Gonorrhoea

HIV PREVENTION ENGLAND

The number of gonorrhoea diagnoses has increased dramatically in England in recent years, especially among gay, bisexual and other men who have sex with men, young people and people of Black Caribbean ethnicity. While there is increasing concern over resistance to the antibiotics used to treat the infection, new methods of preventing gonorrhoea and other STIs may be available in the coming years. This briefing reviews the implications for sexual health and HIV services and for advocacy.

Gonorrhoea as a sexual health problem

Symptoms of gonorrhoea, such as discharge from the genitals or anus and burning sensation while passing urine, may appear within a few days of infection. However, many people only have very mild symptoms or none until the infection spreads to other parts of the body.

Gonorrhoea acquired during pregnancy can cause miscarriage or early labour. It can also cause conjunctivitis in infants exposed during childbirth. If left untreated, gonorrhoea can cause pelvic inflammatory disease (an infection in the upper part of the female reproduction system), swelling and pain in the testicles (epididymo-orchitis) and infertility. Untreated gonorrhoea can lead to a disseminated infection that causes joint and tendon pain, a rash, arthritis and dermatitis, and in rare cases, swelling of the heart or meningitis.

If a person living with HIV is not on antiretroviral treatment, untreated gonorrhoea can increase the risk of transmitting HIV to others. It can also increase a person's risk of acquiring HIV if they are not taking PrEP. A diagnosis of rectal or genital gonorrhoea in a person without HIV and not taking PrEP is an indicator of unmet need for PrEP.

In the UK, gonorrhoea is usually treated with a single intramuscular injection of 1g of ceftriaxone (see *Treatment guidelines* below). In other countries, lower doses of ceftriaxone may be used, often in combination with another antibiotic called azithromycin. However, the bacteria that cause gonorrhoea have developed resistance to a succession of medications over the years (see *How does gonorrhoea develop resistance?* below).

Gonorrhoea epidemiology in England

In 2022, 82,592 cases of gonorrhoea were diagnosed in England, the highest number of diagnoses since records began in 1918.[1] Gonorrhoea diagnoses in 2022 increased by 50% compared with 2021 (54,961 cases).

The increase in diagnoses is partly a consequence of an increase in testing. In 2022, 2.19 million sexual health screens (diagnostic tests for chlamydia, gonorrhoea, syphilis, and HIV) were carried out by sexual health services in England, an increase of 37% compared to 2014.

While gonorrhoea can affect anyone, certain populations are disproportionately affected including gay, bisexual and other men who have sex with men (GBMSM), people of Black Caribbean ethnicity and young people.

Two-thirds of cases of gonorrhoea in men and almost half of all gonorrhoea cases (47%) are diagnosed in GBMSM. As shown in Figure 1, the rate of gonorrhoea diagnosis per 100,000 people is around 90 times higher in GBMSM than in men who have sex with women (MSW) and around 75 times higher than rates in women who have sex with men (WSM).

In 2022, gonorrhoea was the most frequently diagnosed STI in GBMSM, while chlamydia was the most frequently diagnosed STI in women and in men who have sex with women. Among GBMSM, increasing PrEP use contributes to more frequent testing for STIs, as regular screening is part of the package of PrEP provision.

Among GBMSM, the rate of gonorrhoea diagnosis was approximately three to four times higher in London than in other regions of England. The rate of diagnosis was highest in those aged 25-34 and 35-44.

Particularly marked differences by age group are seen among heterosexual men and women, as shown in Figure 2. The rate of diagnosis was highest in those aged 15-19 and 20-24, especially young women aged 15-19.

Ethnic disparities in gonorrhoea rates were seen in all regions of England. As shown in Figure 3, rates were approximately two to four times higher in Black people than other ethnic groups. Gonorrhoea rates were particularly high in people of Black Caribbean ethnicity or Mixed Black Caribbean and White ethnicity. These differences are thought to be driven by underlying socio-economic factors and structural determinants of health, rather than differences in behaviour.

Rates of diagnosis rose across all populations, regions and age groups in the decade up to 2019. The rate of gonorrhoea diagnosis increased by 643% among GBMSM between 2009 and 2019.[2]

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Figure 1: Gonorrhoea diagnoses per 100,000 people, by gender and sexual orientation, 2022.

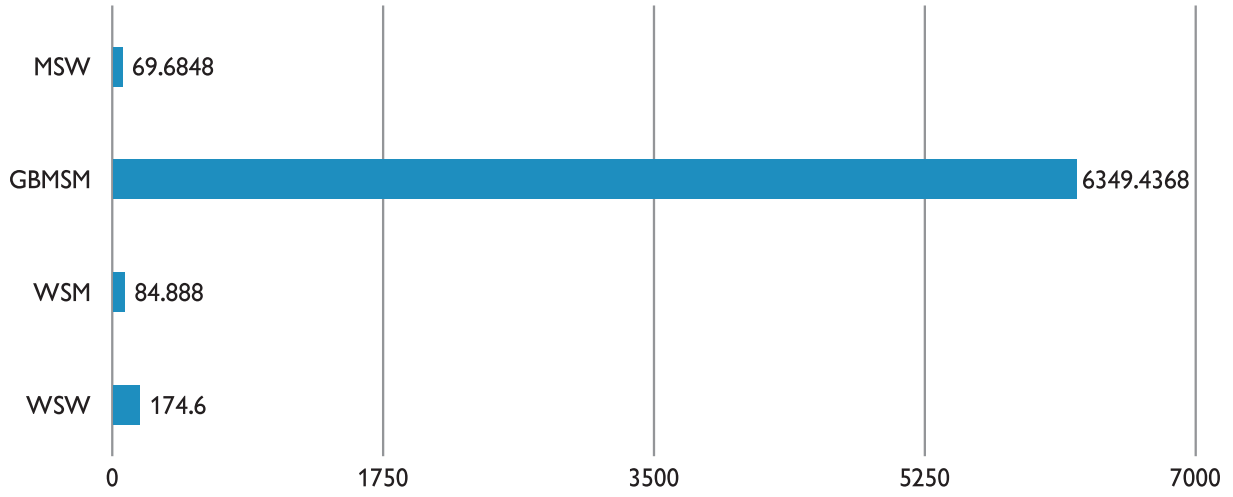


Figure 2: Gonorrhoea diagnoses per 100,000 people, by age, 2022.
Chart only shows men who have sex with women (MSW) and women who have sex with men (WSM).

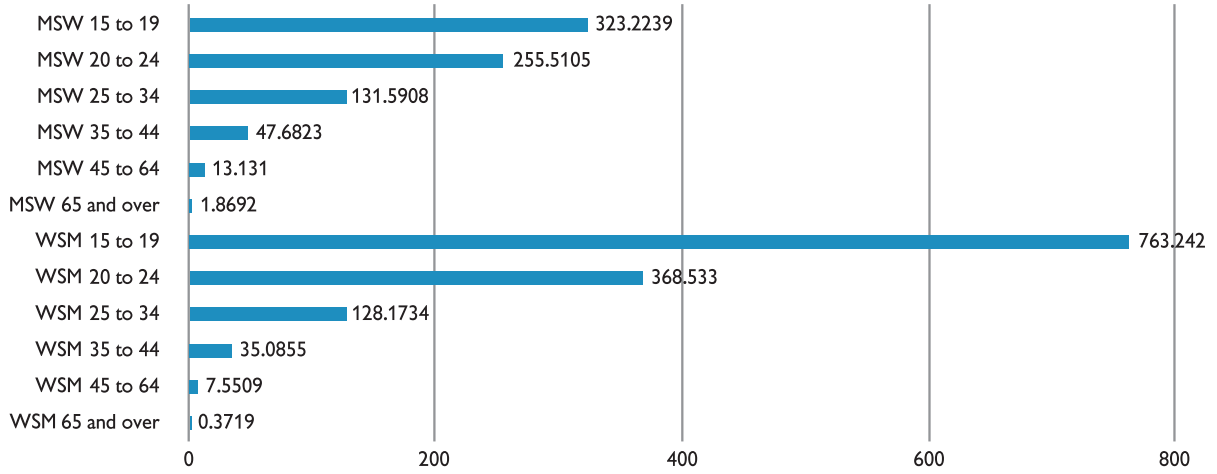
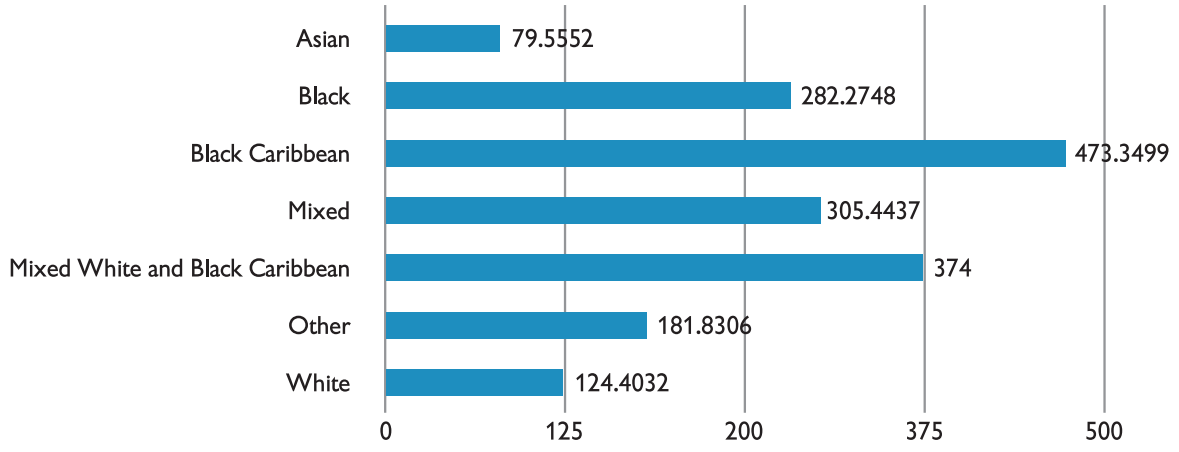


Figure 3: Gonorrhoea diagnoses per 100,000 people, by ethnic group, 2022



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Gonorrhoea resistance in England

A bacteria called *Neisseria gonorrhoea* causes gonorrhoea disease. *N. gonorrhoea* bacteria have developed high-level resistance to a succession of antibiotics over the past 50 years (see *How does gonorrhoea develop resistance?* below). The potential development of gonorrhoea strains that are resistant to currently available antimicrobial medications poses a challenge for sexual health services and HIV prevention, particularly in the context of declining levels of condom use among GBMSM. Since 2000, annual surveillance testing has taken place to assess gonococcal resistance to antimicrobials in England. Between 2013 and 2019, the frequency of resistance to azithromycin doubled to 8.7%, causing the use of azithromycin in first-line treatment to be discontinued in 2018. Resistance to ceftriaxone (now recommended for first-line treatment) increased from 0.3% in 2013 to 7.1% in 2018 but fell to 1.4% in 2020. This decline in detected resistance is probably due to the doubling of the recommended ceftriaxone dose from 500mg to 1g in 2019 UK gonorrhoea treatment guidelines.[3]

Between 2014 and 2018 an outbreak of azithromycin-resistant gonorrhoea emerged in England. The first cases were diagnosed in young heterosexual men and women living in deprived areas of Leeds. Cases had no epidemiological links outside the United Kingdom. In November 2015, cases of azithromycin-resistant gonorrhoea were diagnosed in GBMSM attending sexual health clinics in London. Although it was not possible to establish a direct link between the Leeds and London cases, genetic sequencing of isolates indicated a common ancestor and six men reported sex with men and women. A total of 118 cases were diagnosed during the outbreak, including 36 in GBMSM.[4] The outbreak appears to have persisted for three-and-a-half years due to difficulties in identifying and tracing partners, low rates of re-attendance to test for cure and a high frequency of asymptomatic infection in women and GBMSM.

Ten cases of ceftriaxone-resistant *N. gonorrhoea* were diagnosed in England between December 2021 and June 2022. Nine of the ten cases were associated with travel to the Asia-Pacific region or sexual contact with someone from that region. The remaining case was diagnosed in a woman who had not travelled to the Asia-Pacific region and had no epidemiologic links with the other cases. All cases were diagnosed in heterosexual men and women.[5]

Isolated cases of pharyngeal gonorrhoea resistant to both ceftriaxone and azithromycin have been reported in the United Kingdom since 2016. Rather than pointing to a specifically British problem of drug resistance, these cases are likely to be the tip of the global iceberg according to the World Health Organization, detected due to stringent surveillance and treatment protocols in the UK.[6]

Global epidemiology of gonorrhoea resistance

Several recent cases of antibiotic-resistant gonorrhoea diagnosed in England have been acquired overseas. Less frequent screening and suboptimal treatment practices in other regions of the world compared to the United Kingdom mean that it is especially important to test for antimicrobial susceptibility in cases acquired overseas and essential to carry out test of cure in cases acquired in the Asia-Pacific region.

Surveillance data reported in 2014 showed that up to 30% of *N. gonorrhoea* isolates in China, India, Indonesia, Japan, Malaysia and South Korea had reduced susceptibility to ceftriaxone. Rates of reduced susceptibility to ceftriaxone remained below 5% in Europe, North America, Latin America and Africa.[7]

In the European Union, 10% of isolates tested in a 26-country surveillance survey in 2019 had reduced susceptibility to azithromycin. Three isolates with reduced susceptibility to ceftriaxone were detected. Each of the ceftriaxone-resistant isolates had reduced susceptibility to azithromycin and ciprofloxacin, showing the potential for the emergence of untreatable cases. Most European countries continue to recommend a two-drug regimen of ceftriaxone 500mg and azithromycin rather than single-drug treatment with high-dose ceftriaxone.[8]

How N. gonorrhoea develops resistance

N. gonorrhoea bacteria have evolved rapidly to develop resistance against each successive generation of drug treatment. The first drug treatment for gonorrhoea, the sulfa drugs, began to lose effectiveness within ten years of their introduction in 1937 and by the mid-1940s had been replaced by penicillin, the first antibiotic. Widespread resistance to penicillin emerged in *N. gonorrhoea* bacteria in Asia, Europe and North America by the 1980s. Tetracycline was also abandoned as a treatment for gonorrhoea by the end of the 1980s for the same reason. In England, resistance to ciprofloxacin led to its exclusion from gonorrhoea treatment in 2005

and azithromycin use was halted in 2018 due to a sharp increase in resistance. Since then, treatment for gonorrhoea has relied on the use of ceftriaxone.[9]

Gonorrhoea resistance is measured in two ways:

Loss of sensitivity to antibiotics (phenotypic resistance), expressed as a Minimum Inhibitory Concentration (MIC) required to reduce bacterial activity by half. To overcome the loss of sensitivity, higher and higher doses of an antibiotic can be given. But eventually, these doses will either become too toxic or will cease to be effective.

Genetic changes corresponding to loss of antibiotic sensitivity (genotypic resistance). Gonorrhoea resistance can also be monitored by sequencing the entire genome of *N. gonorrhoea*. The genetic sequence shows where changes have occurred and allows researchers to trace the evolution of resistance and the relationship of one drug-resistant bacterial sample to another. In this way, transmission patterns can be detected.

N. gonorrhoea bacteria can develop resistance to antibiotics in several ways:

- Mutations in bacteria that lead to a loss of susceptibility to an antibiotic
- Acquiring new genes from other bacteria that confer resistance to an antibiotic
- Inactivation of the antibiotic by enzymes produced by *N. gonorrhoea*
- If the dose of an antibiotic is not sufficient to kill all the bacteria, it will leave those with reduced susceptibility to multiply
- If the antibiotic treatment does not reach all sites of gonorrhoea infection adequately, this will lead to insufficient drug levels to kill the bacteria.

Treatment guidelines

UK treatment guidelines were updated by the British Association for Sexual Health and HIV (BASHH) in 2018.[10] The new guidance dropped dual therapy with ceftriaxone and azithromycin and instead recommended treatment with a single intramuscular injection of 1g of ceftriaxone.

Susceptibility testing should be carried out prior to treatment. Oral ciprofloxacin (500mg) should be used in cases where antimicrobial susceptibility testing shows sensitivity to ciprofloxacin in isolates from all sites of infection.

Anyone diagnosed with gonorrhoea should be tested for all sexually transmitted infections, including HIV. Gonorrhoea in people with HIV should be managed in the same way as for people without HIV.

Partner notification should take place for all partners of people diagnosed with gonorrhoea.

Everyone treated for gonorrhoea should return for follow-up testing to ensure that they are cured ('test of cure'). Follow-up testing should take place 7-14 days after treatment. Follow-up testing is especially important in the following circumstances:

- pharyngeal gonorrhoea (because symptoms and their resolution may be less evident)
- when symptoms of genital or rectal gonorrhoea are persistent
- where a non-standard treatment regimen was used
- cases acquired in the Asia-Pacific region.

Gonorrhoea: Implications for HIV prevention and services

The impact of PrEP use on gonorrhoea rates among GBMSM: There is limited UK data on this, apart from the PROUD study which found no significant difference in the incidence of bacterial STIs between immediate PrEP users and deferred PrEP users.[11] Approximately half of participants in each study arm was diagnosed with a bacterial STI. A meta-analysis of studies of early PrEP implementation found that 40% of PrEP recipients were diagnosed with gonorrhoea after one year of PrEP use but found large variation in incidence between studies.[12] A future HPE briefing will explore the relationship between PrEP and STIs in more detail.

Testing frequency in PrEP users: PrEP services currently require PrEP users to undergo three-monthly screening for STIs but this screening frequency may increase costs and antibiotic use without improving outcomes. Although a modelling study showed that three-monthly testing for STIs in a Dutch PrEP programme would reduce the annual incidence of gonorrhoea over ten years by 97%, it found that this testing frequency was not cost-effective.[13] Furthermore, an analysis of 366 participants in the Amsterdam PrEP pilot programme found that at an average screening interval of three months, 77% of gonorrhoea cases diagnosed were asymptomatic (354 out of 458 infections during 1303 patient-years of follow-up).[14] What proportion of these cases might be self-limiting and resolve without treatment is uncertain. A Dutch study found that 20% of

cases of rectal gonorrhoea, 27% of oropharyngeal cases and 33% of genital cases resolved without treatment in the median ten-day interval between screening and treatment visits, avoiding unnecessary antibiotic use.[15] In the Australian national PrEP programme, just under half (45%) of PrEP users were diagnosed with an STI, with most diagnoses concentrated amongst a minority of PrEP users.[16] The Amsterdam PrEP study found that STIs were associated with condomless sex with casual partners, chemsex and taking daily PrEP (rather than event-based PrEP).[17] Further research is needed to develop risk scores that enable services to assess users' need for less frequent screening.

Maintaining access to screening, including self-sampling: Increasing demand for sexual health services in England has encouraged the development of home testing and home sampling services, as well as the streamlining of clinic-based services. Research in England has shown that self-sampling in women and GBMSM achieves a high degree of concordance with clinic sampling for diagnosis of gonorrhoea and chlamydia in the throat and rectum.[18] Maintaining and expanding opportunities for self-sampling and self-testing will be critical for meeting the demand for sexual health services.

Contact tracing and partner notification are important elements of gonorrhoea control and HIV diagnosis. A study of GBMSM attending a sexual health clinic in Brighton showed that those attending due to contact tracing for bacterial STIs contributed 20% of all HIV diagnoses and 23% of all gonorrhoea diagnoses in 2019.[19] Contact tracing and notification are also critical in the management of outbreaks of drug-resistant gonorrhoea but as the 2014-2018 outbreak of azithromycin-resistant gonorrhoea showed, lack of contact details for sexual partners proved an obstacle for contact tracing. Innovations that can support partner notification are needed.

Prioritise treatment of symptomatic gonorrhoea: Contact tracing is important for the diagnosis and treatment of symptomatic cases but there is a risk that empirical treatment of contacts (treating all named contacts prior to the results of testing, including asymptomatic cases) may result in over-use of antibiotics and promote resistance to first-line antibiotic treatment at a population level. In 2019, Sydney Sexual Health Centre stopped empirical treatment of asymptomatic notified contacts. A retrospective review of 1194 asymptomatic contacts found that 64% were negative for both chlamydia and gonorrhoea; 99% of those who tested positive were treated within five days. Halting empirical treatment reduced unnecessary gonorrhoea treatments fivefold.[20]

Follow-up visits and test of cure are essential means of limiting the development of antimicrobial resistance. A test of cure can detect cases where treatment has failed due to resistance. Audit of test-of-cure visit uptake in 2019 in 141 clinics in the UK showed that only 68% of people treated for gonorrhoea returned for a test-of-cure, against a target of 97%.[21] Messaging around PrEP use and STI testing should emphasise the importance of follow-up visits.

Using antibiotics to prevent gonorrhoea: Two studies have shown that post-exposure prophylaxis with doxycycline (taking the antibiotic within 72 hours of sexual activity) reduced the risk of being diagnosed with gonorrhoea. In the DOXYPEP study, the risk of acquiring gonorrhoea was reduced by 55% in HIV-negative GBMSM taking doxycycline and 57% in men with HIV. Use of doxycycline PEP did not result in an increase in the frequency of *N. gonorrhoea* with high-level resistance to doxycycline in DOXYPEP participants.[22]

In the randomised DOXYVAC study, 546 GBMSM were assigned to receive two doses of MenC-4B vaccine or doxycycline post-exposure prophylaxis, both interventions, or neither.[23]

Participants assigned to doxycycline were instructed to take two tablets within 72 hours of sex and reported taking the correct dose on 83% of occasions after sex had taken place. Doxycycline PEP reduced the incidence of first diagnoses of gonorrhoea by 51% compared to no treatment. It was effective in reducing the incidence of anal or urethral gonorrhoea, but not the incidence of pharyngeal gonorrhoea.

However, in the DPEP study, doxycycline PEP did not reduce the incidence of gonorrhoea in cisgender women. The study randomised 449 young women in Kenya taking PrEP to take doxycycline or receive STI testing and treatment. The incidence of gonorrhoea in the two study arms was similar and all cases of gonorrhoea detected at study entry were resistant to doxycycline.[24] An-open-label extension of the IPERGAY PrEP study randomised 232 GBMSM in France to take doxycycline prophylaxis or no prophylaxis. No significant reduction in gonorrhoea incidence was seen in this study and there was a high frequency of tetracycline resistance in *N. gonorrhoea* isolates from both study arms.[25]

Both studies suggest that doxycycline PEP is not effective in settings with high background levels of antibiotic resistance.

See the HPE briefing *Using antibiotics to prevent STIs* for more information.

Meningitis B vaccination has been shown to modestly reduce the risk of acquiring gonorrhoea. In a retrospective study of young people aged 16-23 carried out in the United States, partial vaccination with 4CMenB reduced the risk of being diagnosed with gonorrhoea by 26%. Full vaccination (three doses) reduced the risk by 40%.[26] A case-control study found that a similar vaccine reduced the incidence of gonorrhoea by 31% in young adults in New Zealand.[27]

In the randomised DOXYVAC study, 546 GBMSM were assigned to receive two doses of 4CMenB vaccine or doxycycline post-exposure prophylaxis, both interventions, or neither. Participants received vaccine doses at baseline and month 2 and were followed for one year. While an interim analysis showed large short-term reductions in the incidence of gonorrhoea,[28] the researchers subsequently identified errors in their own data. Final analysis of this study is awaited to determine if these results remain statistically significant.

A study that evaluated the population effects and cost-effectiveness of four 4CMenB vaccine strategies in England concluded that offering a vaccine of 31% efficacy to GBMSM diagnosed with gonorrhoea or reporting more than five sexual partners a year would be cost effective, averting 110,000 cases and saving £7.9 million over 10 years. Offering the vaccine to adolescents would have little impact on gonorrhoea diagnoses, the model showed. Vaccination on sexual health clinic attendance or vaccination according to risk would have the greatest impact on diagnoses but risk-based vaccination would require fewer doses to be administered.[29]

A need for further research on non-antibiotic prevention and treatment methods: A randomised study of 196 GBMSM with culture-positive oropharyngeal gonorrhoea found that men assigned to gargle with *Listerine* were significantly less likely to produce culture-positive pharyngeal swab samples than men assigned to gargle saline solution.[30] However, a larger randomised study in 530 GBMSM diagnosed with oropharyngeal gonorrhoea found that daily use of *Listerine* for 12 weeks did not reduce the cumulative incidence of oropharyngeal gonorrhoea during the follow-up period.[31] Mathematical modelling shows that a mouthwash of moderate efficacy against *N. gonorrhoea* would halve the prevalence of gonorrhoea in GBMSM.[32] Further research is needed to identify effective compounds that will not contribute to antimicrobial resistance and which can reduce antibiotic use.

Implications for advocacy

Sexual health service provision: Although consultation costs fell by 30% between 2013 and 2020 due to innovations in service delivery and sampling, local authorities have warned that the potential for further cost savings and gains in productivity is limited. Sustaining access to services and meeting increases in demand requires further investment in services. Local authorities have called for full funding of public health budgets by central government.[33]

Lack of investment in new antibiotics: The inexorable rise of antibiotic resistance makes it imperative to plan ahead for the potential loss of currently effective antibiotics. Several new and existing agents (zoliflodacin, gepotidacin, ertapenem) have proved effective in early-stage human studies and merit further investigation.[34,35] Experts in antimicrobial resistance advocate public and not-for-profit funding of early-stage development and large-scale efficacy trials of promising antibiotics.[36]

Need for investment in vaccine research: Studies of meningitis B vaccine show the potential for a vaccine that can reduce the risk of acquiring gonorrhoea. However, further evidence on the efficacy of the 4CMenB vaccine is awaited and preliminary trial analysis suggested that the duration of protection was limited. Modelling of vaccine efficacy and cost-effectiveness among GBMSM in England concluded that a vaccine with greater efficacy would have a higher value than one with a greater duration of protection.[37] Key questions for future research include the impact of a vaccine on the prevalence of gonorrhoea and whether reductions in transmission and treatment of gonorrhoea as a result of vaccine uptake might limit the loss of antimicrobial susceptibility to current antibiotics.

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