Written evidence from Dr Peter J White\textsuperscript{1,2,3} and Ms Lilith K Whittles\textsuperscript{4}

\textsuperscript{1}Reader in Public Health Modelling, MRC Centre for Global Infectious Disease Analysis (formerly MRC Centre for Outbreak Analysis and Modelling), Imperial College London, 
\textsuperscript{2}Deputy Director of the NIHR Health Protection Research Unit in Modelling Methodology, and
\textsuperscript{3}Head of the Modelling and Economics Unit, National Infection Service, Public Health England. 
\textsuperscript{4}Research Associate, Imperial College London.

We are making a submission because we are active researchers in sexually-transmitted infections, working to benefit public health. We are writing in a personal capacity and the views expressed are not necessarily those of DHSC, Imperial College London, MRC, NHS, NIHR, or PHE. We have no conflicts of interest to declare.

Summary recommendations
1. A new surveillance system monitoring access to care – both (i) waiting times of those patients who get care, and (ii) how many patients are unable to obtain care.
2. Improvements to existing surveillance systems, including recording whether the patient had symptoms or not, recent sexual risk behaviour, and the patient’s reason(s) for obtaining care.
3. Recording in surveillance the anatomical site(s) of infection. This requires separate testing of each site rather than ‘pooling’ of specimens to perform a single test per patient. Separate testing is more costly but is vital for understanding the epidemiology of infection and the role of infections at different sites in antimicrobial resistance.
4. Development of new methods of mathematical modelling analysis to be packaged into tools to analyse surveillance data, including from whole-genome sequencing, to improve local-level targeting of resources to maximise efficiency and minimise health inequalities. This requires investment in development of new modelling techniques. The NIHR Health Protection Research Unit in Modelling Methodology has been doing valuable work in this area.
5. Whole-genome sequencing is needed to gain a better understanding of the transmission patterns of different strains of gonorrhoea, including strains with resistance to different antibiotics, so that we are able to respond rapidly and effectively. Targeted use of WGS should be part of this surveillance system.
6. Research studies to address specific questions relating to natural history, e.g. different anatomical sites’ rates of transmission and natural clearance, and their roles in antimicrobial resistance.
7. \textit{Mycoplasma genitalium} needs further study urgently to determine an appropriate public health approach.

1.A vicious circle: inadequate treatment capacity leads to avoidable transmission and continuing unmet need
1.1.There is an impending crisis in management of gonorrhoea, caused by a combination of overstretched sexual health services [Foley et al. 2017], high-risk sexual behaviour, and antimicrobial resistance. Gonorrhoea in on the World Health Organization’s list of priority pathogens requiring new antibiotics.

1.2.In summary, “Beginning in the late 1990’s, increases in sexual risk behaviour led to an increase in incidence, which was exacerbated by a vicious circle in which overstretched sexual health services resulted in reduced access to care, further promoting transmission of infection [White et al. 2005]. Substantial investment in sexual health services in the early 2000’s reversed the trend. However, in recent years, there has been another resurgence in the epidemic, and once again, health services are struggling to cope. This epidemic is much larger than 15 years ago and is aggravated by the threat of antimicrobial resistance [White 2017]”[Whittles et al. 2018a].

1.3.Modelling work [White et al. 2005] showed that inadequate treatment capacity creates a vicious circle where untreated infection leads to further transmission, maintaining high demand for inadequate services. Importantly, it showed that the usual approach of providing a small increase in funding and requiring demonstration of improvements before further funds are released would not work in this case. The way out is a step-change increase in capacity – not an incremental increase, which would produce little measurable benefit – sufficient to break the vicious circle, which is ultimately cost-saving. This was widely reported, including in a BBC Panorama documentary. Breaking the vicious circle is an investment, with the pay-off being reduced transmission leading to improved health and reduced future costs of treatment. See White et al. 2005; Mercer et al. 2007, 2012.

1.4.The vicious circle caused by inadequate capacity applies to sexually-transmitted infections (STIs) in general, but the problem is particularly acute for gonorrhoea due to the growing antimicrobial resistance. “Increased transmission means greater numbers of infections of already-resistant, hard-to-treat gonorrhoea, which are at risk of further
transmission due to failure of initial treatment. Furthermore, greater numbers of infections result in more treatment events, each being an opportunity for selection for resistance, including multidrug resistance in already mono-resistant strains [Grad et al. 2016]” [White 2017].

2. Action required to break out of the vicious circle

2.1. Breaking the vicious circle requires increased capacity to meet the need for services. Redesigning clinical services to increase efficiency by “triaging” patients so that clinicians’ attention can be directed towards those patients who most need it is part of the solution. Improved targeting of services to improve efficiency requires an improved understanding of the epidemiology of STIs, which requires better data and more research.

2.2. Adequate funding is also required – recognising that regaining control of the spreading of infection is ultimately cost-saving by averting future need for care [White et al. 2005].

2.3. To ensure that sexual health services have sufficient capacity we need better monitoring of the performance of services. It is important to monitor patients’ waiting times to get care, but this omits those who fail to get care.

2.4. Modelling shows that the biggest contributor to avoidable onward transmission is not people having to wait longer for treatment and remaining infectious for additional days or weeks; rather it is people not getting care and remaining infectious for months [White et al. 2005]. Recent work found that people can be infectious for longer than is typically assumed [Didelot et al. 2016], and modelling estimated that the large majority of transmission of gonorrhoea comes from people who have asymptomatic infection [Whittles et al. 2017]. For other STIs such as chlamydia and Mycoplasma genitalium, which are more likely than gonorrhoea to be asymptomatic, spreading from asymptomatically infected people is likely to be even more important. Identifying asymptomatic infection requires targeted screening of individuals at high risk, and testing sexual partners of patients diagnosed with infection. Unfortunately, people without symptoms are the least likely to be persistent in getting tested when it is difficult to obtain care from overstretched sexual health services, and partner notification is activity is difficult for overstretched services. Furthermore, test-of-cure is important, to ensure that asymptomatic infections have been successfully treated, but overstretched clinics may find this difficult, particularly if patients without symptoms are reluctant to re-attend.

3. Improved surveillance data are required for all STIs

3.1. Whilst the UK has some of the world’s best surveillance data, an unavoidable limitation is that surveillance data are observational data, which are not fully representative of what is happening in the “real world” because of biases due to variation in individuals’ propensities to get tested and treated. Quantitative assessment of how much the data are likely to be biased is necessary to determine whether apparently-different patterns in different locations or at different times are due to “real-world” differences or just due to differences in the characteristics of patients who are getting care or in patterns of service provision. Therefore, we need to maximise the quality and utility of surveillance data. Recent work on chlamydia has highlighted limitations in current surveillance and recommended improvements, e.g. recording if the patient has symptoms, recent sexual risk behaviour and reason(s) for getting tested [Lewis & White 2017, 2018; White & Lewis 2018].

4. Another “Natsal” population-based survey is required

4.1. Population-based surveys are an essential complement to surveillance data because they are representative of the population and so can be used to assess biases in surveillance data. This is vital to interpreting surveillance data to understand true patterns of disease in the population, including inequalities that need to be addressed. To date there have been three such surveys in Britain, the National Survey of Sexual Attitudes and Lifestyles (Natsal), performed roughly every decade beginning in 1990. It is unclear whether a fourth survey will be conducted, but we strongly advocate that it should be. Collecting samples to test for STIs to measure population-based prevalence, as before, is vital for assessing the impact of the National Chlamydia Screening Programme, as well as the burden of Mycoplasma genitalium, which is rapidly developing antibiotic resistance.
5. New tools are required to improve use of surveillance data
5.1. Improved methods to analyse surveillance data need to be developed and packaged into tools to inform local-level targeting of services to maximise efficiency and minimise health inequalities. Tools based on mathematical modelling techniques, combining information from surveillance, and population-based surveys such as Natsal and other research studies are needed to provide improved information for action. For example, recent work by the NIHR Health Protection Research Unit (HPRU) in Modelling Methodology on chlamydia has enabled estimation of the prevalence of infection at local level [Lewis & White 2017] and over time [Lewis & White 2018]. The approach is not perfect – due to limitations in the surveillance data – and we have described how the data can be improved and what additional research is required to refine the method [Lewis & White 2018; White & Lewis 2018]. Further work using superior surveillance data is required.

6. Improving estimates of natural clearance rates
6.1. It is important to know the natural clearance rates of untreated infections, because many infections do not get treated (typically because they are asymptomatic) and persist in the population leading to onward transmission. Valuable information has come from studies of patients who tested positive for infection and then returned for treatment: taking another sample for testing at the time that treatment was dispensed enables measurement of the rate of natural clearance in the intervening period [Lewis et al. 2017]. There remains a brief window of opportunity to do these studies before point-of-care testing becomes routine and eliminates the delay between testing and treatment, making these studies impossible.

7. The need for better understanding of the STI natural history and epidemiology, including the roles of different anatomical sites of infection
7.1. There are many gaps in our understanding of the natural history and epidemiology of STIs. With colleagues at Harvard PJW published a multidisciplinary research agenda for tackling antimicrobial resistance in gonorrhoea [Grad et al. 2016]. To design effective control strategies we need a better understanding of the epidemiology and natural history of gonorrhoea (and other STIs) in general, since resistance to antibiotics is only one of its characteristics.

7.2. We need to better-understand the roles of urethral, cervical/vaginal, pharyngeal, and rectal infection in the transmission of infection, persistence in the population, and emergence, persistence and transmission of antimicrobial resistance. For example, pharyngeal infection could be particularly important in gonorrhoea becoming drug resistant, because many drugs only reach low concentrations in the pharynx and because the pharynx is often colonised with other bacteria which might already be carrying genes for antibiotic resistance which become shared with the gonorrhoea through transfer of genetic material [Whittles et al. 2018a, 2018b].

7.3. We advocate pharyngeal testing of all individuals who are tested for gonorrhoea, not just men who have sex with men [Whittles et al. 2018b], to enable us to use surveillance data to assess the extent of pharyngeal infection and better-understand its epidemiological role. However, it is likely that cost pressures will lead to clinics combining samples taken from different anatomical sites of a patient in a single sample vessel so that the test result only indicates if the patient has the infection but not where. We advocate funding sentinel clinics to perform separate tests for different anatomical sites as part of an enhanced surveillance activity.

8. The need to quantify evolutionary fitness costs and benefits of resistance
8.1. “We need a better understanding of the evolutionary fitness benefits and costs of resistance to inform future antibiotic prescribing strategies, including optimal use of new antibiotics and consideration of approaches more sophisticated than just having a universal default first-line therapy [Whittles et al. 2017]. This requires better prescribing data, ideally linked to test results and treatment outcomes at the individual level, so that the selective pressure can be quantified by time, location and patient group” [Whittles et al. 2018a].

8.2. We need to design strategies for antibiotic use that do not result in the proliferation of resistance at the population level, and which take account of the diagnostic technologies available in different settings, including their turnaround time and whether than can detect antibiotic resistance. If we had a better quantitative understanding of the evolutionary fitness costs and fitness benefits to the bacterium of antibiotic resistance then we may be able to design treatment strategies that are more sophisticated than the current approach of using one first-line therapy until resistance reaches 5% and then relying on changing to another first-line therapy. An alternative approach could be to have several first-line regimens used in different proportions according to the fitness costs and fitness benefits of
resistance to each regimen. (This is because often there is a net fitness cost to the bacterium if the antibiotic is rarely used and a net benefit if it is commonly used, and in between there is a “tipping point” at which there is no net cost or benefit; if usage is kept below the “tipping point” level then in principle the antibiotic could safely be used indefinitely.) Such an approach could potentially preserve the utility of multiple regimens – which would be very valuable considering the difficulty of developing novel antibiotics. It is important to emphasise that this is speculative at present and much more work is required. However, the ground-breaking paper by Whittles et al. [2017] reporting the first assessment of the evolutionary fitness cost and fitness benefit of resistance to an antibiotic for gonorrhoea is an important first step.

8.3. We need to extend this work to develop detailed mathematical models to allow understanding of the transmission patterns and the fitness costs and fitness benefits (to the bacteria) of possessing resistance to different antibiotics, considering different strains (or, more accurately, evolutionary lineages) of bacteria and different population groups [Whittles et al. 2018a]. This requires detailed surveillance data complemented by whole-genome sequencing.

9. Whole-genome sequencing (WGS)

9.1. WGS is a powerful technology offering a range of important insights. WGS distinguishes different lineages of bacteria. Often there are population sub-groups which have transmission of STIs occurring within them, and different sub-groups typically have different lineages of infecting bacteria. Therefore, distinguishing the lineages gives important information on the epidemiology of infection – and the effectiveness of intervention – in different sub-groups. This allows better targeting of interventions to maximise efficiency and minimise health inequalities.

9.2. “When combined with surveillance and epidemiological data using mathematical modelling techniques [Didelot et al. 2016; Grad et al. 2016], WGS offers important insights into transmission patterns and can inform about the mechanisms of emergence, persistence and propagation of resistance, as well as providing information on the impact of public health interventions” [Whittles et al. 2018a]. WGS can be used in different ways, including “sparse” population-level sampling, in which a small proportion of infections that are detected are sequenced to monitor which lineages are present in which population groups, whether a lineage is increasing or declining over time, whether a lineage is becoming more (or less) resistant to antibiotics, etc. Another approach is “dense” sampling, applying WGS to all infections detected in a particular setting (often in response to an outbreak), to obtain detailed information on transmission patterns. This can improve our understanding of the epidemiology and natural history of infection: detailed data from an outbreak of gonorrhoea revealed that infections may persist and transmit infection for longer than had previously been thought [Didelot et al. 2016].

9.3. Algorithms should be developed to identify from surveillance systems which are the most-informative samples for WGS so that it can be used efficiently, both for “sparse” and “dense” sampling (e.g. to inform rapid effective responses to controlling outbreaks of gonorrhoea, particularly those lineages that are of greatest concern due to antibiotic resistance).

10. Mathematical modelling’s vital roles

10.1. Mathematical modelling is now a well-established approach for analysing data and evaluating intervention options to inform policy-making. Public Health England has a small group dedicated to doing this for infectious diseases: the Modelling and Economics Unit of the National Infection Service. Imperial College has a very large group, including the MRC Centre for Global Infectious Disease Analysis and the NIHR HPRU in Modelling Methodology.

10.2. Mathematical modelling is used to:

- Synthesise evidence from multiple sources, both surveillance data and scientific research studies, to provide situational awareness and gain scientific insight.
- Plan studies: how large does a study have to be for it to have the “statistical power” to detect an effect? What length of follow-up is required?
- Evaluating “what if” scenarios to help decide the best policy option based on current information, whilst accounting for known uncertainties.
- Identifying which gaps in knowledge lead to the greatest uncertainties in the likely impact of policies so that research efforts can be targeted to address the most important gaps.
- Evaluating interventions during and after implementation: is the intervention having the effect that was anticipated or a larger or smaller effect? What are the possible reasons for this?
11. **Mycoplasma genitalium** and antimicrobial resistance

11.1. **Mycoplasma genitalium** could overtake gonorrhoea to become the first untreatable STI. PJW instigated a letter to Lancet Infectious Diseases [Bradshaw et al. 2018] highlighting the importance of not testing patients for M genitalium unless they have symptoms. The reason is there is not a reliable regimen to treat M genitalium without selecting for resistance, so until a suitable regimen has been developed only those infections that clearly need treating now should be treated to avoid creating bigger problems for the future. This approach is advocated in the current BASHH draft guidelines.

11.2. **Mycoplasma genitalium** has a similar prevalence to chlamydia, but its natural history and epidemiology are very poorly understood, leading to great uncertainty about the appropriate public health approach to its control [Birger et al. 2017], and more research is urgently required.

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References


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