  
156 appropriate treatment and partner notification, and also intensified research into: rapid POC  
157 tests to detect both STIs and AMR; novel antimicrobials and/or treatment approaches; and the  
158 understanding of STI transmission or pathogenesis.

159

## 160 **Part 1. Chlamydia control – what should we do?**

161 Twenty years after the publication of the first RCT of an intervention to reduce the incidence  
162 of PID by screening for asymptomatic chlamydia infection in young women,<sup>13</sup> we still need to  
163 ask, “what should we do?” about chlamydia control. Three linked factors make this an  
164 important question. First, *C. trachomatis* remains the most commonly diagnosed bacterial  
165 STI, despite chlamydia testing recommendations that have been in place for years in several  
166 high income countries.<sup>23-27</sup> Second, whilst infection might be asymptomatic in over 80% of  
167 cases,<sup>28,29</sup> chlamydia can cause tissue damage, particularly in the female reproductive tract  
168 where ascending infection can cause PID, which contributes to chronic pelvic pain, ectopic  
169 pregnancy and tubal factor infertility (Figure 2).<sup>12</sup> Third, technological advances make

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

174 Chlamydia control requires “a broad range of deliberate sustained activities that aim to  
175 reduce the incidence and prevalence of chlamydia and the incidence of reproductive tract  
176 complications”.<sup>31</sup> The general definition of infectious disease control involves agreement on  
177 locally acceptable levels,<sup>32</sup> and makes a distinction between the infection and the disease(s)  
178 that it causes. But an acceptable level of genital chlamydia infection or chlamydia-associated  
179 PID, ectopic pregnancy or tubal factor infertility has not been defined in any setting. The  
180 range of chlamydia control activities is broad (Figure 3) and countries should have a  
181 chlamydia control strategy that defines primary and secondary prevention activities and  
182 systems for monitoring and evaluation.<sup>31</sup> Secondary prevention starts with case detection and  
183 management to prevent complications; case management includes history-taking and clinical  
184 examination, diagnostic tests, treatment, partner notifications, health promotion advice,  
185 follow-ups and surveillance.<sup>31</sup> Over time, particularly in high income countries, discussions  
186 about chlamydia control have come to focus more on screening for asymptomatic infections  
187 in young sexually active adults, rather than clinical case management of infection or PID.

188 The WHO Global Health Sector Strategy on STIs 2016-2021 states that, “because best  
189 strategies to control and measure chlamydia infections are still to be defined, further research  
190 and cost-effectiveness analyses are to be encouraged”(p17).<sup>33</sup> With this in mind, in this  
191 section of the *Commission* we first outline the global epidemiology of genital chlamydia and  
192 its complications. We review evidence about current chlamydia control activities and the  
193 effects of screening interventions on chlamydia prevalence and PID. We then discuss the  
194 challenges ahead for chlamydia control and question whether we should shift from an  
195 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.<sup>2</sup> In high income countries, chlamydia is most common in young  
203 heterosexual adults aged  $\leq 26$  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.<sup>34</sup> 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.<sup>35-37</sup> 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,<sup>38-44</sup> prevalence is similar in women and men aged  $\leq 26$   
210 years, and appears similar in countries that promote widespread chlamydia testing (e.g. USA  
211 and England)<sup>44,45</sup> and those without recommendations (e.g. Croatia and Slovenia) (Figure  
212 4).<sup>40,46</sup> Within countries, higher chlamydia prevalence is associated with social disadvantage<sup>47</sup>  
213 and is higher in people from minority ethnic groups.<sup>43,48</sup>

214 In low and middle income countries, population-based surveys of chlamydia prevalence  
215 are also very uncommon.<sup>49-52</sup> 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).<sup>2</sup> The lowest estimate was in women in India ( $< 1\%$ )<sup>50</sup> and the highest in  
218 Papua New Guinea, which estimated a prevalence of 45% among women  $\leq 26$  years.<sup>51</sup> 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.<sup>53,54</sup> Whilst we found no

221 nationally representative surveys in South Africa, chlamydia prevalence amongst pregnant  
222 women was as high<sup>55</sup> as that found in the South Pacific Islands. Reasons for regional  
223 variations have not been examined in detail. In addition to study design issues, social, cultural  
224 and economic conditions, differences in sexual practices, gender inequality and circumcision  
225 practices might play a role.<sup>2,53,56</sup>

226

### 227 **Global epidemiology of PID and reproductive tract morbidity**

228 Compared with international data about chlamydia infection, very little is known about  
229 international variations in the incidence and prevalence of PID and other reproductive tract  
230 morbidity caused by chlamydia. WHO estimated that chlamydial infections caused a total of  
231 1.43 million disability-adjusted life years (DALYs) in 2012, most in low and middle income  
232 countries (36% African Region, 25% South East Asia Region).<sup>57</sup>

233 The rate of hospitalisation for PID from any cause varies from around 37 to 194 per  
234 100,000 women aged 15-39 years in different countries.<sup>58</sup> Chlamydia infection is found in  
235 association with about 20% of PID cases; one study at a large sexual health clinic in Australia  
236 found no causative organism in over 60% of PID cases.<sup>59</sup> A major challenge is the lack of  
237 consensus about criteria for the diagnosis of upper genital tract chlamydial disease and the  
238 lack of non-invasive tests including new radiological imaging. PID is usually diagnosed based  
239 on lower abdominal and cervical signs and symptoms and diagnostic criteria lack sensitivity  
240 and specificity.<sup>27</sup>

241

### 242 **Natural history of *Chlamydia trachomatis* and reproductive complications**

243 The host immune response to chlamydia strongly influences susceptibility, clearance, the  
244 probability of upper genital tract pathogenesis and, ultimately, the effectiveness of

245 interventions.<sup>60,61</sup> Untreated infection that resolves spontaneously might confer some  
246 immunity against further infection,<sup>62</sup> but the duration of immunity is unclear. Antimicrobial  
247 treatment, on the other hand, might reduce the immune response and once treated, people  
248 become susceptible to infection again, increasing their risk of repeat chlamydia infection, the  
249 “arrested immunity hypothesis”.<sup>63,64</sup> Repeat chlamydia infections after treatment are common;  
250 in cohort studies, over 20% of young women enrolled from general practice acquired a repeat  
251 infection within 12 months of treatment.<sup>65,66</sup>

252 Several reviews have examined the risk of sequelae following infection,<sup>12,67-70</sup> but  
253 estimates are limited by diagnostic challenges. Mathematical syntheses of evidence from  
254 different types of studies estimate that the probability of clinical PID following infection with  
255 chlamydia is about 16% (95% credible interval 6% to 25%)<sup>71</sup> and the probability of tubal  
256 factor infertility in women who have ever had a chlamydia infection is about 1% (varies  
257 depending on age).<sup>72</sup> These models also estimate that the proportion of PID, ectopic  
258 pregnancy and tubal factor infertility attributable to chlamydia is 20%, 5% and 29% to 45%,  
259 respectively.<sup>73</sup> The risk of reproductive tract morbidity in women might increase with  
260 repeated infection.<sup>74-76</sup> It is unclear, however, whether the increase in risk is due to an increase  
261 in the cumulative infection time or a higher probability of progression with each subsequent  
262 infection.<sup>12</sup> Ascertainment bias in diagnosis might also explain the observations if physicians  
263 are more likely to test for chlamydia in previously infected women who attend with lower  
264 abdominal pain, or to assign the diagnosis of PID to a woman diagnosed with chlamydia.

265 We do not know how or when chlamydia ascends to the upper genital tract, but there are  
266 two key hypotheses.<sup>61</sup> The cellular paradigm assumes that actively infected epithelial cells  
267 play the key role and that chemokines secreted by these cells damage the tissues directly. The  
268 immunological paradigm assumes that tissue damage occurs due to T cell responses involved  
269 in clearing infection after repeat or persistent infection. If the cellular paradigm is the main  
270 driver of chlamydia pathogenesis, then identifying and treating infections before they ascend

271 should be the main focus of control programmes. If the immunological paradigm is more  
272 important, then prevention of repeat infections should be prioritised.<sup>60</sup>

273 The timing of ascending infection will also affect the impact of a screening intervention. If  
274 chlamydia ascends the canal shortly after infection causing immediate tubal inflammation,  
275 annual screening and treatment will not stop tubal pathology.<sup>77</sup> A mathematical model<sup>78</sup> using  
276 data from a RCT,<sup>79</sup> found that the trial results of the effect of a single chlamydia screen on the  
277 cumulative incidence of PID up to one year later, could only be achieved if progression to  
278 PID occurred at a constant rate or at the end of infection.

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

284

### 285 **Current chlamydia control activities**

286 Case detection and management are central to chlamydia control strategy in addition to  
287 primary prevention of STIs. Clinical guidelines can include recommendations for  
288 opportunistic chlamydia testing to detect asymptomatic infection in people with specified risk  
289 factors for infection (Figure 3). Opportunistic testing can also be implemented at a population  
290 level as a screening programme. Screening programmes require infrastructure not only for  
291 chlamydia testing, but for treatment, partner notification, repeat testing, monitoring and  
292 quality control.<sup>31</sup> Several high income countries including Australia, Canada, England and the  
293 USA recommend yearly opportunistic chlamydia screening for all sexually active women or  
294 both women and men in the age groups at highest risk of infection.<sup>23-27</sup> The coverage of  
295 chlamydia testing has been used to monitor performance,<sup>85-87</sup> but none of these countries sets  
296 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.<sup>26</sup> 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.<sup>26</sup> 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.<sup>26</sup> Ongoing debate about the evidence to support  
305 chlamydia screening<sup>88-90</sup> and its cost effectiveness<sup>88</sup> 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.<sup>91</sup>

313 A systematic review of chlamydia screening interventions<sup>89</sup> found four RCTs that looked  
314 at the effects on PID incidence after a single offer of a chlamydia screening test.<sup>13,79,92,93</sup>  
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<sup>2</sup> 8%).<sup>89</sup> 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)<sup>79,92</sup> than in those at high or unclear risk of bias (RR 0.42,  
319 95% CI 0.22 to 0.83),<sup>13,93</sup> 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.<sup>94</sup>

323 Two cluster RCTs have looked at the effects of repeated rounds of chlamydia testing  
324 targeting 16 to 29 year old men and women in the general population.<sup>14,95</sup> Neither trial found a  
325 reduction in estimated prevalence. The trial in the Netherlands invited people each year by  
326 post (register-based screening) and the trial in Australia offered opportunistic testing in  
327 general practice. Chlamydia test uptake was <20% in both trials, even with individual patient  
328 reminders (Netherlands) or further support for clinicians (Australia). In Peru, a cluster RCT  
329 among female sex workers found that after four years of a multifaceted intervention,  
330 estimated prevalence was 28% lower in women in the intervention areas (RR 0.72, 95% CI  
331 0.54 to 0.98).<sup>96</sup>

332 Only one trial reported on the impact of screening on ectopic pregnancy, female infertility  
333 and epididymitis in men. The intervention involved a single offer of screening, uptake was  
334 low and outcomes did not differ between intervention and control groups.<sup>92</sup> No RCT to date  
335 has reported the effects of an intervention that offers chlamydia screening during pregnancy  
336 on pregnancy or neonatal outcomes. One RCT in the USA that compared antibiotic treatment  
337 with placebo in women with chlamydia detected at 23 to 29 weeks of gestation, found no  
338 reduction in low birth weight, preterm birth or neonatal death in intention to treat analysis.<sup>97</sup>  
339 One cluster RCT in Uganda of presumptive antibiotic treatment found reductions in low birth  
340 weight, neonatal death and ophthalmia neonatorum; the antibiotic regimen, azithromycin,  
341 cefixime and metronidazole covered several genital tract infections other than chlamydia.<sup>98</sup>

342 A review of cost-effectiveness studies found that chlamydia screening might be cost-  
343 effective at nationally accepted thresholds of cost per quality adjusted life year in certain  
344 circumstances in high income countries.<sup>88</sup> Incremental cost-effectiveness ratios are sensitive  
345 to assumptions about the epidemiology and natural history of chlamydia including the  
346 probability of developing sequelae, screening uptake, the type of model used, assumptions  
347 about quality of life and the cost of management of the sequelae.<sup>88,99</sup>

**349 Effects of chlamydia control from observational data**

350 Whilst RCTs provide data about the efficacy of chlamydia screening interventions under  
351 research conditions, surveillance, *ad hoc* surveys and routine data are used to monitor the  
352 performance of STI control strategies over time. These sources of data provide valuable  
353 information but need to be interpreted carefully, taking into account selection, measurement,  
354 ecological and response biases.

*355 Chlamydia incidence and prevalence*

356 There are no data available to monitor population-based chlamydia incidence over time. In  
357 Great Britain and the USA, population-based chlamydia prevalence surveys have been  
358 repeated during the time when chlamydia testing rates have increased. In Great Britain, two  
359 surveys ten years apart found similar estimates among women and men aged 18 to 24 years in  
360 2010-2011 (women, 3.2%, 95% CI 2.2 to 4.6%; men, 2.6%, 95% CI 1.7 to 4.0%) and in  
361 1999-2000 (women, 3.1%, 95% CI 1.8 to 5.2%; men, 2.9%, 95% CI 1.3 to 6.3%);<sup>44</sup>  
362 chlamydia test coverage increased from about 8% per year in 2008<sup>100</sup> to about 30% in  
363 2011.<sup>101</sup> In the USA, chlamydia prevalence in women aged 15-24 years was 4.1% (95% CI  
364 2.4 to 6.8%) in 1999–2000 and 3.8% (2.4 to 6.0%) in 2007–2008 with fluctuations in the  
365 years between;<sup>43</sup> chlamydia testing coverage among 16 to 24 year old women was reported to  
366 be >35% per year.<sup>85,102,103</sup> More intensive chlamydia screening in a small cohort of adolescent  
367 women in Indiana, USA did not reduce prevalence.<sup>104</sup> The women were tested every three  
368 months and treated if they had a positive chlamydia test result; at each interval around 10% of  
369 women tested were chlamydia test positive.<sup>104</sup>

370 Several factors might help explain why the estimated chlamydia prevalence in the general  
371 population does not appear to have declined during a period of increasing chlamydia testing.

372 First, the size of chlamydia prevalence surveys limits statistical precision and modest  
373 reductions cannot be ruled out. Second, chlamydia test uptake might not have been  
374 sufficiently high for long enough; mathematical modelling studies show that any level of a  
375 hypothetical chlamydia screening intervention will reduce prevalence over time, but that  
376 coverage of around 35% per year or more would be needed to achieve substantial reductions  
377 within a ten-year period.<sup>105,106</sup> Third, suboptimal case management with low levels of partner  
378 notification, antimicrobial treatment failure and an increasing incidence of repeated infection  
379 following antimicrobial treatment for chlamydia might sustain levels of prevalent infections.  
380 Fourth, it is possible that testing and treatment is reducing levels of immunity against  
381 chlamydia in the population leading to increased susceptibility to infection.<sup>64</sup> Fifth, auto-  
382 inoculation in women of cervical chlamydia infection from the rectal site has been suggested  
383 as a factor that could contribute to repeated detection of chlamydia in genital samples;<sup>107</sup>  
384 reports of rectal chlamydial infection in women have increased.<sup>108,109</sup> Finally, persistent forms  
385 of *C. trachomatis* might contribute to sustained prevalence. Chlamydia under the selective  
386 pressure of beta-lactam antibiotics,<sup>110</sup> interferon-gamma (IFN- $\gamma$ ) or deprivation of nutrients  
387 such as iron and amino acids, can enter a persistent, metabolically inactive state<sup>111,112</sup> where  
388 they are viable but semi-refractory to treatment.<sup>110,113,114</sup>

### 389 *PID and other reproductive tract complications*

390 Routine data about diagnoses on discharge from hospital have shown declining trends in PID  
391 and ectopic pregnancy during periods of increasing chlamydia testing and increasing  
392 chlamydia diagnosis rates in several countries.<sup>115-121</sup> Ecological associations between  
393 chlamydia testing and PID need careful interpretation.<sup>60</sup> Comparisons across larger numbers  
394 of countries and longer time periods show that the degree to which chlamydia control efforts  
395 account for the declining trend in PID incidence is not so clear. The Organisation for  
396 Economic Cooperation and Development (OECD) collates hospital discharge by diagnostic



397 categories for its member countries.<sup>122</sup> Figure 5 shows data for “inflammatory diseases of  
398 female pelvic organs”, which includes PID from any cause (supplement table 1). There are  
399 limitations in comparing the absolute rates between countries because of differences in how  
400 the conditions are diagnosed, investigated and coded. However, trends over time show a  
401 general decrease in the rate of discharge from hospital for inflammatory diseases of the pelvis  
402 over the last two decades in countries that have very different levels of chlamydia control  
403 activity. For example, in Belgium, Ireland and Slovenia, countries with little chlamydia  
404 testing,<sup>26</sup> hospitalisations have dropped by about 30% over the past 15 years. In countries with  
405 data from the early 1990s, the biggest declines in hospitalisations coincide with sudden sexual  
406 behaviour changes and with falls in the rates of other STIs, which are attributed to responses  
407 to the HIV pandemic.<sup>22,90,123</sup> A cross-country analysis that compared PID, ectopic pregnancy  
408 and infertility hospitalisation data<sup>58</sup> also found similar trends in high chlamydia testing  
409 countries (Denmark, New Zealand, Sweden)<sup>26,124</sup> and low testing countries (Australia,  
410 Netherlands, Switzerland)<sup>26,125</sup> from 1999 to 2008. Whilst inpatient admissions for these  
411 conditions have become less common, in countries that collect data from ambulatory and  
412 primary care settings, PID diagnoses have also fallen.

413

#### 414 **Future challenges for the control of chlamydia**

##### 415 *Shift of focus from monitoring test uptake to measuring PID incidence*

416 To date, chlamydia control strategies in several high income countries promote screening for  
417 asymptomatic infection with a focus on monitoring chlamydia test uptake and chlamydia  
418 prevalence. It is surprising therefore, that limited attention has been given to monitoring PID  
419 incidence and its complications given that prevention of PID and its associated complications  
420 is a key goal of chlamydia control. There has also been limited attention on research to further  
421 our understanding of the natural history and immunopathology of *C. trachomatis* infection

422 including the development of non-invasive measures of clinical and subclinical tubal  
423 infection, inflammatory and damage and biomarkers to predict upper genital tract pathology.<sup>60</sup>  
424 We urgently need investment in research to further our understanding of chlamydia natural  
425 history and develop non-invasive tools to detect upper genital tract disease and to establish  
426 surveillance systems to record and monitor trends in PID and other chlamydia related  
427 complications over time.

428

429 *Realistic targets for chlamydia prevalence and incidence should be established*

430 Strategies for chlamydia control should be appropriate to levels of chlamydia prevalence and  
431 incidence in the general population and key populations such as pregnant women, sex workers  
432 and MSM. In countries with longstanding case detection activities, including opportunistic  
433 testing and screening (mostly high income countries), it is conceivable that chlamydia  
434 prevalence has reached an equilibrium and that further investments to increase the overall  
435 coverage of chlamydia testing might not achieve additional gains in reducing the burden of  
436 infection in the population. Within these countries, however, chlamydia control efforts should  
437 focus on reducing social and ethnic inequalities in rates of chlamydia and PID, improving  
438 health outcomes through better case management of those diagnosed with chlamydia and  
439 establishing surveillance systems to more reliably and accurately monitor PID, ectopic  
440 pregnancy and infertility incidence in both primary care, ambulatory and hospital settings.

441 In low and middle income countries efforts should be directed towards strengthening  
442 primary prevention and case management for people presenting with symptomatic chlamydia  
443 infection (see Part 4), as well as research to better define the prevalence of infection and  
444 burden of chlamydial disease. In a limited number of countries, such the South Pacific  
445 Islands, chlamydia prevalence in the general population appears to be very high. Here,  
446 intensive research is needed to understand the reasons for high chlamydia prevalence and to

447 plan for evidence-based sustainable interventions. Mass drug administration of azithromycin  
448 for trachoma control has been associated with a reduction in the prevalence of genital  
449 chlamydia.<sup>126</sup> Given the high probability of re-infection, possible increase in susceptibility to  
450 PID after treatment, and selection pressure for antimicrobial resistance (AMR), mass  
451 treatment should not be introduced to control genital chlamydia infections in the absence of a  
452 sustainable comprehensive chlamydia control strategy and health service infrastructure.  
453 Nevertheless, in all countries, there are opportunities to improve case management of  
454 diagnosed cases to reduce the risk of chlamydia associated complications.

455

#### 456 *Improved case management*

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

467

468 *Partner notification:* Partner notification has been recommended as a part of most STI  
469 management strategies, including syndromic management (see Part 4), to help interrupt  
470 transmission of infections, prevent potential re-infection, and prevent complications.  
471 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.<sup>138</sup>  
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.<sup>139</sup> 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.<sup>138</sup> APT, its equivalent in the UK, is acceptable to healthcare  
481 providers and patients<sup>140</sup> 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<sup>141</sup> and to ensure that opportunities to  
484 test for HIV and other STIs are not missed.<sup>139</sup>

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,<sup>26</sup> others recommend testing to find repeated  
491 infections within three to six months.<sup>26,27,142,143</sup> A mathematical modelling study suggests that  
492 an interval of two to five months after treatment optimises the detection of repeat infection.<sup>144</sup>  
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.<sup>145,146</sup>

496

497 *Rapid and POC tests*

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

501

502 *Chlamydia vaccine*

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

511

512 **Conclusion**

513 Over the last 20 years, awareness about chlamydia as a common STI worldwide has  
514 increased.<sup>2,33</sup> Over the same period, research to increase knowledge about the natural history  
515 of chlamydia or its disease burden has not kept up, even though the first RCT of a chlamydia  
516 control intervention was primarily focused on the prevention of PID.<sup>13</sup> The focus of  
517 chlamydia control efforts in high income countries has been on increased coverage of testing  
518 for asymptomatic chlamydia infection, whilst fewer advances have been made in research to  
519 improve primary prevention and case management. Chlamydia control priorities could be set,  
520 in future, based on infectious disease principles, to define acceptable levels of chlamydia  
521 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 associated 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<sup>60,150,151</sup> 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.<sup>2</sup>  
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.<sup>2,152-154</sup> *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*.

546

547 **Emergence and spread of AMR in *N. gonorrhoeae***

548 Since the first antimicrobials, sulphonamides, were introduced for the treatment of gonorrhoea  
549 in the mid-1930s gonococci have repeatedly shown an extraordinary ability to develop  
550 resistance to all antimicrobials that have been introduced, using almost all known AMR  
551 mechanisms.<sup>153</sup> The hypothesis is that, in modern times, AMR in gonococci has usually  
552 developed first in the WHO Western Pacific Region (frequently Japan) followed by  
553 international spread.<sup>153,155,156</sup> For many infectious diseases including gonorrhoea, overuse and  
554 misuse (including unrestricted access, suboptimal quality and dosing) of antimicrobials has  
555 resulted in AMR in bacterial species that share their AMR determinants through horizontal  
556 gene transfer and subsequent recombination. Horizontal gene transfer is particularly likely in  
557 the pharynx, which harbours many non-gonococcal *Neisseria* species, and can facilitate the  
558 emergence and spread of AMR<sup>157</sup> particularly in high-frequency populations such as MSM  
559 and commercial sex workers. Inadequate monitoring of *in vitro* AMR,  
560 pharmacokinetics/pharmacodynamics, and clinical efficacy of antimicrobials facilitate both  
561 the initial emergence of AMR and the subsequent spread of resistant strains, particularly in  
562 settings with a high incidence of gonorrhoea and ineffective control measures.<sup>152,153,155,156,158</sup>  
563 It is crucial to improve the understanding of the dynamics and drivers of the emergence of  
564 AMR as well as transmission of gonococcal strains and their AMR, which can provide an  
565 enhanced rationale for antimicrobial stewardship and management. Whole-genome  
566 sequencing and other new molecular technologies will be invaluable to elucidate the evolution  
567 and transmission of gonococcal strains and their AMR, locally, nationally and  
568 internationally.<sup>159</sup>

569 Many countries already have high prevalence rates of gonococcal resistance to all  
570 antimicrobials that have been used for treatment, including sulphonamides, penicillins,  
571 tetracyclines, fluoroquinolones and early generation macrolides and cephalosporins.<sup>152-154,158</sup>

572 The prevalence of multidrug-resistant (MDR)<sup>155</sup> gonococcal strains significantly increased  
573 during the last decade.<sup>152-154,158</sup> 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)<sup>155</sup> 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.<sup>160-162</sup> 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,<sup>163-</sup>  
581 <sup>165</sup> showing that both ceftriaxone-resistant strains and ceftriaxone resistance-determining  
582 penicillin-binding protein 2 (PBP2) segments (lethal target for ESCs) are spreading.<sup>165</sup>  
583 Additional sporadic gonococcal strains with low-level ceftriaxone resistance have been  
584 described internationally.<sup>158,166</sup> 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.<sup>158,166</sup> 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.<sup>158,167-172</sup>

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  $\geq 95\%$  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  $\geq 95\%$ , or that  $>99\%$  or  $>97\%$  of strains from  
614 high-frequency transmitting populations should be susceptible.<sup>173-175</sup> 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.<sup>153,158,176</sup>

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.<sup>152-156,158,170</sup> 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.<sup>156,158</sup> 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.<sup>177-180</sup> 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.<sup>181</sup> 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.<sup>181</sup> 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*

646 Several agencies and countries recommend dual antimicrobial therapy for empirical first-line  
647 gonorrhoea treatment in response to emerging ESC resistance, including WHO (global  
648 recommendations), Europe, Germany, United Kingdom, Australia, USA, and Canada.<sup>27,167-172</sup>  
649 To summarise, all these guidelines, except those of WHO<sup>172</sup> and Canada,<sup>171</sup> recommend only  
650 ceftriaxone plus azithromycin as first-line for uncomplicated anogenital gonorrhoea in adults.  
651 There are no RCTs that provide optimal doses of ceftriaxone and azithromycin for currently  
652 circulating gonococcal strains and recommendations vary: ceftriaxone doses range from 250  
653 mg×1 IM (WHO, USA and Canada) to 1 g×1 IM (Germany); and doses of azithromycin range  
654 from 1 g×1 orally (WHO, USA, Canada, UK and Australia) to 2 g×1 orally (Europe).<sup>27,167-172</sup>  
655 WHO<sup>172</sup> and Canadian<sup>171</sup> guidelines additionally recommend an oral first-line dual therapy,  
656 cefixime 400 mg×1 (WHO) or 800 mg×1 (Canada) plus azithromycin 1 g×1.<sup>171,172</sup>  
657 Pharmacodynamic studies have shown that cefixime 800 mg (especially 400 mg×2, given 6  
658 hours apart) increases the cefixime  $fT_{>MIC}$  compared to 400 mg×1.<sup>181</sup> In most countries,  
659 however, only cefixime 400 mg×1 is licensed because gastrointestinal adverse events are  
660 more common with 800 mg×1.<sup>182</sup> Many clinical failures have been verified with cefixime 400  
661 mg×1,<sup>156,158</sup> but also with cefixime 800 mg×1.<sup>182</sup> Finally, WHO also recommends  
662 monotherapy with ceftriaxone 250 mg×1, cefixime 400 mg×1, or spectinomycin 2 g×1, but  
663 only if up-to-date, local, high-quality AMR surveillance data support their use.<sup>172</sup> Owing to  
664 low cure rates, spectinomycin monotherapy should only be used if pharyngeal gonorrhoea has  
665 been excluded; otherwise, azithromycin should also be given.<sup>152</sup>

666 The recommendations for dual therapy with ceftriaxone plus azithromycin are not based on  
667 evidence from RCTs. The selection of these antimicrobials and their doses has been based on  
668 AMR surveillance data, predicted AMR trends, old clinical trials, case reports of clinical  
669 failures with ESCs,<sup>156,158</sup> pharmacokinetic/pharmacodynamic simulations,<sup>181</sup> and expert  
670 opinion.<sup>170</sup> Unfortunately, these recommended antimicrobials might not protect each other  
671 from the development of resistance.<sup>183</sup> 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.<sup>152,153,158</sup> Gonococcal strains with high-level azithromycin resistance (MIC $\geq$ 256  
679 mg/L) have been isolated in several countries worldwide and an outbreak of such strains is  
680 ongoing in the UK.<sup>134,158</sup> All the recommended and alternative dual antimicrobial regimens  
681 include azithromycin 1-2 g $\times$ 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 $\times$ 1 IM plus azithromycin 1 g $\times$ 1  
684 orally), due to a ceftriaxone- and azithromycin-resistant gonococcal XDR strain, was recently  
685 verified in the UK.<sup>15</sup> 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<sup>27,167-172</sup> 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

697 safety. Furthermore, susceptibility to spectinomycin is exceedingly high  
698 globally,<sup>152,153,158,170,172</sup> and it would be valuable to have this drug widely available again.  
699 There are concerns that spectinomycin resistance would be rapidly selected if it was more  
700 frequently used but it has been used in Korea for decades (52%-73% of treatments in 2009-  
701 2012) and no resistant isolates have been found since 1993.<sup>184</sup> Nevertheless, spectinomycin  
702 only eradicates a proportion of pharyngeal gonorrhoea (52%)<sup>185</sup> and should, ideally, be used  
703 in a dual therapy combination, e.g. with solithromycin, which might protect it from resistance  
704 development.

705 Novel accessible and cost-effective antimicrobials are essential. Ideally, these should be  
706 used in new dual therapies, to preserve their effectiveness, and, if there are oral preparations,  
707 in FDCs that increase activity and adherence and mitigate resistance development. One RCT  
708 has evaluated two novel dual regimens, gentamicin (240 mg×1 IM) plus azithromycin (2 g×1  
709 orally), and gemifloxacin (320 mg×1 orally) plus azithromycin (2 g×1 orally), for the  
710 treatment of uncomplicated urogenital gonorrhoea in men and women.<sup>186</sup> Gentamicin plus  
711 azithromycin cured 100% of cases (202/202) and gemifloxacin plus azithromycin 99.5% of  
712 cases (198/199). No serious adverse events occurred, but mild-moderate gastrointestinal  
713 adverse events such as nausea and diarrhoea were frequent. Of concern, 3.3% and 7.7% of  
714 patients, respectively, vomited within one hour and might have lost a substantial amount of  
715 the drugs.<sup>186</sup> Consequently, these two regimens should mainly be considered for treatment of  
716 ceftriaxone-resistant cases, treatment failures with recommended regimen, or ESC allergy.

717

### 718 *Repurposing old antimicrobials*

719 Old antimicrobials, such as gentamicin, ertapenem, and fosfomycin, have been suggested for  
720 future therapy. Several shortcomings with these antimicrobials have been previously  
721 reviewed. Briefly, clinical data are lacking (ertapenem) or old, incomplete, mainly low-  
722 quality, and only from limited geographic areas, patient populations (only males), and

723 anatomical sites (only urogenital); <95% cure rate; appropriate  
724 pharmacokinetic/pharmacodynamic parameters for gonorrhoea, relationship between MIC  
725 and treatment outcome, and resistance breakpoints are lacking.<sup>152,153,156,158,176,187-189</sup> These  
726 limitations preclude their widespread use as empirical monotherapies, but particularly in new  
727 dual antimicrobial regimens they might be useful in case of ceftriaxone resistance or ESC  
728 allergy. A multi-centre (n=8) non-inferiority Phase 3 RCT, aiming to enrol 718 participants,  
729 evaluating gentamicin 240 mg×1 IM plus azithromycin 1 g×1 orally for treatment of  
730 uncomplicated anogenital and pharyngeal gonorrhoea is ongoing  
731 ([www.research.uhb.nhs.uk/gtog](http://www.research.uhb.nhs.uk/gtog)); the comparator is ceftriaxone 500 mg×1 IM plus  
732 azithromycin 1 g×1 orally. Finally, using timely molecular prediction of resistance to  
733 ciprofloxacin, based on targeting *gyrA* mutation(s), this old antimicrobial can be used as  
734 personalised treatment for patients in whom ciprofloxacin susceptibility has been  
735 confirmed.<sup>190-193</sup>

736

### 737 *New antimicrobials with only in vitro data available*

738 Several new antimicrobials (derivates of earlier developed antimicrobials or new  
739 antimicrobial classes) have proven relatively potent *in vitro* activity against gonococcal  
740 strains, but clinical data are lacking. These antimicrobials include the fluoroquinolones  
741 avarofloxacin (JNJ-Q2), delafloxacin (RX-3341), sitafloxacin (DU-6859), and WQ-3810;  
742 bicyclic macrolides (bicyclolides) modithromycin (EDP-420/EP-013420/S-013420) and EDP-  
743 322; tetracyclines eravacycline (TP-434) and tigecycline (fluorocycline and glycylcycline,  
744 respectively); 2-acyl carbapenems SM-295291 and SM-369926; aminomethyl  
745 spectinomycin;<sup>194</sup> lipoglycopeptide dalbavancin, pleuromutilin lefamulin (BC-3781), boron-  
746 containing inhibitor AN3365, LpxC inhibitors, FabI inhibitor e.g. MUT056399, tricyclic  
747 topoisomerase inhibitor REDX05931 (evaluated also in mice),<sup>195,196</sup> and topoisomerase II  
748 inhibitor VXc-486 (VT12-008911), which all have been recently reviewed.<sup>152,153,156,158,176,194-</sup>

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

752

### 753 *Novel antimicrobials in clinical trial evaluation*

754 Solithromycin (CEM-101), zoliflodacin (AZD0914/ETX0914), and gepotidacin  
755 (GSK2140944) are novel orally administered antimicrobials in clinical evaluation for  
756 treatment of gonorrhoea.<sup>197-217</sup> The main characteristics of these antimicrobials are  
757 summarised in table 1.

758 Solithromycin: The first fluoroketolide solithromycin is structurally similar to the ketolide  
759 telithromycin but it is less toxic and has increased stability and activity.<sup>202,208,212</sup>  
760 Solithromycin, like other macrolides and ketolides, inhibits protein synthesis, but  
761 solithromycin has three bacterial 23S rRNA binding sites that increase the activity and delay  
762 development of resistance.<sup>208</sup> Solithromycin has proven a high *in vitro* activity against  
763 geographically, temporally and genetically diverse wild type, MDR and XDR international  
764 gonococcal reference strains and clinical isolates, with *in vitro* and clinical resistance to all  
765 currently and previously recommended antimicrobials.<sup>202,212</sup> No major cross-resistance with  
766 other antimicrobials has been observed, but strains with high-level azithromycin resistance  
767 (MIC<sub>2</sub>≥256 mg/L) can be resistant to solithromycin (MICs=4-32 mg/L).<sup>202</sup>

768 Administering a single solithromycin dose (50-1600 mg) to healthy adults, the time-to-  
769 peak concentration (T<sub>max</sub>) was 1.5-6 hours and the plasma half-life (T<sub>1/2</sub>) 3.2-7.4 hours.<sup>214</sup> A  
770 Phase 1 study evaluating pharmacokinetic properties, safety and tolerability of a 1 g oral dose  
771 within plasma, vaginal, cervical, seminal, rectal, and pharyngeal samples is ongoing  
772 (<https://clinicaltrials.gov/ct2/show/NCT02348424>).

773 A Phase 2 clinical trial evaluating the efficacy of solithromycin 1 g×1 or 1.2 g×1 orally in  
774 the treatment of males and females with uncomplicated urogenital gonorrhoea was performed

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

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

797 Zoliflodacin: The first spiropyrimidinetrione (non-fluoroquinolone topoisomerase II  
798 inhibitor) zoliflodacin targets DNA gyrase (specifically GyrB), but likely also topoisomerase  
799 IV, and has novel mechanisms of action different from all other available  
800 antimicrobials.<sup>197,198,201</sup> Zoliflodacin initially showed high *in vitro* activity against 250



801 geographically, temporally and genetically diverse wild type, MDR and XDR international  
802 gonococcal reference strains and clinical isolates, with *in vitro* and clinical resistance to all  
803 currently and previously recommended antimicrobials.<sup>206</sup> Additionally, consecutive,  
804 contemporary and clinical isolates in Europe (873 isolates from 21 European countries), USA  
805 (100 isolates), and China (187 isolates) have been examined.<sup>211,215,216</sup> The main zoliflodacin  
806 target in GyrB is highly conserved in clinical isolates.<sup>206</sup> No cross-resistance with other  
807 available antimicrobials, including the frequently used topoisomerase II inhibitor  
808 ciprofloxacin, has been observed and no zoliflodacin resistant clinical gonococcal isolate has  
809 been identified.<sup>206,211,215,216</sup> The frequency of induced or selected zoliflodacin resistance  
810 mutations is very low and, interestingly, some of the selected *gyrB* resistance mutations  
811 appear to increase ciprofloxacin susceptibility.<sup>197,201</sup>

812 Administering doses ranging between 200-4000 mg to healthy volunteers (18-55 years) in  
813 a Phase 1 study (<https://clinicaltrials.gov/ct2/show/NCT02298920>),<sup>207</sup> dose-proportional  
814 increases in plasma concentration up to 800 mg were observed. Doses >800 mg resulted in  
815 slightly smaller dose-proportional increases up to 4000 mg. The median T<sub>max</sub> was 1.5-2.3  
816 hours, and the mean terminal elimination T<sub>1/2</sub> was reasonably consistent, ranging between 5.3-  
817 6.3 hours. There were no serious adverse events, or drug discontinuations due to adverse  
818 events. Transient dysgeusia (60%), attributed to suspension formulation, followed by mild  
819 transient headache (38%) were the most common adverse events.<sup>198,207</sup>

820 A Phase 2 RCT evaluating the efficacy, tolerability and safety of zoliflodacin 2 g×1 or 3  
821 g×1 orally for treatment of uncomplicated urogenital gonorrhoea in men and women has been  
822 performed (<https://clinicaltrials.gov/ct2/show/NCT02257918>).<sup>217</sup> In total, 48/49 (98%)  
823 patients and 47/47 (100%) patients achieved microbiological cure with zoliflodacin 2 g×1 and  
824 zoliflodacin 3 g×1, respectively. Only 12% of patients reported any adverse events, i.e. mostly  
825 mild gastrointestinal adverse events.<sup>217</sup> Accordingly, single oral dose of zoliflodacin was  
826 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 (triazacenaphthylene) targeting DNA gyrase (GyrA subunit) and topoisomerase IV (ParC  
831 subunit), but with a different binding mode compared to fluoroquinolones.<sup>200,213</sup> The  
832 gepotidacin MICs have been shown relatively low, however, the MIC<sub>90</sub> 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.<sup>213</sup> *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.<sup>204</sup> 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.<sup>209</sup>

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.<sup>27,167-172</sup> 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<sup>192</sup>), 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.<sup>152,153,156,158,176</sup> Solithromycin, gepotidacin and particularly zoliflodacin can be  
867 promising for gonorrhoea treatment and deserve further attention.<sup>197-217</sup> Ultimately, as for  
868 chlamydia, a gonococcal vaccine might be the only sustainable solution for gonorrhoea  
869 control.<sup>150</sup>

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.<sup>218</sup> 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,<sup>219</sup> 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,<sup>220,221</sup> 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.).<sup>222</sup> 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.<sup>223,224</sup> 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.<sup>225,226</sup> 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.

901

902 **BV is common and associated with serious reproductive and obstetric sequelae**

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

915

916 **Epidemiological evidence for sexual transmission of BV**

917 While the weight and strength of available data support that BV can be acquired through  
918 sexual activity, there has been slow progress in determining the actual transmitted agent or  
919 agents. Epidemiological data have consistently linked sexual exposure to the development of  
920 BV in cross-sectional and longitudinal studies. Detection of BV has been associated with  
921 inconsistent condom use and increased numbers of sexual partners in meta-analyses.<sup>16</sup>  
922 Women with BV have an earlier median age of sexual debut than women without BV.<sup>240</sup>  
923 Although several studies reported BV in “virgins”, the definition was limited to women with  
924 no history of penile-vaginal sex and self-report from potentially vulnerable populations.<sup>241-243</sup>  
925 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.<sup>244</sup> Incident BV has been associated with exposure to a new sexual partner,<sup>227,240,245</sup> while  
930 recurrence after treatment has been associated with sex with an ongoing male partner,<sup>20,246</sup>  
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.<sup>20,247,248</sup> Although other behaviours have been associated with BV, including  
934 smoking,<sup>249-252</sup> douching,<sup>253</sup> dietary factors,<sup>254</sup> and stress,<sup>255</sup> 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.<sup>251,256-259</sup> BV has been associated with practices that implicate sexual  
939 transmission between women,<sup>251,260</sup> 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.<sup>259,261</sup> Marrazzo and colleagues showed that monogamous  
942 female couples share *Lactobacillus* strain types,<sup>262</sup> 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.<sup>259</sup> 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.<sup>263,264</sup> These BV-associated species  
956 are more prevalent in the male partners of women with BV than without.<sup>17</sup> In monogamous  
957 couples, specific BV-associated species are highly concordant between women with BV and  
958 their male partners.<sup>265</sup> Concordance of oligotypes of *G. vaginalis* has also been reported  
959 among heterosexual couples,<sup>266</sup> confirming earlier culture-based studies showing concordance  
960 of biotypes of *G. vaginalis* among heterosexual partners.<sup>267</sup> Overall, these data indicate sexual  
961 exchange of BV-associated bacterial taxa between heterosexual partners is common,<sup>265</sup>  
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.<sup>268</sup>

965 The composition of the coronal sulcus microbiota is not only influenced by sexual activity  
966 but also by male circumcision.<sup>269</sup> Male circumcision has been prospectively associated with a  
967 significant reduction in BV-associated genera,<sup>263,264</sup> and a striking 40-60% reduction in BV  
968 incidence in female partners over 12 months.<sup>270</sup> 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.<sup>225,271,272</sup> 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.<sup>230</sup>

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.<sup>273</sup> 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.<sup>274</sup> Manhart and colleagues examined the association between  
989 NGU and a broader range of BV-associated bacteria,<sup>275</sup> 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,<sup>276</sup> 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?**



1001 RCTs conducted in the 1980 and 1990s did not provide consistent evidence for a reduction in  
1002 BV recurrence in women when their male partners were concurrently treated.<sup>277-282</sup> These data  
1003 formed the evidence base for subsequent BV treatment guidelines that do not recommend  
1004 partner treatment, however, these trials have recently been examined in two systematic  
1005 reviews.<sup>220,221</sup> Mehta reported that none of the trials had sufficient power to detect reasonable  
1006 effect sizes, randomisation methods were deficient or insufficiently reported, adherence to  
1007 therapy was only reported in males in two trials, and many of the treatment regimens,  
1008 including single dose therapy, would not now be considered effective.<sup>221</sup> A Cochrane review  
1009 by Amaya-Guio and colleagues concluded that low to very low quality evidence suggests that  
1010 antibiotic treatment does not lead to a lower recurrence rate.<sup>220,221</sup> Overall the trials are  
1011 considered inconclusive by current standards. The inconsistency between trial findings and  
1012 epidemiological and microbiological data may be explained by a number of factors. The  
1013 findings were clearly influenced by issues in trial design,<sup>221</sup> but these trials were also  
1014 conducted prior to advances in molecular methods that have provided evidence of detection of  
1015 BV-associated bacteria in the sub-preputial space of males. It is possible that optimal therapy  
1016 to promote clearance of BV-associated bacteria from penile and urethral sites requires a  
1017 combination of both topical and oral antibiotics. Alternatively, it is possible that non-bacterial  
1018 agents such as viruses or bacteriophages, which have been implicated in the pathogenesis of  
1019 BV, are being sexually transmitted, and if this is the case these agents will not be influenced  
1020 by male partner treatment with antimicrobials.

1021

### 1022 **Do bacteriophages play a role in bacterial vaginosis?**

1023 Phage mediated lysis of lactobacilli has been postulated as a cause of BV, but there have been  
1024 very few publications in this area. Kilic and Pavlova reported that lysogeny of *Lactobacillus*  
1025 species (infection with bacteriophages) in women was common, but that the rate of

1026 lactobacillus phage detection was higher in women with BV than without.<sup>283,284</sup> In *in vitro*  
1027 studies they demonstrated that phages could infect lactobacilli both from the host and  
1028 different women.<sup>284</sup> Following this work, Blackwell hypothesised that a sexually transmitted  
1029 lactobacillus phage might destroy healthy lactobacilli allowing secondary overgrowth of  
1030 anaerobes, which could explain why BV behaves epidemiologically like an STI but BV  
1031 recurrence rates were unaffected by male partner treatment.<sup>285</sup> The phage theory can be  
1032 biologically linked to the association between BV and smoking,<sup>249-252</sup> as tobacco products  
1033 accumulate in cervical secretions, and the cigarette product benzol(a)pyrone diol epoxide  
1034 promotes phage induction.<sup>249,285</sup> Blackwell again hypothesized that smoking in women or  
1035 their partners might be associated with BV through tobacco product induction of endogenous  
1036 bacteriophages or sexually acquired phages.<sup>285</sup> Further studies to clarify if bacteriophages  
1037 play a role in the pathogenesis of BV in women and their male partners are clearly needed.

1038

### 1039 **Limitations of current management and the need for new approaches**

#### 1040 *Antimicrobial therapy*

1041 Figure 6 provides a schematic representation of the broad range of approaches that have been  
1042 attempted for the management and prevention of BV. As the inciting event that results in the  
1043 development of BV is unknown, traditional treatment approaches have aimed to reduce the  
1044 vaginal burden of anaerobes and to ameliorate concomitant symptoms. Overall, antimicrobial  
1045 compounds with broad activity against most anaerobic bacteria—metronidazole and  
1046 clindamycin—administered for 5-7 days, appear to achieve relatively high short term cure  
1047 rates (80-90%),<sup>27,286,287</sup> with use of intravaginal formulations resulting in fewer systemic side  
1048 effects.<sup>288</sup> Symptomatic BV persists or recurs in 50%-70% of women within 3-6 months,  
1049 however, and long-term recurrence rates approach 80% in certain populations.<sup>246,289-291</sup>  
1050 Possible reasons for this include: re-inoculation with these organisms from an exogenous

1051 source (i.e. sexual partner) or an endogenous source (i.e. rectal reservoir); failure to  
1052 completely suppress the growth of BV-associated bacteria (i.e. located within a biofilm);  
1053 persistence of host risk factors (for example, douching or smoking); failure to recolonise the  
1054 vagina with desirable lactobacilli; and transmission of or activation of *Lactobacillus* phages  
1055 that destroy vaginal lactobacilli.<sup>283-285,292</sup> None of these mechanisms has been conclusively  
1056 shown to explain the high rates of BV recurrence, or to identify women at increased risk for  
1057 BV incidence, recurrence, or sequelae. If sexual transmission is involved in the pathogenesis  
1058 of BV, as hypothesised, it is still not clear what is being transmitted - a single founder  
1059 organism (a bacterium or virus), a bacteriophage that lyses protective lactobacillus species or  
1060 a polymicrobial bacterial consortium in the form of biofilm.

1061 Factors that determine whether a woman with BV will respond to standard antimicrobial  
1062 regimens are also not clear. One prospective study indicated that detection of specific BV-  
1063 associated bacteria prior to treatment with intravaginal metronidazole predicted treatment  
1064 failure at 30 days.<sup>291</sup> Investigators have examined whether AMR plays a role and, while  
1065 clindamycin-resistant bacteria have been detected among women treated with vaginal  
1066 clindamycin, their presence was not associated with reduced cure rates.<sup>293,294</sup> Metronidazole is  
1067 active against Gram-negative anaerobes and *Mobiluncus mulieris*, but it is less active against  
1068 *G. vaginalis*, anaerobic Gram-positive cocci and *Mobiluncus curtisii*, and inactive against *M.*  
1069 *hominis* and *A. vaginae*.<sup>293,294</sup> Despite that, many of these *in vitro* non-susceptible species are  
1070 eradicated following metronidazole therapy, indicating that inhibition or elimination of  
1071 metronidazole-susceptible members of the vaginal bacteria in BV might result in a decline in  
1072 some non-susceptible members as well. In an attempt to effect higher BV cure rates,  
1073 investigators have increased the dose and duration of nitroimidazoles. Metronidazole, when  
1074 used as monthly presumptive therapy, was effective in preventing BV over 12 months of  
1075 use.<sup>295</sup> Twice weekly vaginal metronidazole gel was also found to be effective in suppressing  
1076 BV during use, with the rationale being that suppression of overgrowth of BV-associated

1077 bacteria may offer greater symptom relief, and eventually increase the chance of restoration of  
1078 a normal vaginal microbiota.<sup>296</sup> While a number of prolonged or intermittent suppressive  
1079 regimens appear effective during use, relapse on discontinuation remains common, and none  
1080 has improved long term cure rates in women. Whether treating women with recurrent BV  
1081 with a longer initial course of metronidazole (10-14 days with vaginal gel or oral tablets) or a  
1082 one week course of oral tinidazole will improve cure rates has not been established. One study  
1083 that compared 14 days with seven days of metronidazole treatment found statistical evidence  
1084 of a benefit when cure was assessed seven days after completion of therapy, but not at 21  
1085 days.<sup>248</sup>

1086

#### 1087 *Biofilm disruption*

1088 The presence of a BV-associated biofilm might also contribute to the high rates of failure of  
1089 antimicrobial therapy. Biofilms not only reduce antimicrobial penetration enabling susceptible  
1090 microbes to persist, but contain microbes in varying states of metabolic activity with some in  
1091 more dormant inactive states.<sup>292,297,298</sup> When visualised with specific fluorescent probes, *G.*  
1092 *vaginalis* has been detected in large quantities within adherent biofilms among women with  
1093 BV, and some studies indicate that these biofilms persist in women experiencing treatment  
1094 failure.<sup>299,300</sup> Biofilm disruption might be necessary to achieve optimal efficacy of  
1095 antimicrobials. Agents that display activity against biofilms include: octenidine, boric acid,  
1096 DNAses, retrocycline, and naturally occurring antimicrobials (subtilisin, ploy-L-lysine, and  
1097 lauramide arginine ethyl ester).<sup>301-306</sup> Boric acid and octenidine are currently the only agents  
1098 to have been evaluated in human studies. While use of metronidazole after 21 days of boric  
1099 acid reduced BV recurrence on treatment, late post-treatment recurrence was common.<sup>301</sup>  
1100 Similarly, early BV cure rates looked promising with intravaginal octenidine, but BV  
1101 recurrence occurred in a significant proportion of women and bacterial resistance to  
1102 octenidine also emerged.<sup>302</sup> A recent *in vitro* study showed that metronidazole and tobramycin

1103 were highly effective against biofilm formation but ineffective against established biofilm.  
1104 Amphoteric tenside sodium cocoamphoacetate was, however, highly effective in disrupting  
1105 biofilm, reducing biomass by 51% and augmented the effect of metronidazole, indicating that  
1106 this might have potential as a combination approach for BV.<sup>307</sup> As *G. vaginalis* biofilms  
1107 contain extracellular DNA, enzymatic disruption by DNase has been shown to inhibit *G.*  
1108 *vaginalis* biofilm formation and to disrupt biofilms *in vitro*.<sup>303</sup> DNase appears to be even more  
1109 effective *in vitro* when combined with metronidazole,<sup>303</sup> but has not yet been subject to  
1110 human studies for BV. RC101, a retrocycline and potent inhibitor of vaginolysin (a toxin  
1111 produced by *G. vaginalis*), also inhibits the formation of *G. vaginalis* biofilms *in vitro*,<sup>305,306</sup>  
1112 and might be another potential candidate for human studies in BV. Lastly, an emerging area  
1113 of research involves inhibition of quorum sensing, a strategy that some bacteria use to  
1114 coordinate expression of genes involved in virulence, biofilm formation and  
1115 pathogenicity.<sup>298,308</sup> While quorum sensing inhibitors have not been evaluated in human  
1116 studies, they are active *in vitro* against biofilms produced by *Pseudomonas aeruginosa* and  
1117 *Staphylococcus spp.*<sup>308,309</sup> Overall, the development of safe and effective topical biofilm-  
1118 disrupting agents that can be combined with antimicrobials has been suggested as an  
1119 important area of current research.<sup>298</sup>

1120

#### 1121 *Approaches to restore a healthy vaginal microbiota*

1122 Because of the apparent ecological shift in the vaginal microflora in BV, therapies that either  
1123 act as vaginal disinfectants or aim to restore the vaginal ecosystem have been evaluated.  
1124 Although repletion of desirable *Lactobacillus* species would seem to be key, this strategy has  
1125 presented challenges, and probiotic trials to date have not demonstrated consistent benefit.<sup>310</sup>  
1126 One of the barriers to progress has been lack of suitable vaginal species for probiotic  
1127 formulations, but a *L. crispatus* vaginal capsule, first known as CTV 05 and now termed

1128 LACTIN-V, has recently been shown to achieve vaginal colonisation, to be safe<sup>311-313</sup> and to  
1129 prevent recurrent urinary tract infections in a Phase 2B RCT;<sup>314</sup> it is now under study for  
1130 treatment of BV. The efficacy of vaginal acidifiers such as lactic acid, in the form of gels,  
1131 suppositories and acid-soaked tampons, has varied widely. Vaginal acidifiers will suppress,  
1132 but not kill, vaginal anaerobes, so may suppress without affecting a cure. A systematic review  
1133 of these agents found they were either ineffective or not adequately tested due to limitations in  
1134 study size, design or analysis, and that more data are needed.<sup>315</sup>

1135

## 1136 **Conclusion**

1137 The adverse impact of BV is felt by the women who experience it, their partners and infants,  
1138 and their health care providers who struggle to effectively treat it. As we have discussed, the  
1139 available epidemiological and microbiological data provide strong evidence of carriage of  
1140 BV-associated bacteria in male genitalia and exchange of either these species within sexual  
1141 partnerships or another agent capable of inciting BV. There is also compelling evidence for  
1142 the impact of male circumcision and condom use on reducing the risk of BV acquisition and  
1143 recurrence. Overall, these data strongly suggest that sexual transmission is an integral  
1144 component of the pathogenesis of incident and recurrent BV. Earlier partner treatment trials  
1145 had substantial methodologic limitations, and do not provide an adequate body of proof to  
1146 discount the possibility that male partner treatment may reduce BV recurrence in women.  
1147 New partner treatment trials, conducted in accordance with current clinical trial standards, and  
1148 employing modern microbiologic tools, are needed to determine the contribution of  
1149 reinfection to recurrence, and to provide an accurate evidence base for treatment guidelines.  
1150 Given the data supporting an anatomic reservoir of BV-associated bacteria in male genitalia, a  
1151 logical approach might emphasise trials that study a potential role of topical antimicrobials in  
1152 addition to oral agents; eradication of cutaneous carriage of these bacteria from the penile skin

1153 may reduce the risk of reinfection and optimise BV cure. Female partner treatment trials could  
1154 also facilitate understanding of pathogenesis, and identify new approaches to management.  
1155 While the relative contribution of persistence of BV-associated bacteria versus reinfection to  
1156 BV recurrence is not clear, both mechanisms are likely to play a role. It is also possible that  
1157 other factors including failure to recolonise the vagina with desirable lactobacilli, persistence  
1158 of host risk factors or lactobacillus phages contribute. Ultimately, optimal treatment strategies  
1159 are likely to require combination approaches such as use of antimicrobials, biofilm-disrupting  
1160 agents and partner treatment. Efforts to optimise the therapeutic and preventive approach to  
1161 this complex syndrome will, however, require allocation of the necessary resources and  
1162 commitment be made to a disease that remains largely hidden from public view. Yet BV is  
1163 not rare or benign, it is a condition of high global burden in women of reproductive age and is  
1164 associated with serious and costly sequelae, including preterm delivery and increased risk of  
1165 HIV acquisition and transmission. Recognition for this neglected condition—in the form of a  
1166 coherent, progressive research agenda and concomitant resource allocation—is well past due.

1167

#### 1168 **Part 4. STI case management and control in low and middle income** 1169 **countries: the role of point of care tests**

1170 In 2012, over 90% of new estimated cases of gonorrhoea, chlamydia, trichomoniasis and  
1171 syphilis were from low and middle income countries (Figure 1).<sup>2</sup> These curable STIs can lead  
1172 to severe complications and long-term sequelae, burdening already over-stretched health care  
1173 systems. Primary prevention of STIs in low and middle income countries has shown some  
1174 success with vaccines against human papillomavirus (HPV) and hepatitis B and with male  
1175 circumcision, but less so with interventions to promote sustained behaviour change and  
1176 condom promotion.<sup>316</sup> 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;<sup>133,317</sup> 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.<sup>33</sup>  
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.<sup>2,318</sup> The proportion of pregnant women not tested for syphilis  
1191 in antenatal care fell from 2008 to 2012 in all regions except Africa.<sup>319</sup> 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.<sup>320</sup> 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.<sup>321,322</sup> 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.<sup>323</sup>  
1199 Periodic presumptive treatment in targeted populations, such as commercial sex workers, has  
1200 shown promise but overtreatment with antibiotics is still a concern.<sup>324</sup>

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



1203 completion of testing, communication of results that guide clinical decisions and follow-up to  
1204 take place at the same clinical encounter.<sup>147</sup> There are affordable highly sensitive and specific  
1205 POC tests for syphilis. While there are several hopeful tests in the pipeline for chlamydia and  
1206 gonorrhoea, the available POC tests have low accuracy or require expensive equipment.<sup>325</sup>  
1207 Yet, even with well performing, affordable POC tests, challenges will remain for  
1208 implementing POC testing into national health systems. This section of the *Commission*  
1209 reviews current challenges facing case management and STI control related to secondary  
1210 prevention of curable STIs in low and middle income countries, and provides an update of the  
1211 state of the art of POC tests.

1212

### 1213 **Case management of symptomatic STIs in low and middle income countries**

1214 Case management is the treatment of infections to alleviate signs and symptoms, and to  
1215 prevent sequelae, and includes history-taking and clinical examination, diagnostic tests,  
1216 treatment, partner notification, health promotion advice, follow-up and surveillance.<sup>31</sup> Case  
1217 management is an integral part of an STI control strategy; early treatment can disrupt onward  
1218 transmission if treatment and partner notification are successful. The treatment of clinical  
1219 syndromes, commonly called syndromic management, was developed in the late 1970s and  
1220 early 1980s to address the practical difficulties of managing STIs where diagnostic tests are  
1221 not available.<sup>326</sup> In 1985, the first WHO guidelines for STI management included four simple  
1222 algorithms for the management of syndromes that are associated with common STIs: genital  
1223 ulcers, urethral discharge, vaginal discharge and PID. Patients are treated for all the probable  
1224 causes of these syndromes. These guidelines gained recognition in the growing HIV epidemic  
1225 in the early 1990s, when the link between STI and HIV became clear, and have become the  
1226 backbone of case management for STIs in many low and middle income countries. The  
1227 current WHO syndromic management guidelines have algorithms for six syndromes: urethral

1228 discharge, genital ulcers, scrotal swelling, vaginal discharge, low abdominal pain, and  
1229 neonatal conjunctivitis.<sup>133</sup>

1230 The advantages of syndromic management include low cost, modest training requirements  
1231 and provision of immediate treatment. The main disadvantage is that syndromic management  
1232 unnecessarily treats for infections that are not present, and misses asymptomatic infections,  
1233 which are the majority of STIs globally.<sup>327</sup> This is especially true for vaginal discharge  
1234 syndrome which is more commonly caused by BV, candidiasis or trichomoniasis, than by  
1235 chlamydia and gonorrhoea.<sup>43</sup> Several studies have shown poor sensitivity and specificity of  
1236 syndromic management for chlamydia and gonorrhoea in women.<sup>328-331</sup> Efforts to increase  
1237 accuracy for the vaginal discharge syndrome with a risk assessment were evaluated, but  
1238 sensitivity and specificity remained poor.<sup>332</sup> This is because most women with vaginal  
1239 discharge do not have these infections, and most women (up to 70%) with chlamydia and  
1240 gonorrhoea have no symptoms.<sup>17</sup> Unfortunately, asymptomatic infection is still likely to cause  
1241 harmful sequelae. A study among female sex workers in South Africa has shown that  
1242 cervicovaginal inflammatory markers were elevated in women with an STI whether or not it  
1243 was symptomatic.<sup>331</sup> Previous studies have suggested that elevated inflammatory markers may  
1244 facilitate HIV transmission,<sup>333</sup> and thus, women with asymptomatic STIs might be as  
1245 susceptible to HIV infection as those with symptoms. Additionally, it is estimated that the use  
1246 of syndromic management results in the unnecessary treatment of 60-98% of women  
1247 presenting with vaginal discharge for chlamydia and gonorrhoea.<sup>334</sup> Any use of antibiotics  
1248 encourages resistance, so it is important that the unnecessary use of antibiotics is limited. As  
1249 noted by *Unemo* in Part 2, increased resistance to most antibiotics used to treat gonococcal  
1250 infections has been reported worldwide, raising concerns about the eventual development of  
1251 untreatable gonococcal infections with serious sexual and reproductive health consequences.

1252

1253 **Partner notification**

1254 In Part 1, *Low and Hocking* discuss partner notification strategies for the management of  
1255 diagnosed chlamydia. In the context of syndromic management in low and middle income  
1256 countries, partner treatment often results in over-prescription of antibiotics, especially of  
1257 partners of women with vaginal discharge, most of whom do not have an STI.<sup>335</sup> A systematic  
1258 review of partner notification in developing countries found that partner notification for STIs  
1259 was feasible in low and middle income countries and that most patients diagnosed with STIs  
1260 were willing to self-notify their regular partners.<sup>336</sup> There are, however, major barriers to  
1261 successful partner notification, including fear of abuse and rejection resulting from partner  
1262 referral, especially for women. Economic vulnerability of women must be considered in the  
1263 design of partner notification strategies in low and middle income countries in which female  
1264 partners may be blamed for the infection.<sup>335</sup> There is a need for the development and  
1265 evaluation of partner notification strategies in low and middle income countries using  
1266 biological outcomes, such as reinfection.<sup>138</sup>

1267

1268 **Targeted presumptive treatment**

1269 Presumptive treatment is the treatment for a presumed infection in populations with a high  
1270 burden of STIs without confirmation of infection by an examination or laboratory test.  
1271 Presumptive treatment for STIs may be given at repeated intervals, in which case it is known  
1272 as periodic presumptive treatment. Periodic presumptive treatment is complementary to  
1273 syndromic management and targets asymptomatic infection in high burden, key populations –  
1274 many of whom are stigmatised and hard to reach, such as female sex workers. Most periodic  
1275 presumptive treatment targets chlamydia, gonorrhoea and syphilis, and it has been most  
1276 extensively evaluated in sex worker populations. In 2005, a WHO consultation reviewed

1277 experience from nine countries and recommended that periodic presumptive treatment be  
1278 considered as a part of the package of services to rapidly reduce STI prevalence in sex worker  
1279 settings, particularly where STI control is poor.<sup>337</sup> In 2012, a systematic review reported the  
1280 results from 15 studies and showed consistent reductions of about 50% prevalence in  
1281 populations with high chlamydia and gonorrhoea prevalence. There was limited evidence for  
1282 chancroid - one study showed rapid decline of chancroid – and mixed evidence for syphilis.<sup>338</sup>  
1283 Modelling studies have shown that, if sufficient coverage is achieved (>30% of the target  
1284 population), periodic presumptive treatment interventions can effectively reduce the STI  
1285 prevalence among the target population, and that interventions with sufficient coverage  
1286 ( $\geq 40\%$ ) and follow-up ( $\geq 2$  years) could significantly decrease HIV incidence ( $>20\%$ ).<sup>339</sup>

1287 Presumptive treatment can be an effective approach to the treatment of asymptomatic  
1288 infection among women (at least those at high risk) and may interrupt transmission between  
1289 sex workers and their clients, but needs evaluation in other populations. Importantly,  
1290 presumptive treatment must be sustained; once stopped, infections recur. In addition, a  
1291 disadvantage is unnecessary treatment of people who are not infected with an STI and the  
1292 contribution to the development of AMR, as discussed above.

1293

## 1294 **Screening programmes**

1295 Antenatal syphilis screening and treatment is effective and cost-effective for the prevention of  
1296 adverse pregnancy outcomes.<sup>340</sup> Fifty-two low and middle income countries reported testing  
1297 coverage for syphilis during antenatal care for 2012, however, only about a third reported  
1298 coverage of at least 95%, whereas another third reported coverage of less than 50%.<sup>317,341</sup> Of  
1299 14 countries that report current policies for antenatal screening of *C. trachomatis* and *N.*  
1300 *gonorrhoeae* infections, only two (Romania and Bulgaria) are in the category of low and

1301 middle income; most low and middle income countries use WHO recommended syndromic  
1302 management for the treatment of symptoms during antenatal care.<sup>342</sup>

1303 Screening of high-risk populations, including sex workers has shown some success in  
1304 research studies and demonstration projects,<sup>343,344</sup> but has not been widely replicated in low  
1305 and middle income countries due to the cost of diagnostics and laboratory capacity.<sup>343</sup>  
1306 Evidence about chlamydia screening is discussed in detail in Part 1.

1307

### 1308 **The use of POC testing for case management and STI control**

1309 POC tests provide prompt diagnosis for case management, provide a definite diagnosis of an  
1310 STI which can further justify and facilitate partner notification, and can be used for screening  
1311 antenatal care attendees and populations at high risk for STIs. There are several low cost  
1312 techniques for STI diagnosis that can be done at the POC, including wet mount and Gram  
1313 stain microscopy, but they require laboratory equipment and lack sensitivity, particularly for  
1314 diagnosing infections in women. Rapid plasma reagin (RPR), a non-treponemal test for  
1315 syphilis, can also be done at the POC, but it requires separation of serum, refrigeration and  
1316 equipment, and has low accuracy in settings with insufficient training or facilities.<sup>345-347</sup> In  
1317 addition, RPR tests are often batched or sent to a central laboratory, resulting in patients not  
1318 returning or staying for treatment.<sup>345,348,349</sup>

1319 To guide the development of simple and rapid POC tests, WHO developed the ASSURED  
1320 benchmarking in 2006. ASSURED POC tests are Affordable by those who are at risk for the  
1321 infection; Sensitive, very few false negatives; Specific, very few false positives; User-  
1322 friendly, very simple to perform (minimal steps required with minimal training); Rapid and  
1323 Robust, to enable treatment at visit of diagnosis (rapid) and does not require refrigeration  
1324 storage (robust); Equipment free, easily collected non-invasive specimens (e.g. saliva and  
1325 urine) and not requiring complex equipment; and Delivered to end users.<sup>350</sup> Three recent

1326 systematic reviews summarise the available information on POC tests for STIs: Tucker and  
1327 colleagues;<sup>351</sup> Gaydos and Hardick;<sup>352</sup> and Herbst de Cortina and colleagues.<sup>353</sup> Reviews  
1328 evaluated available POC tests and those in the pipeline. The WHO landscape analysis of POC  
1329 tests by Murtagh provides a listing of currently available POC tests and those in the  
1330 pipeline;<sup>325</sup> this analysis will be updated annually by WHO. Available POC tests have been  
1331 summarised in table 3.

1332

### 1333 *POC tests for chlamydia and gonorrhoea*

1334 Most POC tests currently available for the detection of *C. trachomatis* or *N. gonorrhoeae* are  
1335 based on antigen detection in lateral flow devices and do not meet ASSURED criteria because  
1336 of low sensitivity and/or specificity. While the aQcare Chlamydia TRF and BioStar Optical  
1337 Immunoassay for gonorrhoea have been shown to be highly sensitive and specific, both have  
1338 only been evaluated in one study each (for BioStar Optical Immunoassay only a pilot study  
1339 including five confirmed *N. gonorrhoeae* positive specimens).<sup>354,355</sup> There is general  
1340 agreement that most current POC tests for the detection of *C. trachomatis* or *N. gonorrhoeae*  
1341 do not perform well, and there is a need for improved assays. Nevertheless, modelling studies  
1342 have suggested that even insensitive POC tests may increase the proportion of infections  
1343 treated in scenarios where it would be difficult to ensure a high patient return rate, and in  
1344 populations where there is potential for further STI transmission during the delay in treatment  
1345 from using laboratory STI tests.<sup>356-358</sup>

1346 GeneXpert (Cepheid, Inc), a NAAT-based test with high sensitivity and specificity for  
1347 detection of *C. trachomatis* and *N. gonorrhoeae* has been termed a *near*-POC test as it  
1348 requires equipment, is expensive and has a relatively long turnaround time (approximately 90  
1349 minutes). There are many new technologies in the pipeline (Figure 7) which are likely to be  
1350 highly accurate and require minimal training and processing time including the io® Platform  
1351 (Atlas Genetics), GeneXpert® Omni (Cepheid), RT Cross-priming Amplification CT Test

1352 (Ustar Biotechnologies), Truelab™ Real Time micro PCR System (Molbio Diagnostics Pvt.  
1353 Ltd), Alere™-i Platform (Alere, Inc), CT/NG MAMEF-based detection, and MobiLab (Johns  
1354 Hopkins University BioMEMS Lab).<sup>325,351,353</sup> The latter test employs smartphones for reading  
1355 results.

1356

#### 1357 *POC tests for trichomoniasis*

1358 The OSOM® Trichomonas Test (Sekisui Diagnostics) for detection of *T. vaginalis* infection  
1359 has been shown to perform well against wet mount and culture (83·3-90·0% sensitivity and  
1360 98·8-100% specificity).<sup>325,353</sup> The OSOM test for detection of *T. vaginalis* meets the  
1361 ASSURED benchmark by having few steps and taking only 10 minutes to perform.  
1362 GeneXpert platform also has an assay to detect *T. vaginalis* and this test has been evaluated in  
1363 two studies and found to be sensitive and specific (95·0-95·6% and 95·7-100%  
1364 respectively);<sup>359,360</sup> however, the GeneXpert platform does not meet ASSURED  
1365 benchmarking as stated above. In the pipeline, Atlas io™ has an assay in development as well  
1366 as AmpliVue® (Quidel Corporation).<sup>325</sup>

1367

#### 1368 *POC tests for syphilis*

1369 Four treponemal POC tests for syphilis have been evaluated and met the ASSURED criteria,  
1370 and these are recommended in resource-limited settings: Determine™ Syphilis TP (Alere,  
1371 Inc), SD Syphilis 3.0 (Alere SD Bioline), Syphicheck® WB (The Tulip Group/Qualpro), and  
1372 Visitect® Syphilis (Omega Diagnostics).<sup>350,361</sup> These tests are accurate, cost less than \$1 if  
1373 purchased through the WHO bulk procurement programme for low and middle income  
1374 countries, can provide results in 15 to 20 minutes, and are easy to use with minimal training.  
1375 In addition to these tests that have been extensively evaluated, other POC tests for syphilis are  
1376 on the market including Crystal TP Syphilis Test (Span Diagnostics), *OnSite*™ Syphilis Ab

1377 Combo rapid Test (CTK Biotech Inc.), Syphilis Health Check™ (Diagnostics Direct), and  
1378 Uni-Gold™ Syphilis Treponemal (trinity Biotech).<sup>325</sup>

1379 Treponemal POC tests have been implemented and evaluated in rural antenatal care clinics  
1380 in Tanzania, Uganda and China; both rural and urban clinics in Peru and Zambia; and in  
1381 remote indigenous communities in Brazil.<sup>362</sup> The introduction of POC tests increased the  
1382 proportion of antenatal care attendees screened for syphilis to 90%, and the proportion of  
1383 pregnant women with syphilis who were treated the same day exceeded 90% in all countries.  
1384 Modelling from this study has shown that POC tests are more cost-effective in screening and  
1385 treating syphilis than laboratory-based testing methods such as the RPR.<sup>363</sup>

1386 Treponemal POC tests have also been used in hard-to-reach populations. In Brazil, health  
1387 care workers in remote communities succeeded in screening 55% of the sexually active  
1388 population (defined as  $\geq 10$  years of age) for syphilis, exceeding the 30%–40% target  
1389 originally set.<sup>362</sup> Modelling studies have estimated the impact of using rapid POC tests to  
1390 screen female sex workers for syphilis and shown that rapid POC test screening could  
1391 dramatically reduce syphilis prevalence amongst this hard-to-reach group, but strategies to  
1392 reduce re-infection from regular non-commercial partners are needed to maximise impact.<sup>364</sup>

1393 Once a person has been infected with *T. pallidum*, all future treponemal tests will be  
1394 positive; therefore, there is concern that treponemal POC tests cannot distinguish between  
1395 current and past infection, resulting in over treatment for syphilis. This is particularly  
1396 important in settings in which access to confirmatory testing using non-treponemal tests is  
1397 limited. Therefore, combination POC platform tests have been developed which include both  
1398 treponemal and non-treponemal antigens. The Dual Path Platform test is the first of these, and  
1399 has good sensitivity and specificity for both treponemal (90.1–98.2% and 91.8–98.0%,  
1400 respectively) and non-treponemal (80.6–98.2% and 89.4%, respectively) tests.<sup>365</sup>

1401

1402 *POC tests for syphilis and HIV*



1403 There is also a need for dual syphilis and HIV tests. These could be used in populations at  
1404 high risk for both HIV and syphilis, and accelerate programmes for the elimination of mother  
1405 to child transmission of both HIV and syphilis, especially in countries in Africa that have  
1406 made excellent progress towards the elimination of mother to child transmission of HIV but  
1407 not syphilis. In 2017, WHO published an information note to provide advice for countries  
1408 using or planning to introduce dual HIV/syphilis POC tests in antenatal services and other  
1409 testing sites.<sup>366</sup> There are currently five combination HIV/syphilis POC tests on the market  
1410 (Figure 8), of which three have published data on sensitivity and specificity: Standard  
1411 Diagnostics (SD) Bioline HIV/Syphilis Duo Rapid Test; Chembio DPP® HIV-Syphilis  
1412 Assay; and Medmira Multiplo Rapid TP/HIV Antibody Test.<sup>325</sup> In addition to these, there is  
1413 an innovative dual POC test in the pipeline, mChip Assay (Junco Labs and Columbia  
1414 University in collaboration with OPKO Health, Inc), which uses a microfluidic mChip and a  
1415 smart phone for reading results.<sup>325</sup>

1416

#### 1417 *POC tests for AMR gonorrhoea*

1418 There are, as yet, no commercially available diagnostic assays that detect gonococcal  
1419 AMR.<sup>191</sup> There is an urgent need for the development of these diagnostics with a focus  
1420 towards POC tests. Detection of both *N. gonorrhoeae* and its main resistance determinants at  
1421 the POC would improve management and help to slow the spread of AMR, particularly in low  
1422 and middle income countries.<sup>191</sup>

1423

#### 1424 **Challenges for the implementation of POC tests**

1425 POC tests have the potential to transform case management and STI control in low and  
1426 middle income countries. To be effective at the population level, however, they must be  
1427 adopted by national health systems and this requires careful consideration. Decentralising

1428 testing from the laboratory can put tremendous stresses on fragile health care systems in terms  
1429 of supply chain management, training, quality assurance and monitoring impact.

1430 A study in Peru has shown that the use of POC tests offers an opportunity to improve  
1431 screening coverage for syphilis and other aspects of health systems.<sup>362,367</sup> Widespread  
1432 adoption and use depends on engaging the authorities; dissipating tensions between providers  
1433 and identifying champions; training according to the needs identified; providing monitoring,  
1434 supervision, support and recognition; sharing results and discussing actions together;  
1435 consulting and obtaining feedback from users; and integrating with other services such as with  
1436 rapid HIV testing.<sup>362,367</sup> As countries begin to implement POC testing, adequate training and  
1437 quality assurance programmes must be developed in parallel. Smit and colleagues evaluated  
1438 the use of dry blood spots to evaluate quality of POC syphilis and HIV tests in Tanzania, and  
1439 found that quality varied between clinics, which helped to identify which clinics needed  
1440 remedial training.<sup>357</sup>

1441 Ultimately, POC tests pave the way for self-sampling and self-testing outside of a clinical  
1442 setting including community-based organisations, pharmacies and at home. Home-based  
1443 testing for HIV has been shown to reach wide sections of communities in a diverse range of  
1444 contexts and settings, and is viewed to be the gateway to accessing early treatment and  
1445 care.<sup>368</sup> However, important lessons can be learned from the roll out of simple and rapid HIV  
1446 POC tests in which the major challenges have been well recognised including poor quality  
1447 control, unreliable supply chains, non-standardised training, and limited number of healthcare  
1448 workers.<sup>369</sup> Decentralising testing for curable STIs might increase access to testing and  
1449 awareness of STIs, but linkage to the health care system will be critical for diagnostic  
1450 confirmation, treatment, counselling and follow-up.<sup>351</sup> POC tests that meet ASSURED  
1451 benchmarks are likely to fill an important gap for STI control in low and middle income  
1452 countries, yet the technological innovation of POC tests needs to be mirrored by innovation in  
1453 health care delivery and careful planning for implementation.

1454

1455 **Conclusion**

1456 Low and middle income countries shoulder the majority of global incident cases of STIs,  
1457 yet national health systems are less resourced to manage STI cases or carry out secondary  
1458 prevention. POC tests that meet the WHO ASSURED benchmark could bridge the gap for  
1459 STI case management and control in these settings. Currently there are POC tests for  
1460 syphilis and trichomoniasis which meet the ASSURED benchmark. In contrast, there are no  
1461 ASSURED POC tests for chlamydia or gonorrhoea, and there is an urgent need for the  
1462 development and evaluation of POC tests for these infections, as well as for AMR *N.*  
1463 *gonorrhoeae*. Importantly, while development of ASSURED POC tests is a crucial target,  
1464 the successful implementation of POC tests into health care systems for the prevention and  
1465 control STIs is the goal. Indeed, the goal for the implementation of POC tests into antenatal  
1466 screening for syphilis is 100% screening and treatment of syphilis worldwide. Future  
1467 ASSURED POC tests for curable STIs will need to be integrated into syndromic  
1468 management guidelines as well as control strategies such as partner notification and  
1469 targeted presumptive treatment. It will be essential that implementation research guides  
1470 integration of POC tests into current strategies for STI case management and control in low  
1471 and middle income countries.

1472

1473 **Part 5. STIs in MSM in the era of biomedical interventions for HIV**

1474 **prevention**

1475 A historical perspective provides insights into the epidemiology of STIs in MSM in the 21<sup>st</sup>  
1476 century as we enter a new era of antiretroviral-based biomedical interventions for HIV  
1477 prevention in high income countries. The first relevant trend was the rise in notification rates

1478 of gonorrhoea and syphilis in men from the 1960s onwards in countries such as England and  
1479 Wales (Figure 9A) and the USA (Figure 9B). The increase in infections amongst MSM is  
1480 reflected in the rising ratio of male to female notifications in surveillance systems that do not  
1481 record the route of acquisition of STIs. Sexual acts between men were illegal in these  
1482 countries in the 1960s and levels of stigma towards both homosexuality and STIs were still  
1483 extremely high.<sup>370</sup> The availability of penicillin was already stated to have encouraged  
1484 morally sanctioned behaviours by removing fear as a deterrent, particularly of syphilis.<sup>8</sup>

1485 Feldman remarked that “to the astute venereologist AIDS is an almost inevitable  
1486 consequence of the increase in sexually transmitted diseases”.<sup>371</sup> Rates of gonorrhoea and  
1487 syphilis, and the male to female ratio of infections, reached a peak in the late 1970s (Figures 9  
1488 and 10). Other STIs were also common; 50-70% of MSM had serological evidence of  
1489 hepatitis B infection<sup>372</sup> and outbreaks of infections, such as lymphogranuloma venereum  
1490 (LGV) were reported.<sup>373</sup> Infections such as hepatitis A and enteric pathogens, such as *Giardia*  
1491 *lamblia*, *Entamoeba histolytica* and *Shigella* spp., were common causes of gastrointestinal  
1492 disease in MSM and resulted in terms (now considered inappropriate) such as ‘gay bowel  
1493 syndrome’.<sup>374</sup> Given what is now known about the biological effects of STIs to increase both  
1494 infectiousness of, and susceptibility to, HIV,<sup>5</sup> these infections are likely to have facilitated the  
1495 early spread of HIV before it became clinically manifest as opportunistic infections and  
1496 cancers.

1497 Links between the opportunistic conditions comprising AIDS, risky sexual practices and a  
1498 history of multiple STIs in MSM were noted early on,<sup>375</sup> well before a retrovirus was  
1499 discovered as the cause of AIDS. Rates of gonorrhoea and syphilis actually began to fall in  
1500 the late 1970s but the rate of decline accelerated rapidly after the first deaths from AIDS were  
1501 reported in the early 1980s.<sup>123,376,377</sup> Campaigns that arose in the gay community advised  
1502 MSM to reduce numbers of partners and to use condoms, resulting in the development of the  
1503 terminology of ‘safer sex’ within the context of harm reduction. Government-sponsored

1504 public health campaigns for the general population followed.<sup>123</sup> 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.<sup>123,373</sup> 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).<sup>378-381</sup> 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.<sup>381</sup> New outbreaks of LGV,<sup>373</sup> hepatitis  
1514 C, and shigellosis have also appeared, particularly in HIV-infected MSM.<sup>379</sup> Combination  
1515 ART (cART) became available in the mid-1990s and drastically improved the prognosis for  
1516 people with HIV infection,<sup>382</sup> 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.<sup>383</sup> 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.<sup>384</sup> 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.<sup>385,386</sup> Treatment as prevention (TasP; also known as  
1526 “test and treat”<sup>387</sup>) 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.<sup>388</sup> 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

1530 limitations of PEP and is the third and most recent way of using cART for MSM to prevent  
1531 HIV.<sup>389-391</sup>

1532 All three uses of cART for HIV prevention have been accompanied by concern about their  
1533 possible unintended negative consequences for sexual behaviour and STIs,<sup>392</sup> in an analogy  
1534 with earlier fears about penicillin and syphilis.<sup>8</sup> These concerns have been framed within the  
1535 risk compensation hypothesis, which was first applied to sexual behaviour to explain why  
1536 increases in condom use were not reflected in reductions in HIV incidence.<sup>393</sup> Risk  
1537 compensation occurs when an intervention prevents an adverse outcome, paradoxically  
1538 making risk-taking behaviour more attractive; compensatory increases in risky behaviours  
1539 then result in a failure to reduce the adverse outcome. The links between biomedical HIV  
1540 treatment and prevention strategies and sexual risk are dynamic and complex.<sup>22,392</sup>  
1541 Behavioural surveillance amongst MSM, such as surveys carried out yearly in Sydney,  
1542 Australia for 20 years (Figure 11) and the US National HIV Behavioral Survey (NHBS)  
1543 conducted using venue-based sampling in 21 cities in the USA every three years since  
1544 2005,<sup>394,395</sup> show a gradual decline in condom use could be a manifestation of risk  
1545 compensation with several contributing factors over time. “Treatment optimism” about the  
1546 benefits of improved cART has been associated with increased risky behaviour; MSM with  
1547 stronger perceptions that cART has reduced the threat from HIV and that cART reduces the  
1548 need for safer sex engage more often in risky behaviours such as non-condom receptive anal  
1549 intercourse.<sup>396,397</sup> “Safer sex fatigue”<sup>398</sup> and the adverse effects of HIV on mental health<sup>399</sup>  
1550 also contribute to sexual risk taking. Serosorting (choosing sexual partners with the same HIV  
1551 serostatus) results in sexual networks stratified by HIV serostatus with reduced condom use<sup>395</sup>  
1552 and increased risk of STI transmission.<sup>400</sup> In this section of the *Commission* we give an  
1553 overview of the HIV prevention strategies of PEP, TasP and PrEP and examine evidence of  
1554 whether their use results in risk compensation and increases in STI prevalence in MSM. In the  
1555 discussion, we speculate on the potential influence of biomedical interventions on future STI

1556 epidemiology in MSM once implemented more broadly and discuss alternative options for  
1557 STI prevention other than condom use.

1558

### 1559 **Post-exposure prophylaxis (PEP)**

1560 Guidelines for the use of PEP recommend it after both occupational and non-occupational  
1561 exposures with a ‘substantial risk’ of HIV acquisition and with an HIV-positive index or an  
1562 index with an unknown HIV status belonging to a high risk group.<sup>401,402</sup> The efficacy of PEP  
1563 has not been studied in RCTs, but there is a wide consensus about its effectiveness, based  
1564 mainly on one case-control study in a hospital setting, which found an 81% reduction of HIV  
1565 transmission in the group that used PEP.<sup>384</sup> The increased availability of PEP led to concern  
1566 that it may increase in risk taking.<sup>403</sup> Two studies did find a higher risk of non-condom sexual  
1567 behaviour and a higher incidence of HIV in the group of MSM after receipt of PEP but these  
1568 studies did not find a correlation between PEP use and changes in risk behaviour.<sup>404,405</sup> The  
1569 authors concluded that many MSM requesting PEP simply already belong to a high-risk  
1570 group.<sup>405</sup> In high income countries, most PEP requests come from MSM, but uptake remains  
1571 low; 183 requests from one large public health centre in Amsterdam, The Netherlands, over a  
1572 five-year period.<sup>406</sup> Successful awareness campaigns have increased uptake of PEP.<sup>403</sup> The  
1573 limitations associated with ascertaining exposure and eligibility, and suboptimal effectiveness,  
1574 mean that PEP use is unlikely to have any impact on sexual risk behaviour or STIs at the  
1575 population level.

1576

### 1577 **Treatment as prevention (TasP)**

1578 The concept of using cART to prevent sexual transmission of HIV began with the finding that  
1579 transmission between serodiscordant heterosexual couples was rare when the HIV-infected  
1580 partner had a very low or undetectable level of HIV-1 RNA.<sup>385,386</sup> Based on these

1581 observational studies, the Swiss AIDS Commission stated in 2008 that a serodiscordant  
1582 couple could have non-condom sex if the HIV-infected partner was taking cART with  
1583 sustained viral suppression and no other STI.<sup>407</sup> The “Swiss statement” in effect promoted  
1584 widespread HIV testing and immediate treatment to reduce HIV transmission and catalysed  
1585 the initiation of RCTs to examine the impact of TasP at the population level.<sup>387</sup> Mathematical  
1586 modelling studies showed how, assuming zero transmissibility with suppressed viral load,  
1587 universal HIV testing and immediate cART could eliminate HIV within ten years of  
1588 implementation.<sup>408</sup> In 2012, an individual-level RCT in nine countries (HPTN 052, Botswana;  
1589 Kenya; Malawi; South Africa; Zimbabwe; Brazil; India; Thailand; USA) showed that early  
1590 diagnosis and initiation of cART reduced the risk of sexual transmission within stable, mostly  
1591 heterosexual, HIV-serodiscordant couples by 96% (95% CI 73 to 99%) compared with later  
1592 treatment.<sup>409</sup> To extrapolate these benefits to a whole population, a sufficiently high  
1593 proportion of all HIV-infected individuals would need receive and adhere to effective cART  
1594 from very early in the course of infection.<sup>410</sup> The first of the population level trials, a cluster  
1595 RCT in Kwazulu-Natal, South Africa, did not find a reduction in HIV incidence in  
1596 communities that received the TasP intervention.<sup>411</sup> Suboptimal uptake of testing, particularly  
1597 in young men, and delays in linkage to care are likely to have limited the public health  
1598 benefits of TasP,<sup>412</sup> even though an earlier ecological study in the same population had  
1599 suggested that HIV-incidence was lower in people living in communities with higher cART  
1600 coverage.<sup>413</sup>

#### 1601 *Risk compensation, STIs and the TasP strategy*

1602 There is little published about the effects of the TasP strategy on sexual behaviour and on the  
1603 incidence of bacterial STIs in MSM. In most countries; ART recommendations have moved  
1604 gradually towards starting treatment at high CD4 counts. At the individual level, in the HPTN  
1605 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.<sup>409</sup>  
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.<sup>411</sup>

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.<sup>414</sup> 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.<sup>414</sup> 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).<sup>329,415-</sup>  
1620 <sup>417</sup> 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.<sup>329,415-417</sup> 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.<sup>418</sup> 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

1632 from 2000 onwards. A piecewise linear regression analysis showed a sudden change with a  
1633 marked increase in non-condom sex from 2008 to 2013, after the publication of the Swiss  
1634 statement that promoted TasP.<sup>419</sup> Data from the US NHBS surveys amongst MSM, showed  
1635 that condom use has decreased from 2005 up to 2014 over a large geographic area and that  
1636 these trends were not explained by serosorting, seropositioning, PrEP use or cART  
1637 treatment.<sup>395</sup> Figures 10 and 11, show rates in the bacterial STI notifications in England and  
1638 the fall in condom use in Sydney, Australia, suggest that opposing trends in STI rates and in  
1639 condom use have taken place over a 20 year period and cannot be attributed to any one factor,  
1640 such as TasP. Nevertheless, there is a consensus that knowledge about the effects of cART on  
1641 reduced infectiousness of HIV have contributed to risk compensation.<sup>22</sup> A disadvantage  
1642 inherent to TasP is that its success depends on the behaviour of others.<sup>420</sup> The uninfected  
1643 person has to trust that their HIV-infected sexual partners are adherent to cART and that the  
1644 cART is sufficiently effective to mitigate transmission risk. In contrast, with PrEP and PEP,  
1645 the at-risk individual takes the preventive treatment.

1646

#### 1647 **Pre-exposure prophylaxis (PrEP)**

1648 Three RCTs have studied the effects of PrEP on the acquisition of HIV infection as part of an  
1649 HIV prevention package for MSM that includes risk reduction counselling, condom provision  
1650 and regular HIV and STI testing.<sup>389-391</sup> Across these trials, the use of tenofovir disoproxil  
1651 fumarate/emtricitabine (TDF/FTC), in combination with comprehensive sexual health care,  
1652 reduced HIV incidence ranging from 44% to 86%. Two of the RCTs studied daily use of  
1653 TDF/FTC<sup>389,390</sup> and one studied intermittent use (two tablets between 24 and 2 hours before  
1654 sex, followed by two times one tablet at 24 and 48 hours after sex).<sup>391</sup> The first landmark  
1655 study, the Preexposure Prophylaxis Initiative (iPrEX), looked at the effect of daily TDF/FTC  
1656 among 2499 MSM from six countries (Peru, Ecuador, South Africa, Brazil, Thailand and the

1657 USA) and was published in 2010.<sup>389</sup> 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.<sup>390</sup> 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.<sup>391</sup> In all  
1662 PrEP trials, adherence was a strong determinant of PrEP effectiveness.<sup>421</sup>

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.<sup>421-424</sup> 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.<sup>421</sup> International  
1671 guidelines for PrEP from the US Centers for Disease Control and Prevention and WHO  
1672 reflect these eligibility criteria.<sup>329,425</sup>

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<sup>392</sup> 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

1682 participants were blinded and all received the same risk reduction advice. The PROUD RCT  
1683 was designed as a pragmatic open-label study that would allow risk compensation to be  
1684 observed. The total number of different anal sex partners was similar in the two groups, but a  
1685 larger proportion of participants allocated to immediate than deferred PrEP reported non-  
1686 condom receptive anal sex with ten or more partners (21% vs. 12%,  $p=0.03$ ). The proportions  
1687 diagnosed with STIs during the 12 month follow-up period were similar in men receiving  
1688 immediate and deferred PrEP, however; rectal gonorrhoea or chlamydia, 36% vs. 32% (odds  
1689 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).

1690 Open-label studies should allow a more realistic assessment of the influence of PrEP on  
1691 sexual behaviour. In an open-label observational study that included MSM who had taken part  
1692 in the iPrEx trial and two other studies, the proportions reporting non-condom receptive anal  
1693 intercourse, non-condom insertive anal intercourse, and numbers of sexual partners all  
1694 decreased to a similar extent during follow-up in both groups and syphilis incidence (7.2  
1695 infections per 100 person years in PrEP recipients and 5.4 per 100 person years, hazard ratio  
1696 1.35, 95% CI 0.83 to 2.19) was also similar.<sup>422</sup> The authors concluded that there was no  
1697 evidence of risk compensation during open label access to PrEP use, but that cohort  
1698 participation and access to comprehensive prevention services might have encouraged other  
1699 safer sexual behaviours. In the Demo project in San Francisco, Washington DC and Miami,  
1700 USA, early findings (up to 48 weeks) amongst men receiving PrEP have shown a stable  
1701 proportion overall reported having had non-condom receptive anal sex in the previous three  
1702 months (65.5%; 365/557), although the mean number of condom-protected sex acts  
1703 decreased. The proportions with early syphilis, gonorrhoea and chlamydia at quarterly visits  
1704 initially fell and then returned to baseline values.<sup>423</sup> Qualitative data from participants suggest  
1705 that men integrate PrEP in a dynamic way into existing risk reduction strategies, rather than  
1706 relying on it as a solitary method of HIV prevention.<sup>426</sup>

1707 The longer term impact of PrEP for risk compensation and STI rates are not yet known.  
1708 Taken together, trials of PrEP with one to two years of follow up show a large reduction in  
1709 HIV incidence in MSM who adhere to the regimen, high but similar levels of bacterial STIs in  
1710 MSM who received and did not receive PrEP and mixed effects on sexual  
1711 behaviours.<sup>395</sup> Additional studies suggest that increasing use of PrEP as a method of  
1712 biomedical HIV prevention could change patterns of sexual partner seeking and condom  
1713 use.<sup>394,427</sup> Newcomb and colleagues have coined the term “Biomed-matching” as a new  
1714 strategy amongst MSM who meet up using geosocial networking applications and disclose  
1715 their use of biomedical HIV prevention medication; they then have non-condom anal sex  
1716 when the partner is also taking PrEP or has undetectable viral load on cART.<sup>427</sup> MSM who  
1717 receive PrEP will need to be followed carefully over time using both quantitative and  
1718 qualitative research methods to determine whether and how risk compensation and changing  
1719 patterns of sexual partnerships and practices are affecting STI rates.

1720

### 1721 **STI prevention in the era of biomedical HIV prevention**

1722 The use of cART to prevent HIV acquisition and transmission, TasP and PrEP in particular,  
1723 are changing the HIV prevention landscape for MSM. The continued fall in HIV positivity in  
1724 San Francisco, USA has been attributed to TasP and a rapid increase in the number of MSM  
1725 using PrEP in London, UK might have influenced a 40% reduction in new HIV diagnoses in  
1726 2016 compared with 2015.<sup>428</sup> Trends in HIV infection and other STIs seem to have been  
1727 decoupled. STI rates in MSM have been rising since the late 1990s (Figure 10).<sup>427,429</sup> The  
1728 increases in notifications of bacterial STI appear to be accelerating (Figures 9, 10 and 12). In  
1729 England, HIV-infected MSM account for almost all of the increase in STI notifications in  
1730 MSM; for syphilis, the proportion diagnosed in HIV-infected MSM increased from around  
1731 25% in 2009 to around 40% in 2013.<sup>379</sup> In the absence of denominator data, how much of the

1732 increase is the result of more frequent testing is not known. Widening PrEP use, together with  
1733 other behavioural changes, including an increase in the adoption of seroadaptive  
1734 behaviours<sup>394,395</sup> and use of geosocial networking mobile applications, such as Grindr,<sup>427,429</sup>  
1735 could affect sexual networks and influence rates and patterns of STI. For example, if non-  
1736 condom sex partnerships between HIV-uninfected MSM using PrEP and HIV-infected MSM  
1737 on cART become more common, outbreaks of syphilis, LGV, hepatitis, and shigellosis that  
1738 have occurred mostly amongst HIV-infected MSM could spread to networks of HIV-  
1739 uninfected MSM. STIs that increase HIV infectiousness through inflammatory mechanisms<sup>5</sup>  
1740 could then reduce the impact of biomedical HIV prevention methods. Additional surveillance  
1741 and interventions to control STIs amongst MSM in this new era are needed, especially if  
1742 behavioural risk reduction interventions cannot reverse trends in condom use.

1743 Treatment of curable STIs has long been considered an integral component of combination  
1744 HIV prevention packages.<sup>430</sup> Regular STI testing to detect and treat asymptomatic infections  
1745 is now widely recommended for STI control in MSM. MSM starting PrEP are advised to be  
1746 tested for bacterial STIs every three months and MSM in general are usually advised to be  
1747 tested every year, although only about 40% of at-risk MSM in Australia were receiving  
1748 annual screening in 2014.<sup>87</sup> One mathematical modelling study suggested that screening  
1749 MSM for chlamydia could reduce the prevalence of both chlamydia and HIV.<sup>431</sup> These  
1750 findings should be considered in the light of evidence presented in two other sections of the  
1751 *Commission*. First, modelling studies also suggest that chlamydia screening in heterosexual  
1752 populations will reduce chlamydia prevalence,<sup>105,106</sup> but evidence from RCTs<sup>14,95</sup> and repeated  
1753 population-based cross-sectional studies<sup>43,44</sup> have not found appreciable reductions in  
1754 chlamydia prevalence in the target populations (Part 1). Second, as AMR in *N. gonorrhoeae*  
1755 spreads (Part 2), the potential impact of increasing STI testing rates also needs to be  
1756 considered. Mathematical modelling studies of MSM populations show that, at least for some  
1757 antimicrobials, increasing the rate of gonorrhoea treatment might reduce prevalence

1758 temporarily, but that the increased selection pressure accelerates the spread of AMR, resulting  
1759 in increased prevalence over time.<sup>432,433</sup> On the other hand, models of syphilis transmission  
1760 have shown a reduction in incidence with frequent testing and one ecological study using  
1761 national surveillance data in Australia showed that when syphilis testing rose from 1.6 tests a  
1762 year to 2.3 tests a year, there was a reduction in secondary syphilis cases (from 45% to  
1763 26%).<sup>434,435</sup> There was also a commensurate rise in early late infections (from 23% to 45%)  
1764 suggesting that frequent testing was detecting syphilis infection before it reached the  
1765 secondary stage.<sup>434</sup>

1766 Another possible STI intervention that has undergone limited investigation is daily use of  
1767 doxycycline.<sup>436</sup> A single small double blind randomised trial of 30 individuals followed for  
1768 one year showed lower rates of STI in the doxycycline arm.<sup>437</sup> Interventions involving  
1769 prophylactic use of antimicrobials have not been pursued further because of concern about  
1770 AMR. One group is investigating the use of antibacterial mouthwash for the prevention of  
1771 pharyngeal gonorrhoea. The hypothesis is that saliva, used as a lubricant for both anal sex and  
1772 oral sex, gives pharyngeal gonorrhoea a central role in the persistence of gonorrhoea at all  
1773 anatomical sites in MSM, even though relatively little is known about the transmission of  
1774 STIs between anatomical sites in MSM.<sup>438</sup> Mouthwash has been shown in laboratory  
1775 experiments to inhibit *N. gonorrhoeae* growth and when used in individuals with pharyngeal  
1776 gonorrhoea, it reduces the chance of detecting *N. gonorrhoeae* five minutes later.<sup>439</sup> Longer  
1777 term prevention studies are underway using mouthwash. More research is required on STI  
1778 control in MSM that does not rely on condom use including a better understanding of  
1779 infectiousness and transmission between anatomical sites in men.

1780

## 1781 **Conclusions**

1782 Rates of bacterial STIs in MSM have been rising for about 20 years now and are approaching  
1783 the levels seen in the late 1970s before HIV first appeared. During this time ART strategies  
1784 have become powerful and important methods for HIV prevention. Evidence for a major  
1785 contribution of TasP and PrEP to reductions in future HIV incidence and prevalence is  
1786 accumulating. Risk compensation in response to the success of cART in reducing the  
1787 infectiousness of and susceptibility to HIV, mediated through increases in non-condom sexual  
1788 intercourse or increased numbers of sexual partners, has occurred.<sup>22,390</sup> The contributions of  
1789 behavioural responses to the biomedical HIV prevention strategies and of other factors  
1790 influencing sexual behavioural change remain unknown.<sup>394,423,427</sup> Quantifying the effect of  
1791 biomedical HIV prevention interventions on STI rates is methodologically difficult.<sup>377,379</sup>  
1792 Based on surveillance data from places with large populations of MSM,<sup>329,379</sup> it is likely that  
1793 the incidence and prevalence of STI in MSM will continue to increase.

1794 STI control interventions that complement the highly effective biomedical interventions for  
1795 HIV prevention are needed as part of combination prevention packages. Indeed, biomedical  
1796 HIV interventions play a positive role in STI control through frequent contacts with sexual  
1797 health services that allow regular continued opportunities for primary prevention and  
1798 comprehensive case management of STIs including prompt diagnosis and treatment, partner  
1799 notification, condom promotion and risk reduction interventions.<sup>440</sup>

1800 Nevertheless, continued research is needed to investigate and understand the effects of  
1801 TasP and PrEP on sexual behaviours and networks that might increase STI transmission and,  
1802 through STI-HIV interactions, might drive renewed HIV transmission. Enhanced biological  
1803 and behavioural surveillance activities are needed to monitor changes in STIs in HIV-  
1804 uninfected and HIV-infected MSM, AMR, and the emergence or re-emergence of new  
1805 sexually transmissible pathogens including enteric infections and Ebola and Zika viruses.<sup>441</sup>

1806



## 1807 **Call to action**

1808 Action is required to address the substantial challenges facing STI control globally (table 4).  
1809 AMR in *N. gonorrhoeae* is increasing relentlessly and adverse consequences of chlamydia  
1810 infection remain prevalent. STIs in MSM are rising rapidly, new sexually transmissible  
1811 infections are emerging or re-emerging and there is evidence that BV, one of the most  
1812 common, but often ignored, genital conditions in women, might also be sexually  
1813 transmissible. These issues are magnified in low and middle income countries that bear the  
1814 burden of STIs worldwide. To address these issues we need to reach our policy makers and to  
1815 convince them to invest in clinical and public health strategies to improve the control of STIs,  
1816 based on carefully considered analytical decisions, founded in science. If they do not, we may  
1817 suffer more than we should, and spend more than we need.<sup>442</sup> In putting this case, we  
1818 recognise that social, cultural and structural conditions are major determinants of sexual  
1819 behaviour, sexual risk and STIs.<sup>443</sup> Research evidence provides the scientific support for  
1820 prioritising interventions, but successfully influencing health policy will require the  
1821 involvement of stakeholders, including researchers, clinicians, and members of civil society  
1822 as well as policy makers themselves.<sup>444</sup>

1823 One of the most important messages about STI control is that good policy decisions matter  
1824 much more than poor individual ones.<sup>442,445,446</sup> This is because effective policy interventions  
1825 can put strong downward pressure on STI incidence,<sup>33</sup> while individual behaviour has a  
1826 relatively weak effect on the population prevalence of STIs and sustained and substantial  
1827 behaviour change is difficult to achieve.<sup>442,446,447</sup> We need to make the case to policy makers  
1828 that STIs cost less to keep under control than to treat, and manage their sequelae, when  
1829 endemic levels are high.<sup>442</sup>

1830 The cornerstone of the health sector response to effective STI control is easily accessible  
1831 quality health care, and is the principle behind the provision of free STI services in many

1832 countries.<sup>445</sup> Accessible health care helps to ensure that STIs are treated early, before  
1833 substantial transmission can occur.<sup>33</sup> Communities with poor access to health care have high  
1834 rates of symptomatic STIs such as gonorrhoea or trichomoniasis, and those with accessible  
1835 health care have much lower rates, even though the number of sexual partners in both  
1836 communities might be similar.<sup>448</sup> For example, gonorrhoea in heterosexuals is relatively easy  
1837 to control with accessible primary health care and, as a result, most high income countries  
1838 rates of reported gonorrhoea are well below 100 per 100,000 population. Rates in  
1839 heterosexuals exceed these levels in high income countries in populations whose access to  
1840 health care is limited, such as among uninsured Americans or Indigenous Australians living in  
1841 remote communities.<sup>448,449</sup> STI services are a key goal of the WHO strategy to help achieve  
1842 universal health coverage, a key target of the 2030 Agenda for Sustainable Development.<sup>33</sup>  
1843 We call on policy makers to ensure their citizens have accessible, affordable and quality STI  
1844 care.

1845 Largely asymptomatic STIs such as chlamydia provide a much greater challenge to  
1846 control. Despite substantial proportions of the population being tested for chlamydia in some  
1847 high income countries it has proven difficult to reduce the prevalence and we remain  
1848 uncertain about the long term impact that widespread testing for chlamydia has on the key  
1849 health outcomes including PID, ectopic pregnancy and infertility. Chlamydia control  
1850 strategies should define acceptable local targets for chlamydia prevalence, so that appropriate  
1851 interventions can be prioritised. Improving case management of those diagnosed with  
1852 chlamydia and PID (e.g. effective antimicrobial treatment, partner notification and retesting to  
1853 detect repeated infection) might achieve more than promoting widespread testing alone. We  
1854 should also establish and adapt surveillance systems so that we know what impact our  
1855 chlamydia control activities are having on PID and its complications. We call on policy  
1856 makers to invest in the research agendas that has been repeatedly called for by international  
1857 experts,<sup>60,150,151,450</sup> to further our understanding about the natural history of chlamydia and

1858 develop non-invasive measures of tubal infection, inflammation and damage and biomarkers  
1859 to predict upper genital tract pathology. Further we must invest in chlamydia vaccine research  
1860 because without an effective vaccine, it is unlikely that we will be able to control it.

1861 The effective control of gonorrhoea is a global health priority<sup>33</sup> because of the relentless  
1862 rise in AMR, and the high incidence in low and middle income countries and increasing  
1863 incidence in key populations, including MSM (Figure 10).<sup>379</sup> In this context we call on policy  
1864 makers to ensure adequate and sensitive surveillance programmes are in place and industry to  
1865 support the development of effective agents should the current ones fail. The control of  
1866 gonorrhoea in MSM presents a similar problem to chlamydia because asymptomatic  
1867 pharyngeal and rectal infection are common and frequently occur in the absence of concurrent  
1868 symptomatic urethral infection, so cases are only detected through testing or partner  
1869 notification.<sup>451</sup> Some have advocated more frequent screening, but at least with some  
1870 antimicrobials an increased rate of gonorrhoea treatment might accelerate the spread of AMR  
1871 and might outweigh any gains in reducing prevalence.<sup>433</sup> Another problem with gonorrhoea  
1872 control in MSM is that it is not prevented by consistent condom use for anal sex, because the  
1873 pharynx appears to play a key role in transmission of both infection and AMR.<sup>157,452,453</sup>  
1874 Effective control will require understanding how gonorrhoea is transmitted between MSM so  
1875 evidence-based interventions can be developed just as interventions for HIV control were  
1876 developed by understanding its transmission. Ideally condoms should not be a critical part of  
1877 these interventions given condoms rates are falling and may fall further.<sup>453</sup> Recent research  
1878 has suggested a potential non-condom based intervention.<sup>439</sup> Researchers have found that *N.*  
1879 *gonorrhoeae* is commonly present in the saliva of men with pharyngeal infection, and that  
1880 saliva is frequently used as a lubricant for anal sex.<sup>454</sup> Early work has shown that antibacterial  
1881 mouthwash might inhibit *N. gonorrhoeae* growth and studies of mouthwash for gonorrhoea  
1882 prevention are underway.<sup>439</sup> We call on policy makers to fund research to better understand

1883 how STIs are transmitted between MSM to allow the development of new control  
1884 programmes not based only around condoms.

1885 BV in women is another commonly asymptomatic infection with a substantial global  
1886 burden that poses similar control issues to chlamydia but has the additional problem that there  
1887 is a lack of a proven transmitted pathogen. Effective control is complicated by its high relapse  
1888 rate which is likely to be due, at least in part, to our failure to recognise the importance of  
1889 sexual transmission in its pathogenesis and the contribution of reinfection to recurrence.<sup>20,246</sup>  
1890 Current treatment strategies are entirely focused on the female partner, while accumulating  
1891 epidemiological and microbiological data provide evidence of male carriage and exchange of  
1892 BV-associated bacteria within sexual partnerships.<sup>265,423</sup> In order to make significant advances  
1893 in the treatment and prevention of BV and its costly sequelae we need to better understand the  
1894 contribution of persistence of BV-associated bacteria versus reinfection to BV recurrence.  
1895 New treatment strategies are required but we also need to revisit male partner treatment trials  
1896 with more evidence-based approaches.

1897 Effective STI control in low and middle income settings provide a particular challenge  
1898 because of the high cost of diagnostic tests and limited laboratory capacity that accompany  
1899 weak health service infrastructure. POC tests that fulfil the WHO ASSURED benchmarking  
1900 programme can play an important role in effective STI control, but understanding their  
1901 limitations is critical. Policy makers should fund programmes that optimise and evaluate all  
1902 aspects of STI control in low and middle income countries with the implementation of the  
1903 validated POC tests including, but not limited to, screening of antenatal care attendees and  
1904 high risk populations, improved partner notification strategies, and symptomatic case  
1905 management. Policy makers should fund programmes that optimise and evaluate all aspects of  
1906 STI control including, but not limited to, improved partner notification programmes,  
1907 presumptive treatment, POC tests, syndromic management and combinations of all of these.

1908 It is important to acknowledge that STI control strategies that rely *only on reducing sexual*  
1909 *risk practices* at a population level will not work well because on their own, they afford a  
1910 relatively modest effect on STI prevalence. Large multicentre studies of behavioural  
1911 interventions for condom use for example have relatively modest effect sizes (~20% effective  
1912 at one year).<sup>446,447</sup> In contrast, biomedical interventions such as the HPV vaccine programme  
1913 in women have been outstandingly successful and resulted in almost complete elimination of  
1914 the oncogenic HPV in the vaccine in both vaccinated women and unvaccinated heterosexual  
1915 men in Australia.<sup>11,455</sup> Similarly large effect sizes for reducing HIV acquisition are seen in  
1916 RCTs of PrEP when adherence levels are high.<sup>389-391</sup> Biomedical methods to prevent HIV  
1917 have, however, contributed to increased rates of STIs amongst MSM as a result of risk  
1918 compensation. No single measure will effectively control all STIs at a population level.  
1919 Effective STI control will require the political will to prioritise and invest in new  
1920 interventions together with the optimisation of both primary and secondary prevention  
1921 strategies including; integrated sex education programmes in schools, strong partner  
1922 notification programmes that utilise the latest information technology systems and legislative  
1923 changes for partner delivered antibiotic treatment where appropriate, legalised frameworks for  
1924 sex work, active targeted health promotion, accurate surveillance programmes and of course  
1925 accessible health care for all.

1926

1927 **FIGURE LEGENDS**

1928 **Figure 1: WHO estimates of the number of cases (in millions) of four curable STIs**  
1929 **trichomoniasis (TV), chlamydia (CT), gonorrhoea (NG), and syphilis (TP) globally in**  
1930 **2012. Source: reference<sup>2</sup>**

1931 **Figure 2: Natural history and sequelae of *Chlamydia trachomatis* infection in women.**  
1932 **Length of arrows are not proportional to time. Dotted lines are conditions that can**  
1933 **resolve.**

1934 **Figure 3: Interventions for the control of chlamydia in the population. Source:**  
1935 **reference<sup>31</sup>**  
1936 Evidence<sup>31</sup>-based case management includes partner notification, prevention of re-infection  
1937 [advice on sexual behaviour and condom use] and re-testing within a recommended time  
1938 period after treatment)

1939 **Figure 4: Chlamydia prevalence estimates among sexually experienced women  $\leq 26$**   
1940 **years estimated in cross sectional suveys of randomly sampled individuals from the**  
1941 **general population in WHO regions.**

1942 **Source:**

1943 Europe

1944 Croatia (N=151);<sup>46</sup> France (N=106);<sup>38</sup> The Netherlands (N=2626);<sup>41</sup> Norway (N=930);<sup>42</sup>  
1945 Slovenia (N=265);<sup>40</sup> Spain (N=157);<sup>49</sup> United Kingdom (N=992)<sup>44</sup>

1946 Americas

1947 USA (N=unavailable);<sup>45</sup> Argentina (N=148);<sup>49</sup> Colombia (N=278)<sup>49</sup>

1948 Africa

1949 Nigeria (N=120)<sup>49</sup>

1950 South-East Asia

1951 China 1 (N=194);<sup>52</sup> China 2 (N=46);<sup>49</sup> India;<sup>50</sup> Thailand 1 (N=69);<sup>49</sup> Thailand 2 (N=129);<sup>49</sup>

1952 Vietnam 1 (N=158);<sup>49</sup> Vietnam 2 (N=123)<sup>49</sup>

1953 Western Pacific

1954 Australia (N=135);<sup>39</sup> Papua New Guinea (PNG; N=73)<sup>51</sup>

1955 **Figure 5: Hospital discharge rates for inflammatory disease in female pelvic organs.**

1956 **Source: reference<sup>122</sup>**

1957 See supplementary table 1 for further detail.<sup>122</sup>

1958 **Figure 6: Interventions attempted for the management and prevention of bacterial**  
1959 **vaginosis**

1960 **Figure 7: Point-of-care (POC) or near-POC tests for STIs that are available or in the**  
1961 **pipeline. The dotted line means that no market launch date has been set by the**  
1962 **company. Source: updated from reference<sup>325</sup> XenoStrip-TV<sup>TM</sup> rapid diagnostic test for *T.*  
1963 *vaginalis* (Xenotope Diagnostics, Inc, San Francisco, USA), OSOM<sup>®</sup> rapid diagnostic test for  
1964 *T. vaginalis* (Sekisui Diagnostics, Lexington, USA); GeneXpert<sup>®</sup> for *C. trachomatis*, *N.*  
1965 *gonorrhoeae*, duplex *C. trachomatis* and *N. gonorrhoeae*, *T. vaginalis*, HPV (Cepheid Inc.,**

1966 Sunnyvale, USA); AmpliVue® for *T. vaginalis* (Quidel Corporation, San Diego, USA); Atlas  
1967 io™ for *C. trachomatis*, duplex *C. trachomatis* and *N. gonorrhoeae*, *T. vaginalis* (Atlas  
1968 Genetics, Trowbridge, UK); Truelab™ Real Time micro PCR System for *C. trachomatis*, *N.*  
1969 *gonorrhoeae* (Molbio Diagnostics Pvt. Ltd., Goa, India); Alere™-i for duplex *C. trachomatis*  
1970 and *N. gonorrhoeae* (Alere Inc., Waltham USA); GeneXpert® Omni for duplex *C.*  
1971 *trachomatis* and *N. gonorrhoeae*, HPV (Cepheid Inc., Sunnyvale, USA); Cobas® Liat  
1972 Analyser (Roche, Basel, Switzerland); RT CPA *C. trachomatis* (Ustar Biotechnologies,  
1973 Hangzhou, China); PanNAT® (Micronics, Inc., Portsmouth, USA).

1974 **Figure 8: Point-of-care tests for dual syphilis and HIV diagnosis that are available.**

1975 **Source: updated from reference**<sup>325</sup> Standard Diagnostics (SD) Bioline HIV/Syphilis Duo  
1976 Rapid Test (Alere, Waltham USA)/(Standard Diagnostics, Republic of Korea); DDP  
1977 ®HIV-Syphilis Assay (Chembio Diagnostic Systems, Inc., Medford, USA); Multiplo Rapid  
1978 TP/HIV Antibody test (MedMira, Inc., Halifax, Canada); INSTI Combined HIV/Syphilis  
1979 test (Biolytical Laboratories Inc., Richmond, Canada); mChip Assay (Junco Labs,  
1980 Columbia University, New York, USA in collaboration with OPKO Health, Inc., Miami,  
1981 USA).

1982 **Figure 9A: Notifications of infectious syphilis 1950-2015 by sex and male:female ratio**  
1983 **in England and Wales. Source: Public Health England.**

1984 **Figure 9B: Primary and Secondary Syphilis in the US 1995-2015 by sex and**  
1985 **male:female ratio in United States. Source: Centres for Disease Control and**  
1986 **Prevention.**

1987 **Figure 10: Notifications of HIV, syphilis (primary, secondary, early latent), gonorrhoea**  
1988 **and chlamydia, 1996-2015 in men who have sex with men, England. Source: 2001-2015,**  
1989 **Public Health England (<https://www.gov.uk/government/statistics/hiv-annual-data-tables>),**  
1990 **2000 and earlier, National Archive (<http://webarchive.nationalarchives.gov.uk/>). cART,**  
1991 **combination antiretroviral therapy; cPEP, combination post-exposure prophylaxis; Swiss**  
1992 **statement; TasP, treatment as prevention; PROUD results made public.**

1993 **Figure 11: Condom use for anal sex among men who have sex with men in Sydney,**  
1994 **Australia 1997-2016. Source: Gay Community Periodic Survey**

1995 **Figure 12: Percentage of tests positive for HIV, primary and secondary syphilis and**  
1996 **gonorrhoea, 2005-2014, and mean number of sexual partners in last three months, 2008-**  
1997 **2013, San Francisco, USA. Source: San Francisco Department of Health.**

1998

1999

2000 **Contributors**

2001 Each group of authors takes responsibility for the text and views expressed in their individual  
2002 sections. CKF conceived the *Commission* and coordinated its preparation. CSB wrote the  
2003 executive summary together with MU and CKF. MU and CSB wrote the introduction; JSH  
2004 and NL wrote Part 1; MU wrote Part 2; CSB, JAS and JMM wrote Part 3; SCF, RWP and  
2005 DM wrote Part 4; HJCV, GJBS, EH, SSP, CKF and NL wrote Part 5; CKF wrote the call for  
2006 action. NL, CSB, CKF and MU were involved in editing the final *Commission*. All authors  
2007 approved the final manuscript.

2008

2009 **Declaration of interests**

2010 We declare that we have no conflicts of interest.

2011

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2015



Antimicrobial (other names)	Class	Mode of action	Bacterial target (known resistance mutations)	<i>In vitro</i> activity against <i>Neisseria gonorrhoeae</i> (MIC range/MIC <sub>50</sub> /MIC <sub>90</sub> (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 <sup>202,457</sup> )	0.001-32/0.064-0.125/0.125-0.25 <sup>202,210</sup>	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 <sup>a</sup>
Zoliflodacin (AZD0914, ETX0914)	Spiropyrimidinetrone	DNA biosynthesis inhibition and accumulation of double-strand cleavages	DNA gyrase and Topoisomerase IV? (D429N, D429A, and K450T in GyrB, <sup>197,201</sup> overexpressed MtrCDE increases MIC <sup>201</sup> )	≤0.002-0.25/0.064-0.125/0.125-0.25 <sup>206,211,215,216</sup>	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 <sup>213</sup>	Phase 2 (100 participants)	1.5 g×1 p.o. or 3 g×1 p.o.	-	Data not available

<sup>a</sup>Adverse events observed in  $\geq 10\%$  of patients using solithromycin 1 g $\times$ 1 in published Phase 2 trial. Most nausea and vomiting appeared  $\geq 1$  hour after ingestion of solithromycin, which indicates that the drug was already absorbed.<sup>203</sup>

**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;<sup>157</sup>
  - 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),<sup>152,153,158,458</sup> a gonococcal vaccine,<sup>150</sup> rapid molecular methods for predicting AMR (for AMR surveillance but ideally also to inform individualized treatment),<sup>190-192</sup> rapid point of care tests for diagnosis of gonorrhoea (ideally with combined prediction of AMR);<sup>190,191</sup> ideal phylogenomics of gonococci and their AMR (also in non-cultured samples);<sup>159,457,459-464</sup> 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 (%)
<b><i>Chlamydia trachomatis</i><sup>a</sup></b>			
Biostar OIA Chlamydia test <sup>b</sup>	Endocervical swabs	59.4-73.8	98.4-100
Clearview Chlamydial test <sup>b</sup>	Endocervical swabs	49.7	97.9
	Vaginal swabs	32.8	99.2
Quick Vue Chlamydia rapid test <sup>b</sup>	Endocervical swabs	25.0-65.0	100
	Vaginal swabs	83.5	98.9
aQcare Chlamydia TRF <sup>c</sup>	Endocervical and urethral swabs	93.8	96.8
	Urine	88.2	94.7
Chlamydial Rapid Test, Diagnostics for the Real World <sup>c</sup>	Male urine	41.4	89.0
	Vaginal swabs	39.4-74.2	94.4-96.8
ACON Chlamydia Rapid Test Device <sup>c</sup>	Vaginal swabs	66.7	91.3
	Endocervical swabs	22.7-30.5	99.8-100
	Male urine	43.8	98.3
GeneXpert CT/NG <sup>b</sup>	Endocervical swabs	97.4	99.6
	Vaginal swabs	98.7	99.4
	Female urine	97.6	99.8
	Male urine	97.8	99.9
<b><i>Neisseria gonorrhoeae</i><sup>a</sup></b>			
Biostar OIA GC Test <sup>b</sup>	Endocervical swabs	60.0	89.9
	Urine	100	93.0-98.0
ACON Duo CT/NG <sup>c</sup>	Endocervical swabs	12.5	99.8
GeneXpert CT/NG <sup>b</sup>	Endocervical swabs	100	100
	Vaginal swabs	100	99.9
	Female urine	95.6	99.9
	Male urine	98.9	99.9
<b><i>Trichomonas vaginalis</i></b>			
OSOM TV rapid test <sup>b</sup>	Vaginal swabs	83.3-90	98.8-100

GeneXpert TV <sup>d</sup>	Vaginal swabs	95·0-95·6	95·7-100
Affirm VPIII microbial identification test <sup>a,b</sup>	Vaginal swabs	46·3	100
<b><i>Treponema pallidum</i> (syphilis)</b>			
Alere Determine Syphilis TP <sup>e</sup>	Whole blood/serum/plasma	59·6-100	95·7-100
Omega VisiText Syphilis <sup>e</sup>	Whole blood/serum/ plasma	72·7-98·2	98·1-100
Qualpro Syphicheck-WB <sup>e</sup>	Whole blood/serum/ plasma	64-97·6	98·4-99·7
SD Bioline Syphilis 3.0 <sup>e</sup>	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 <sup>f</sup> (Chembio Diagnostic Systems, Inc)	Treponemal antibody	90·1-98·2	91·2-98·0
	Non-Treponemal	80·6-98·2	89·4
<b>Dual HIV/TP Syphilis</b>			
SD Bioline HIV/Syphilis Duo Rapid Test <sup>g</sup> (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 <sup>g</sup> (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 <sup>g</sup> (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<sup>352</sup>; c= Data taken from<sup>359,360</sup>; d = Data taken from<sup>353</sup>; e= Data taken from<sup>350</sup>; f=Data taken from<sup>365</sup>; g= Data taken from<sup>325</sup>

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

**Table 4: Call to Action**

<b>Policy Priorities</b>	<b>Research Priorities</b>
Ensure accessible health care for early treatment of symptomatic STIs	Develop measures of 'access to health care services' and set minimum benchmarks
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

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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 <sup>150</sup>	Undertake the laboratory and subsequent clinical research necessary for successful vaccines

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<sup>150</sup>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.**<sup>122</sup>

Country	Source	Comment
Australia	Australian Institute of Health and Welfare Hospital Morbidity Database	<p>Reference period: 1 July to 30 June.</p> <p>Coverage:</p> <ul style="list-style-type: none"> <li>- Data are derived using AIHW analysis of the AIHW National Hospital Morbidity Database (NHMD). Please see <a href="http://meteor.aihw.gov.au/content/index.php/tml/itemId/611030">http://meteor.aihw.gov.au/content/index.php/tml/itemId/611030</a> 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.</li> <li>- 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.</li> <li>- Data presented are based on overnight admitted patient separations. They exclude same-day separations.</li> </ul>
Austria	Statistics Austria, Hospital discharge database; raw data: Austrian Ministry of Health	<p>Reference period: 31 December.</p> <ul style="list-style-type: none"> <li>- <i>Coverage by hospital type</i>: The Austrian hospital discharge database covers all inpatient institutions classifiable as HP.1 according to SHA/OECD.</li> <li>- <i>Missing records</i>: The database includes all inpatient discharges and day cases: <ul style="list-style-type: none"> <li>- Day cases are all cases admitted and discharged on the same day (before midnight).</li> <li>- Inpatients include discharges to home, other inpatient-institutions and deaths in hospitals.</li> </ul> </li> </ul> <p>The Austrian hospital discharge database is based on the Austrian DRG system (DRG =</p>

Country	Source	Comment
		diagnosis related group).
Belgium	The Federal Public Service of Health, Food Chain Safety and Environment, Directorate 1 -Minimal Clinical Data.	<p>Reference period: during the year.</p> <p>Coverage:</p> <ul style="list-style-type: none"> <li>- The Federal Public Service of Health, DG 1 "Organisation of health institutions" is responsible for the registration of the Minimal Hospital Data.</li> <li>- Hospital days for inpatients concern only acute admissions in acute hospitals (with at least 1 overnight stay in the hospital).</li> <li>- Patient data in psychiatric hospitals are NOT included.</li> <li>- Long lasting stays are excluded (more than 6 months or 184 days).</li> <li>- Deceased patients are included.</li> </ul>
Canada	<p>Statistics Canada, <i>Hospital Morbidity Database</i>, 1980/81 to 1993/94.</p> <p>- Canadian Institute for Health Information, <i>Discharge Abstract Database</i> and <i>Hospital Morbidity Database</i> starting in 1994/95 (the Hospital Morbidity Database was transferred from Statistics Canada to the Canadian Institute for Health Information in 1994/95), <i>Ontario Mental Health Reporting System</i> starting in 2006/07 until 2012/13, and <i>Hospital Mental Health Database</i> starting in 2013/14.</p>	<p>Reference period: April 1 to March 31<sup>st</sup></p> <p>Coverage:</p> <ul style="list-style-type: none"> <li>- 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.</li> <li>- Separations in Canada include discharges both alive and dead for the condition most responsible for the length of stay.</li> <li>- Data are for acute care hospitals only, except for the data on mental and behavioural disorders which include psychiatric hospitals starting in 2013/14.</li> <li>- 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</li> </ul>

Country	Source	Comment
		<p>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.</p> <p>- 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.</p>
Chile	Ministry of Health (MINSAL), Department of Health Statistics and Information (DEIS).	<p>Hospital discharges from 2001-2013</p> <p>Coverage:</p> <p>- Data coverage is nationwide. Data include both public and private sectors.</p> <p>- Data include same-day separations and deaths.</p> <p>- 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).</p>
Estonia	<p>Ministry of Social Affairs, Department of Health Information and Analysis, routinely collected aggregate hospital statistics.</p> <p>- Since 1st January 2008: National Institute for Health Development, Department of Health Statistics</p>	<p>Reference period: Calendar year.</p> <p>Coverage:</p> <p>- <i>Coverage by hospital type</i>: All hospitals (HP.1), public and private, are covered.</p> <p>- ICD-10 is used for data collection.</p> <p>- <i>Inpatient cases</i>: 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.</p>

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).	<p>Reference period: Calendar year.</p> <p>Coverage:</p> <p>- 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.</p>
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 ( <a href="http://www.hpo.ie">www.hpo.ie</a> ).	<p>Reference period: Data are based on the year of discharge.</p> <p>Coverage:</p> <p><i>Coverage by hospital type</i></p> <p>- HIPE data covers all inpatients and day cases receiving curative and rehabilitative care in publicly funded acute hospitals in the State.</p> <p>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</p>

Country	Source	Comment
		Australian Coding Standards.
Slovenia	National Institute of Public Health, Slovenia; National Hospital Health Care Statistics Database.	<p>Reference period: During the year.</p> <p>Coverage:</p> <ul style="list-style-type: none"> <li>- <i>Coverage by hospital type</i>: 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).</li> <li>- Data include: <ul style="list-style-type: none"> <li>- Inpatient discharges</li> <li>- Day-cases discharges</li> <li>- All patients (including uninsured, foreigners)</li> <li>- Long duration stays in hospitals</li> <li>- Palliative care in hospitals</li> <li>- Healthy newborn babies (since 2003)</li> </ul> </li> </ul> <p><i>Definition of main diagnosis</i>: 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.</p>
Switzerland	FSO Federal Statistical Office, Neuchâtel. Medical Statistics of Hospitals, 2002 and following years.	<p>Reference period: Annual census.</p> <p>Coverage:</p> <ul style="list-style-type: none"> <li>- <i>Coverage by hospital type</i>: 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.</li> <li>- <i>Definition of main diagnosis</i>: The main diagnosis is defined as the condition</li> </ul>

Country	Source	Comment
United Kingdom	<p>Data have been aggregated by the NHS Information Centre for Health and Social Care from the following sources:</p> <ul style="list-style-type: none"> <li>- <i>England</i>: Hospital Episode Statistics (HES); Inpatients, Health &amp; Social Care Information Centre (HSCIC), England. <a href="http://www.hscic.gov.uk">http://www.hscic.gov.uk</a>.</li> <li>- <i>Wales</i>: Patient Episode Database for Wales (PEDW), NHS Wales Informatics Service (NWIS). <a href="http://www.statswales.wales.gov.uk/index.htm">http://www.statswales.wales.gov.uk/index.htm</a>.</li> <li>- <i>Scotland</i>: Information Services Division (ISD), National Health Service Scotland (SMR01 records). <a href="http://www.isdscotland.org/Health-Topics/Hospital-Care/Data_Sources_and_Clinical_Coding.doc">http://www.isdscotland.org/Health-Topics/Hospital-Care/Data_Sources_and_Clinical_Coding.doc</a>.</li> <li>- <i>Northern Ireland</i>: Hospital Inpatient System (HIS), The Department for Health, Social Services and Public Safety in Northern Ireland (DHSSPSNI). <a href="http://www.dhsspsni.gov.uk/hospital-activity">http://www.dhsspsni.gov.uk/hospital-activity</a>.</li> </ul>	<p>diagnosed at the end of the hospitalisation period, primarily responsible for the patient's need for treatment or examination at the hospital.</p> <p>Reference period:</p> <ul style="list-style-type: none"> <li>- <i>England, Wales and Scotland</i>: Data is based on Financial Discharge Years 1st April to 31st March.</li> <li>- <i>Northern Ireland</i>: Data have been tabled by calendar year.</li> <li>- Includes records for discharge dates occurring in the reference year, regardless of admission date.</li> </ul> <p>Coverage:</p> <ul style="list-style-type: none"> <li>- <i>Coverage by hospital type</i>: <ul style="list-style-type: none"> <li>☑ <i>England</i>: Inpatient data cover activity in English NHS Hospitals and English NHS commissioned activity in the independent sector. ☑ <i>Scotland</i>: 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.</li> <li>☑ <i>Wales</i>: All NHS commissioned data carried out in private sector hospitals is included.</li> <li>☑ <i>Northern Ireland</i>: Inpatient data cover activity in Northern Ireland HSC hospitals including independent sector activity carried out in HSC hospitals.</li> </ul> </li> </ul>
USA	Centers for Disease Control and Prevention/National Center for Health Statistics/National Hospital Discharge	<p>Coverage:</p> <ul style="list-style-type: none"> <li>- National representative sample of the U.S.</li> </ul>

Country	Source	Comment
	<p data-bbox="341 264 791 459">Survey Annual Summary, Advance Data from Vital and Health Statistics Summary (published annually). Vital and Health Statistics, Series 13, completed by unpublished tables.</p> <p data-bbox="341 495 791 566"><a href="http://www.cdc.gov/nchs/about/major/hdasd/nhds.htm">http://www.cdc.gov/nchs/about/major/hdasd/nhds.htm</a>.</p>	<p data-bbox="831 264 1375 293">civilian non-institutionalised population.</p> <ul style="list-style-type: none"> <li data-bbox="831 331 1375 734">- 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.</li> <li data-bbox="831 772 1375 1086">- 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.</li> <li data-bbox="831 1124 1375 1236">- All U.S. discharges were coded to the International Classification of Diseases, Ninth Revision (ICD-9).</li> <li data-bbox="831 1274 1375 1384">- A hospital discharge is the completion of any continuous period of stay in a hospital as an inpatient.</li> </ul>

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