MICROBIOLOGY SOCIETY

# Microbiology and the challenge of sexually transmitted infections:

## are we up to it?

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Microbiology Society
Charles Darwin House
12 Roger Street
London WC1N 2JU
UK

Tel. 020 7685 2400
Email policy@microbiologysociety.org
Web www.microbiologysociety.org



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# FOREWORD

Dr Julian Huppert MP

Public health data show that sexually transmitted infections (STIs) have been on the rise in Britain for the last decade; in the particular case of gonorrhoea, antibiotic resistance has also risen, with the potential to make the infection untreatable.

These trends are obviously worrying. But there are also good reasons to believe we can respond effectively – above all, due to the UK's extensive health surveillance infrastructure, open access clinics and well-developed screening and vaccination programmes.

In this context, I am pleased to see that the Microbiology Society has highlighted another strand of action that will help us combat STIs over the longer term. An Expert Panel, convened by the Society, and including representatives from the scientific, public health and advocacy communities, was set the task of identifying how microbiological research can best contribute to broader efforts to improve sexual health.

The Panel found three major challenges – antimicrobial treatments, diagnostic devices and vaccines – that they believe need expanded scientific efforts to improve the prevention, diagnosis and treatment of STIs over the coming decade.

The results of scientific research in these areas could have impacts both in the UK and overseas in countries where the HIV burden, in particular, is very high.

As a scientist myself, I acknowledge the role that microbiology plays in tackling infectious diseases. I believe that the scientific community will continue to rise to the challenges posed by STIs. New technology and new knowledge, as well as new ways of working that emphasise interdisciplinary collaboration, will help us reduce the burden of disease.

**DR JULIAN HUPPERT MP**

The diagnostic laboratory plays a vital role in patient care. This is where microbiologists help to diagnose infectious disease.

Sotiris Zafeiris / Science Photo Library

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# SUMMARY

Sexually transmitted infections (STIs) significantly impact on the health of the nation. They cause mortality [human immunodeficiency virus (HIV) and human papilloma virus (HPV)], can lead to pelvic inflammatory disease and reproductive complications (gonorrhoea, chlamydia), and can infect the unborn foetus (syphilis, herpes). They have been on the rise in Britain for the last decade; in the particular case of gonorrhoea, there has been an associated increase in antibiotic resistance, which has the potential to make this dangerous infection untreatable.

STIs are without doubt a complex and persistent problem. But clear political commitments to improve sexual health[1] – coupled with the UK's effective systems of surveillance, open access clinics and screening and vaccination programmes – imply that STIs are tractable in Britain. This report argues that microbiologists are able to make significant advances in the prevention, diagnosis and treatment of STIs, due to expanding knowledge of the molecular basis of infection, and innovative research tools that will allow us to study the infectious process in unprecedented detail.

New antimicrobial therapies for gonorrhoea are the first of our research challenges. Drug treatment is the main line of defence against this infection because we lack a vaccine. Emerging antibiotic resistance is therefore the most pressing issue in STIs, as for many other infections, as it has the potential to render current treatments useless.

We should prioritise research and government policy (legislation, regulation and industry co-operation) to return to the situation where there are enough new antimicrobial therapies being developed to cope with the inevitable on-going emergence of antibiotic resistance. The recent *UK Five Year Antimicrobial Resistance Strategy 2013–2018* is an extremely positive step, but sustained action is needed to promote and increase research capacity in relevant areas of the basic science.[2]

Our second research challenge is the development of point-of-care (PoC) diagnostic devices that allow physicians to prescribe the most effective, tailored treatments. Such diagnostic devices will, additionally, help tackle the problem of

drug-resistant gonorrhoea, by contributing significantly to antibiotic stewardship.

Vaccines for STIs are the third research challenge. The current drug treatments for HIV are costly, and the emergence of drug resistance remains a constant threat. Studies to develop an HIV vaccine that will solve these problems are international in scale, and the UK should continue to make significant and worthwhile inroads in the basic science, where we already have major local strength. Funders also need to consider vaccine research against chlamydia, gonorrhoea and syphilis.

Preventing these infections remains a critical unmet need; it can and should be addressed. The HPV vaccine illustrates the potential for success.

Much complex, exciting and medically useful science lies ahead. In the final section we outline in simple terms what steps are needed for scientists to collaborate effectively, and exploit the enormous promise of new research tools and new ways of working. These steps will be paramount if we, as a scientific research community, are to develop a successful response to the challenge of STIs.

# RECOMMENDATIONS

## SCIENTIFIC NEEDS

- Future antimicrobial drug development and vaccine research strategies should include provision for research on antimicrobial compounds and vaccines effective against STIs. Antimicrobial drugs for gonorrhoea are particularly urgent.

- Investment is needed for basic research on the correlations between genotype (genetic makeup of the organism) and phenotype (the observed traits of an organism, for example the ability to cause disease, and drug resistance).

- Investment is needed in the research underlying development of better diagnostic tests that allow physicians to detect and treat infection. The Government's commitment to genomics in the NHS is a useful development, but some of this programme will need to focus on microbial as well as human genomes if we are to realise the promise of genomics for the diagnosis of STIs and the swift detection of antimicrobial resistance.

- Funders should make a commitment to develop new research techniques for the study of STIs. These techniques will be essential to realise the scientific approaches proposed in this document.

## RESEARCH INFRASTRUCTURE

- Funders, learned societies and professional bodies should establish a network that links researchers working on STIs. The network should include all scientific disciplines relevant to STIs.

- The current generation of experts must ensure we maintain the relevant skills for the isolation and characterisation of STIs (through the provision of training courses in colleges, laboratories and universities).

## FUNDING

- We encourage research institutions to fund the recruitment and promotion of high-quality research microbiologists to work on STIs; there is a particular need for provision at the most senior level (professorships).

- We encourage the Medical Research Council, Biotechnology and Biological Sciences Research Council, Technology Strategy Board, the National Institute for Health Research and the Department for International Development to come together to establish a Catalyst Fund for research targeted at cutting STI rates. Devolved administration governments should be encouraged to contribute funding, as should relevant organisations from the private, voluntary and philanthropic sectors.

Antibiotics are the most vital line of defence against bacterial infection.

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# RESEARCH CHALLENGES

## RESEARCH CHALLENGE 1: NEW ANTIMICROBIAL THERAPIES

### CORE CHALLENGES

Antimicrobial resistance is an extremely serious issue, particularly in gonorrhoea, where its rapid emergence has now led to the last-line drugs (ceftriaxone combined with azithromycin) becoming the standard therapy in the UK.[3] There is no clear reserve agent once ceftriaxone resistance – already recognised in Japan, France and Spain – proliferates.[4] Dependable therapy for those suspected of having gonorrhoea may become impossible and, left untreated, gonorrhoea is associated with pelvic inflammatory disease, ectopic pregnancy, infertility and disseminated infection, for example inflammation of the joints (as well as eye infection in the newborn).

The immediate answer lies with new antimicrobial therapies. Yet, we have developed fewer antimicrobial drugs in the past 40 years, as compared to the middle part of the 20th century.[5] Between 1940 and 1962, more than 20 new classes of antibiotics were marketed. Since then, only three new classes have entered use.[6] Chemical modification of existing antimicrobial drugs kept pace with the emergence of resistant bacteria until 10–20 years ago. Now, too few drugs are entering use to stem the tide of antibiotic resistance, particularly among Gram-negative bacteria, which include those causing STIs.

Data from 2012 showed there were 19 compounds in late-stage clinical trials, of which 10 may be suitable for Gram-positive infections. Unfortunately, none of these would be useful for the bacterial STIs, due to the structure of the bacteria involved. There were, conversely, only five compounds in development for Gram-negative infections – which include the major bacterial STIs – in addition to four broad-spectrum drugs. There were only two new classes in late-stage clinical development.[7]

The picture has very recently improved, with two new agents in phase II trials against gonorrhoea (Cempra's solithromycin

and AstraZeneca's AZD0914). However, considering the small numbers of antibiotics in early clinical development (particularly of new classes) and the current regulatory hurdles, significant numbers of new drugs will not be marketed soon.

We need to re-invigorate antibiotic discovery, developing agents to face the challenges of the next 20–30 years. There is a need to prioritise research and government policy (legislation, regulation and industry co-operation) to return to the situation where there is a sufficient flow of new antibiotics to cope with the inevitable on-going emergence of antimicrobial resistance. This is a difficult project that goes far beyond scientific research, but it is not impossible, as illustrated by the successful development of new anti-HIV drugs in the past two decades.

One area for examination is the model for intellectual property protection with regard to antibiotics and antibiotic research. An extended period of data protection for products may encourage renewed development activity. Such a change is a major task that would require international legal agreement. However, if there are commercial barriers of this nature, then addressing them is a prerequisite for success of the scientific effort in combatting infectious disease with new treatments.

## RESISTANCE IN OTHER BACTERIAL STIs

The challenges of antimicrobial resistance go beyond that of gonorrhoea. Other important bacteria where resistance is an actual or potential threat include *Chlamydia trachomatis*, *Mycoplasma genitalium* and *Treponema pallidum* (syphilis). There is a risk of current therapy selecting for resistance in these infections.

Chlamydial infection remains treatable with doxycycline. However, increasing treatment failures have been recognised with a group of drugs called macrolides (typically antibiotics), including single-dose azithromycin (the standard therapy); the mechanisms and reasons for treatment failure have yet to be identified.

There is increasing recognition of genetic mutations associated with drug resistance in *M. genitalium*. A large proportion of *M. genitalium* strains are already resistant to tetracyclines; this has made empirical therapy (prescribing drawn from generic guidelines) difficult for non-specific infections or infections where *M. genitalium* is suspected. In syphilis, there are problems with macrolide resistance mediated by mutations in 23S RNA.

## THE POSSIBILITY OF AN HIV CURE

The greatest proliferation of antimicrobial compounds in recent times has been in the field of HIV. There has been active research and collaboration with and between healthcare, academia, biotechnology and pharmaceutical sectors that has yielded more than 25 licensed drugs in various single and combined fixed-dose formulations in the past 25 years.[8] However, there is currently no cure for the disease.

HIV infection results in the establishment of viral reservoirs within the human host. Combination HIV therapy with classes of drugs that target HIV entry, replication and integration into the host genome have achieved good long-term control, but a longer-term priority should be towards developing agents targeted towards 'functional HIV cure', either by inducing acute remission after infection/exposure to HIV, or by activating/reactivating the reservoirs/latent pools of HIV which then could be eliminated by antiretroviral drugs.[9]

These approaches could potentially lead to a functional HIV cure, removing the need for long-term combination antiretroviral drugs. This would release the patient from antiretroviral drug side-effects.

## RESEARCH PRIORITIES

- In parallel to the *UK Five Year Antimicrobial Resistance Strategy 2013–2018*, there needs to be a UK-wide antimicrobial development strategy that focuses on:[10]
  - Active throughput scanning for new antimicrobials including antivirals and antifungals.
  - Improved surveillance and reporting systems for antimicrobial resistance.
  - Closer collaboration between academic researchers and the biotechnology sector to aid development of new therapies.
  - Proactive involvement of NHS clinics with pharmaceutical industry to run clinical trials for antimicrobials, with due safety and regulatory controls.
  - Creation of an 'Antimicrobial Bank', similar to the BioBanks, where STIs would be one of the categories. This could be an integrated source for constitutive data on antimicrobial drug history, genotypic–phenotypic correlates of evolving/established antimicrobial resistance, and also provide a nationwide indexed source of relevant pathogen isolates/nucleic acid extracts aimed towards developing new antimicrobial agents.

- Optimising the use of existing antibiotics and assessing new approaches to therapy in clinical trials.
- Supporting a multidisciplinary STI research network to enable rapid evaluation of new antibiotic strategies for STI treatment.

### RECOMMENDATIONS

- Champion clinical research within the NHS to allow enhanced participation in clinical drug trials for antimicrobial drugs.
- Initiate an antimicrobial drug development strategy that takes account of STIs and addresses the problem of market failure.
- Engage other learned societies and policy institutes to review national and international approaches to regulated use of new and existing antimicrobial drugs in the context of evolving drug resistance.
- Invest in research to track the impact of new interventions. Long-term follow-up studies are vital.
- Extend lessons learned from research on gonorrhoea to understand treatment failure in chlamydia and *M. genitalium*.

## RESEARCH CHALLENGE 2: RAPID DIAGNOSIS OF BACTERIAL STIs

### CORE CHALLENGES

When an individual attends a sexual health clinic with a suspected bacterial STI, the physician will typically make a diagnosis of the infection based on (i) symptoms and/or (ii) results from molecular testing, such as a nucleic acid amplification test (NAAT). The physician will then prescribe an antibiotic treatment drawn from generic prescribing guidelines (an approach known as 'empirical therapy').

The guidelines developed by the British Society for Sexual Health and HIV, for example, are based on the known resistance patterns of bacterial strains currently common in the population. They are designed so that at least 95% of uncomplicated cases should be cured, and also aim to minimise the chance of a patient transmitting the infection to a new partner. However, given that neither the symptoms, nor the NAAT test, give any indication of antibiotic susceptibility, guidelines also mean that the treatment is given empirically and not tailored to the individual case. Potentially effective treatments for an individual may therefore be abandoned

as soon as resistance starts to be seen in the population at large, due to the risk of treatment failure.

A new generation of rapid point-of-care (PoC) diagnostic devices that allow physicians to tailor treatments to the particular infection, rather than drawing on generic prescribing guidelines, could dramatically improve patient care, speed up effective prescribing and contribute significantly to antibiotic stewardship. As such, they are a prime example of stratified medicine that personalises treatment, and they will also have a major public health pay-off by slowing the spread of antibiotic resistance.

## CORRELATING GENOTYPE AND PHENOTYPE

Currently available NAATs rely on detecting particular DNA sequences. This means that, to produce an effective test, we need to correlate a detectable DNA profile (genotype) with the phenotype (the observed traits, for example antibiotic resistance).

Molecular resistance profiling should be straightforward when the resistance phenotype depends on a single acquired gene, as with high-level penicillin and tetracycline resistance; it will be harder (but recent studies show that it is deliverable) where it entails a few localised mutations to specific chromosomal genes, as with fluoroquinolone and high-level azithromycin resistance. Hardest of all will be where it entails a variable geometry of changes to multiple genes, as with low-level penicillin and cephalosporin resistance.[11]

These challenges are not, however, insurmountable. One strategy for the more complex situations is to seek 'normal' DNA sequences implying the *absence* of resistance (rather than seeking all the diverse sequences that can cause resistance).

## DIAGNOSTIC DEVICES

Rapid PoC diagnostics would allow the tailoring of treatment to the infection, based on profiling antibiotic susceptibility.[12] Although the prevalence of antibiotic resistance reduces confidence in empirically administered therapy, many circulating strains are still susceptible to abandoned antibiotics. If it were possible to identify whether the individual was infected with resistant or susceptible gonococci at the time of clinical diagnosis, it would be possible to treat many patients with these 'abandoned' antibiotics, as well as to identify the minority who have exceptionally resistant strains that call for unconventional drug treatment.

Diagnostics manufacturers have developed PoC diagnostic devices for

several infections. PoC means that the care-provider can take a sample, such as a urine or urethral swab, and identify the detail of the disease-causing organism. This approach will be further facilitated by advances in micro-fluidics and nanotechnology.[13] It is now possible to detect tuberculosis from sputum samples, including identification of rifampicin resistance, for example, within 2 hours, proving that rapid target DNA detection (for both disease-causing agent and resistance profile) is feasible. However, the test is based on a single gene mutation and is vastly simpler than would be required to diagnose cephalosporin resistance in gonococci (mutations occur in multiple genes).

Firms have yet to validate commercial STI tests at non-genital sites; this criterion should be part of any test evaluation. Rectal and throat sites are of far greater relative importance when diagnosing gonorrhoea in men-who-have-sex-with-men, but are colonised by many other bacteria, some of which are hard to distinguish from gonococci (thus it is a much more stringent challenge for new tests).

Development of enhanced diagnostic NAATs that detect resistance as well as the presence of bacteria, allowing swift tailoring of the individual's treatment, could in the future meet the need to combine speed with sensitivity, and as such should be a long-term goal for all the bacterial STIs.[14]


In the future, diagnostic devices may allow healthcare workers to diagnose antibiotic susceptibility straightaway.
Wellcome Library, London

## RAPID SEQUENCING TECHNIQUES

The determinants of antimicrobial resistance continue to evolve, with new mutations and lateral gene transfers. New resistance types accumulate under selection pressure and are disseminated by the global migration of people.

An exciting future has, however, emerged from rapid sequencing, a tool that can take the entire DNA content of the sample, sequence it and then analyse it.[15] Rapid sequencing devices can, in principle, provide insight into changes in susceptibility to antibiotics due to the subtle and complex evolution of mechanisms of resistance (including analysing the diversity of different genes that contribute to cephalosporin and penicillin resistance).

Rapid sequencing currently has too high an error rate for clinical use, but it is likely that these error rates will reduce as the technology continues to develop. The cost per genome for rapid sequencing is a tiny fraction of what it was a decade ago.[16] Hence, rapid sequencing, which has previously been largely confined to research, will move into the clinic over the next decade. This will have significant implications for the way we run diagnostic services and these implications have yet to be fully grasped by many in the sector. There is a need to develop user-friendly bioinformatic tools to analyse the data generated, to translate these into predictions of susceptibility and resistance and to support the development of relevant expertise in hospitals and clinics. The UK Government's commitment to genomics in the NHS is a useful step, but some of this programme will need to focus on microbial genomes if we are to realise the promise of genomics for antimicrobial resistance testing.[17] This area of personal medicine and diagnostics has great potential for the development of new products in the biotechnology sector.

## PHENOTYPIC TESTING

Phenotype refers to the observed traits of an organism, such as its antibiotic resistance. Phenotype reflects genotype, but the two may not precisely correspond. Of the two, the phenotype is of more practical significance, as it dictates whether a treatment will succeed or fail. Moreover, DNA-based tests exploring genotype can only detect genetic mechanisms of resistance that we already know about, not new types. Yet chance evolutionary events mean that new resistance mechanisms continue to appear over time. In these circumstances, phenotypic testing will remain essential for the foreseeable future and it is essential that the skills for culturing STI pathogens are maintained in the 'molecular' era.

## PoC DIAGNOSIS AND HOME TESTING

When individuals suspect they have an STI, they may attend a sexual health clinic for advice and treatment; our analysis in this document focuses on new diagnostic technology for use in the clinic by healthcare professionals (at the PoC).

However, to an unknown but possibly growing extent, individuals are also buying home-testing kits, which are available from a plethora of suppliers, often over the internet. From next spring, it will be legal to sell such kits for HIV. For other STIs, particularly chlamydia, it is already possible to buy home-testing kits, often in supermarkets.

It is obviously essential that home-testing kits are properly regulated to ensure they are accurate and reliable. People with STIs should, however, continue to be encouraged to use the UK's excellent infrastructure of sexual health clinics, which offer free, comprehensive, high-quality diagnosis, treatment, counselling and support, which cannot be provided by home-testing.

Phenotypic testing currently relies on growing the organism on agar plates and screening its response to various antibiotics. Significant problems remain with current approaches. Culture is not 100% sensitive – particularly for asymptomatic patients and when processing extra-genital (throat and rectal) samples. The most fundamental problem with phenotypic testing is the delay in providing a result, typically 3–4 days for isolation, identification and antibiotic susceptibility testing of the causative bacterium. This is thought to be of limited use in the clinic, particularly as it is considered too long a period to expect the patient to return for treatment.

We should therefore remain attentive to new (and previously unforeseen) techniques for examining the phenotype. The recent use of mass spectrometry to detect the presence of cancerous cells on a surgeon's knife could equally well be exploited for STI diagnoses from genital swabs. This drives home the need for continued investment in basic research.

### POPULATION-LEVEL ANALYSIS TO SET PRESCRIBING GUIDELINES AT A LOCAL LEVEL

Improvements to the empirical prescribing approach for antibiotics lie with the possibility of real-time analysis

of circulating antimicrobial resistance at a local population level. Whilst the current treatment protocol makes follow-up of cases after microbial culture difficult or impossible, the routine collection of culture data could conceivably facilitate rapid adjustments in the antibiotic (or antibiotic combination) of choice at local and/or regional level in response to one or more confirmed instances of resistance. This approach would also facilitate switching back to a previous antibiotic or combination if the resistance profile disappears from the local population.

## RESEARCH PRIORITIES

- Improve our understanding of the correlations between genotype and phenotype.
- Ensure skills for phenotyping are maintained.
- Support the clinical application of next-generation sequencing and whole-genome sequencing. These techniques will allow us to understand correlations between phenotype and genotype with greater precision, and to design effective NAATs.
- Further respond to the engineering challenges of cheap, effective PoC testing. These particularly relate to sample adequacy and processing.
- Develop specific molecular (DNA/genotype-based) assays that predict gonococcal resistance and evaluate them in clinical settings.
- Maintain phenotypic antimicrobial surveillance and research to detect emerging threats; monitor and have the capacity to investigate mechanisms of resistance.
- Ensure that rapid test technologies that prove to be effective and accurate have rapid routes to market, and are implementable and available to patients.
- Ensure that PoC tests are effective and accurate.
- Investigate the potential impacts of rapid testing on patient care pathways.

## RECOMMENDATION

- Investment is needed in the basic research underlying development of diagnostic tests for antimicrobial resistance, such as studies of the correlations between genotype and phenotype.

## RESEARCH CHALLENGE 3: VACCINES

### CORE CHALLENGES

Vaccines have proved to be remarkably effective public health interventions, and also represent commercial opportunities in the global health market. However, with the exception of HPV, we still lack vaccines against STIs, notably HIV, gonorrhoea, chlamydia and syphilis.

Making vaccines against these infections is difficult due to the particular biology of the causative agents and the way these organisms interact with the host. There is therefore a need for significant continued investment in research on the basic science underlying vaccine development, for example in the workings of mucosal immunity.

### LONG-TERM SURVEILLANCE FOR THE UK'S HPV IMMUNISATION PROGRAMME

HPV is a ubiquitous virus group with more than 120 different genotypes. There are around 40 viral types associated with anogenital infection and disease, most of which are transmitted sexually. Genital warts are an extremely common STI. Although excisional treatment is effective, the cost of treatment is significant and recurrences are common. While vaccination is now available to prevent infection with HPV 6 and 11, the most common causes of genital warts, the UK HPV immunisation programme currently targets only young girls. The HPV vaccine was introduced throughout the UK in 2008. It targets HPV 16 and 18, which are associated with cervical cancer.

The HPV vaccine is preventative only – we still lack a cure. The long-term protective value of the vaccination is unknown, as is the risk of HPV type replacement. We therefore need to monitor how the vaccine is used and the effects it has on public health. Cervical cancers develop several years after infection; long-term research is therefore essential to show effectiveness. Furthermore, given the high cost of the vaccine, post-market surveillance of vaccine uptake, type replacement and duration of immunity is vital to determine whether the vaccine is as effective as trials have suggested.

Public Health England and Health Protection Scotland have introduced complementary surveillance programmes, which need to last for many years. The Scottish Government programme is envisaged to last until 2020 in order to inform future health services for women in relation to cervical disease and cancer prevention.

## MICROBICIDES

Microbicides – antiretroviral agents, such as tenofovir, dapivirine and UC781, delivered to the vagina and/or rectum – are an option to prevent HIV infection; the European Union funds research on this topic.[19] There have been promising results, and microbicides may prove useful as a means to reduce the high rates of HIV infection among women in developing countries.[20] Further phase II and III clinical trials are underway, and research on vaginal and rectal microbicides against HIV should be encouraged.

### AN HIV VACCINE

Strategies against HIV have advanced greatly since the 1980s, but remain imperfect and are not curative. The drugs currently used are costly, the virus persists in a latent state in cellular reservoirs and the emergence of drug resistance remains a constant threat. Cures and vaccines remain critical, unmet needs and possible routes to eradication in the long-term. Much investment has been spent on vaccine development in the past 25 years – it has so far been unsuccessful.[18] There are, nevertheless, good scientific reasons to remain optimistic, particularly on the vital basic science underpinning vaccine development.

Clinical evaluations must be international in scale, but the UK has the capacity to make significant and worthwhile inroads in the basic science, where there is already British strength. Some of the best HIV vaccine research funded from the USA is carried out in the UK and France, with their strong links to, respectively, Anglophone and Francophone Africa.

There is considerable UK potential to develop research on (i) mucosal and innate immunity to HIV and (ii) the correlation of the immune responses in laboratory animals with those in humans through the use of experimental medicine trials in conjunction with para-clinical trials (the latter where animal experiments run in parallel with clinical studies in the human population).

### VACCINATING AGAINST THE BACTERIAL STIs

The rise of antibiotic resistance implies vaccines against the bacterial STIs, particularly gonorrhoea, may have great value in the future. There are, however, difficulties. Unlike with many vaccine-preventable infections, prior infection with gonorrhoea does not confer immunity. Furthermore, the bacterium that causes gonorrhoea, like the influenza virus,

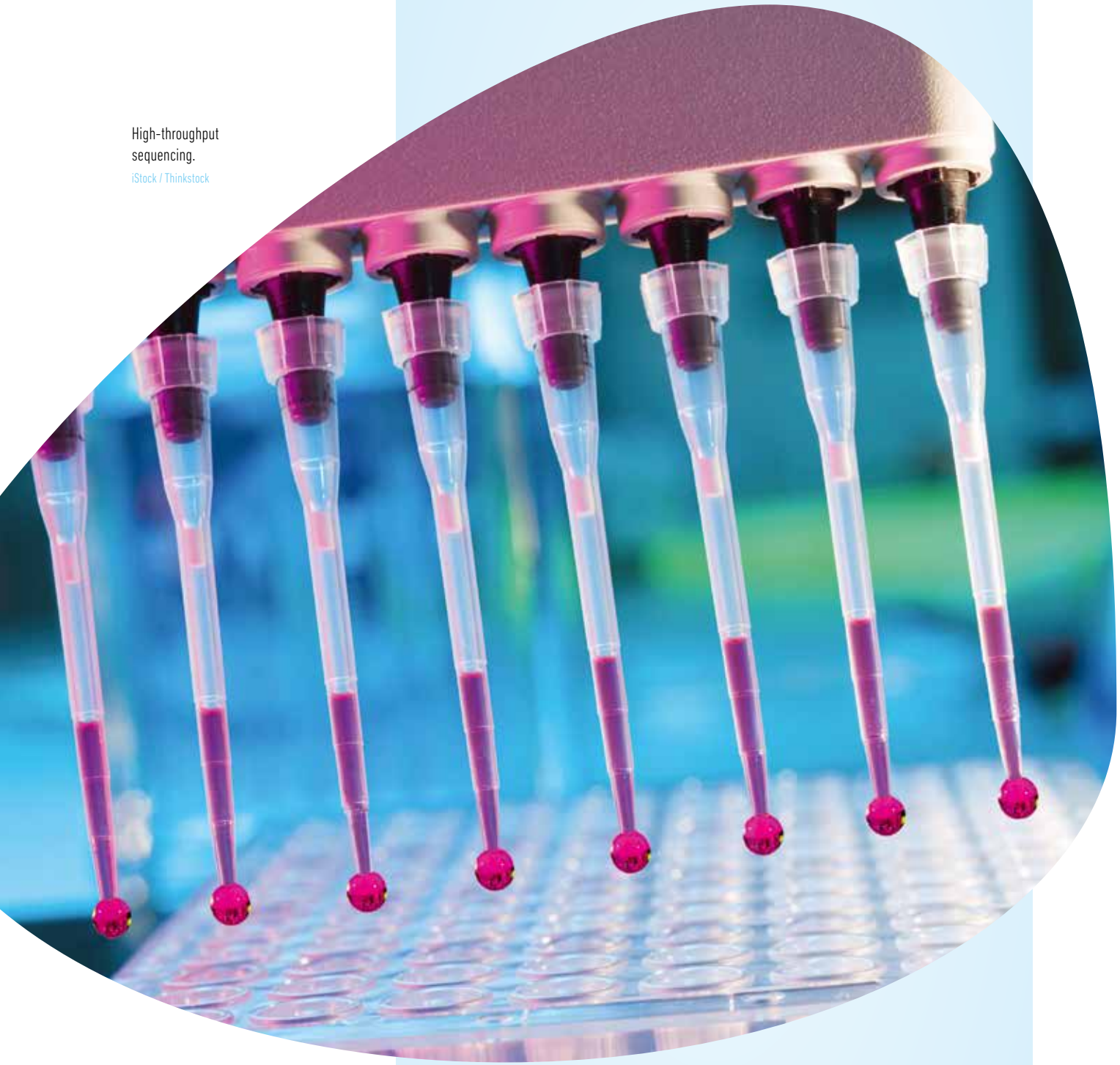
changes the molecular make-up of its surface, making it hard to develop a vaccine. Once again, a focus on the underlying interactions between the bacterium and the mucosa will prove a crucial step in vaccine development.

## RESEARCH PRIORITIES

- Develop the animal models needed for vaccine research:
    - Continue to invest in small animal models, for example mice, used for research on HIV.
    - Continue to invest in non-human primates for the most essential research on HIV (used as a challenge model for evaluation of vaccine efficacy and studies of pathogenesis).
    - Deploy knowledge of pathogenesis, derived from animal models, to develop *ex vivo* model systems.
    - Engineer modified disease-causing organisms appropriate for the mouse models that we already have. This approach will first require a better understanding of the mechanisms of pathogenesis.
- Develop safe and effective methods for para-clinical trials. Make full use of clinical data in research, while ensuring it is used with patient consent and shared confidentially and securely and its use has equitable outcomes.
- Explore the possibility of an organ culture system for bacterial STIs, using human fallopian tubes recovered by hysterectomy. This approach may have value in studying the mechanisms of pathogenicity, particularly for gonorrhoea and *M. genitalium*.
- Research and innovation must not stop when a vaccine enters the market. Continued investment is vital for follow-up monitoring of vaccine effectiveness, as exemplified by the HPV vaccine.

## RECOMMENDATION

- Funders should make a commitment to vaccine research, with particular focus on HIV, and back the basic science.



High-throughput sequencing.
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# NEW WAYS OF WORKING

## THE INFRASTRUCTURE FOR MICROBIOLOGY RESEARCH

With research funding at a premium, we must be collegial. The best people – from the public, private and voluntary sectors – need to be linked to identify the questions, and answer them.

We want to see a community of funders active in sexual health research, articulating diverse strategies in pursuit of the common goal of public health. No single approach will provide the total solution; strength lies in the different perspectives that come from a varied research ecosystem. The particular quality of the Research Councils, for example, lies with their support for broad, cross-cutting research across subjects and disciplines, while the National Institute for Health Research is strong on the clinical side. These perspectives need to be preserved; cross-disciplinary working must not mean homogeneity.

We also emphasise that research in microbiology is critically important for the design and implementation of infectious disease control strategies.

A firm commitment to fundamental basic research in microbiology will allow us to take advantage of the opportunities outlined above. Funders should therefore encourage the training, recruitment and promotion of high-quality research microbiologists, including provision at the most senior level for professorships in research microbiology specifically targeted at STIs.

For diagnosis, treatment and prevention to be effective, they need to be carried out with an understanding of the patient group involved, including their knowledge levels, beliefs and practices. Due recognition should therefore be given to finding combinations of relevant expertise to drive forward research and ensure its benefits reach as widely as possible. This expertise is found across the natural sciences, social sciences, the healthcare professions and patient groups and in the public, private and voluntary sectors.

## IN THE LABORATORY: NEW APPROACHES

In the last decade, new research tools for molecular and modelling studies have appeared (for example high-throughput

sequencing and genomics, transcriptomics and metabolomics). There are, accordingly, highly productive opportunities to revisit old (and often imperfect) techniques in light of these new methods. However, to fully exploit these opportunities, there is a need to develop effective laboratory models as, in many cases, none currently exist. Such models will be needed to successfully develop drugs and vaccines.

STIs can be modelled in the laboratory through:

- growing the bacteria or viruses, respectively, on nutrients or in cells (*in vitro*)
- culturing bacteria or viruses in isolated organ explants (*ex vivo*)
- use of animal models of disease

An ideal model for an STI would need to be inexpensive and proven to mimic a key infectious process (for example cell invasion) and/or a key clinical

## INTERDISCIPLINARY WORKING AT THE MEDICAL RESEARCH COUNCIL (MRC)

Interdisciplinary working will be essential to address the challenges posed by STIs. There have been recent notable successes in co-ordinating research efforts across institutions and sectors. The MRC has invested more than £15m in four major new collaborations that will advance the emerging field of stratified medicine – helping us to understand why different patients with the same diagnosis respond differently to treatments.

The funded programmes will look at stratified medicine approaches in four diseases, namely rheumatoid arthritis, hepatitis C, a rare genetic disorder called Gaucher's disease and primary biliary cirrhosis.

The awards will establish research consortia in each of these diseases that will draw on the expertise of scientists, industry and patient charities, underpinned by the clinical research infrastructure of the UK's health services. The consortia will combine 34 academic groups with 30 industry partners across the UK, and will have participation from public and patient groups throughout.

The nature of the research conducted will vary on the disease, but the stratified medicine programme serves as an example of how researchers with different expertise can be brought together to address challenges within a defined disease area.

problem (for example drug resistance). According to these criteria, only HIV is adequately modelled. Of the bacteria, chlamydia (*C. trachomatis*) and gonorrhoea (*Neisseria gonorrhoeae*) can be modelled to some extent, whereas syphilis (*T. pallidum*) has so far defied most attempts to develop a model.

*C. trachomatis* grows in epithelial cell lines; *N. gonorrhoeae* grows on agar containing blood cells. Additionally, *C. trachomatis* and *N. gonorrhoeae* will grow in fallopian tubes that have been obtained from women undergoing medically necessary hysterectomy.[21] These approaches will probably have little value for vaccine testing but they may be useful for studying the mechanisms of pathogenicity. The effect of sex hormones on organ cultures will need to be examined. Both gonorrhoea and chlamydia can be genetically engineered.

With the exception of transient growth in rabbit epithelial cells, and despite efforts dating back more than a century, it has proved impossible to culture virulent *T. pallidum* outside the body.[22] Moreover, it has also proved impossible to genetically engineer the bacterium so that it can be cultured. Non-animal models of STIs therefore represent a significant challenge for researchers.

In the 1970s and 1980s, primates were used for research on STIs; since that time, however, there have been significant advances in molecular biology, including genome sequencing, cloning and the ability to make chimeras. This opens up the possibility of modelling STIs, after either modifying the pathogen so that it can infect small animals, such as mice, or 'humanising' mouse tissues to allow infection. The latest techniques in molecular biology imply that such goals are possible; proof of principle of altering host specificity has been shown for meningococci, which are close relatives of gonococci.[23]

## STUDIES IN PEOPLE: GATHERING AND LINKING DATA – WHILE PRESERVING PATIENT SAFETY AND CONFIDENTIALITY

There are opportunities to break away from the current approach to drug and vaccine development (with associated high costs and high risks of failure at a late stage), and move towards a potentially safer, less financially risky and faster para-clinical paradigm. Such a paradigm requires that any animal studies be conducted in parallel with clinical work, with the two strands informing each other. There is potential to develop the para-clinical

approach in a safe and effective way for the study of STIs.

Clinical research will be aided by the national network of sexual health and HIV clinics that offer easily and freely accessible STI care and which treat the majority of STI cases. The gathering and linking of data from these clinics has contributed to the research conducted into STIs in the UK, not least by allowing the formation of large cohorts and establishment of some of the best national surveillance systems. The national network will continue to offer opportunities to study ways of reducing the detrimental impact of STIs on patients' health.

For effective clinical research, patient samples and data will need to be shared rapidly but securely, and stored over long periods for cohort studies that seek to identify long-term effects of interventions such as vaccines. At the same time, patients need to be assured of complete confidentiality.

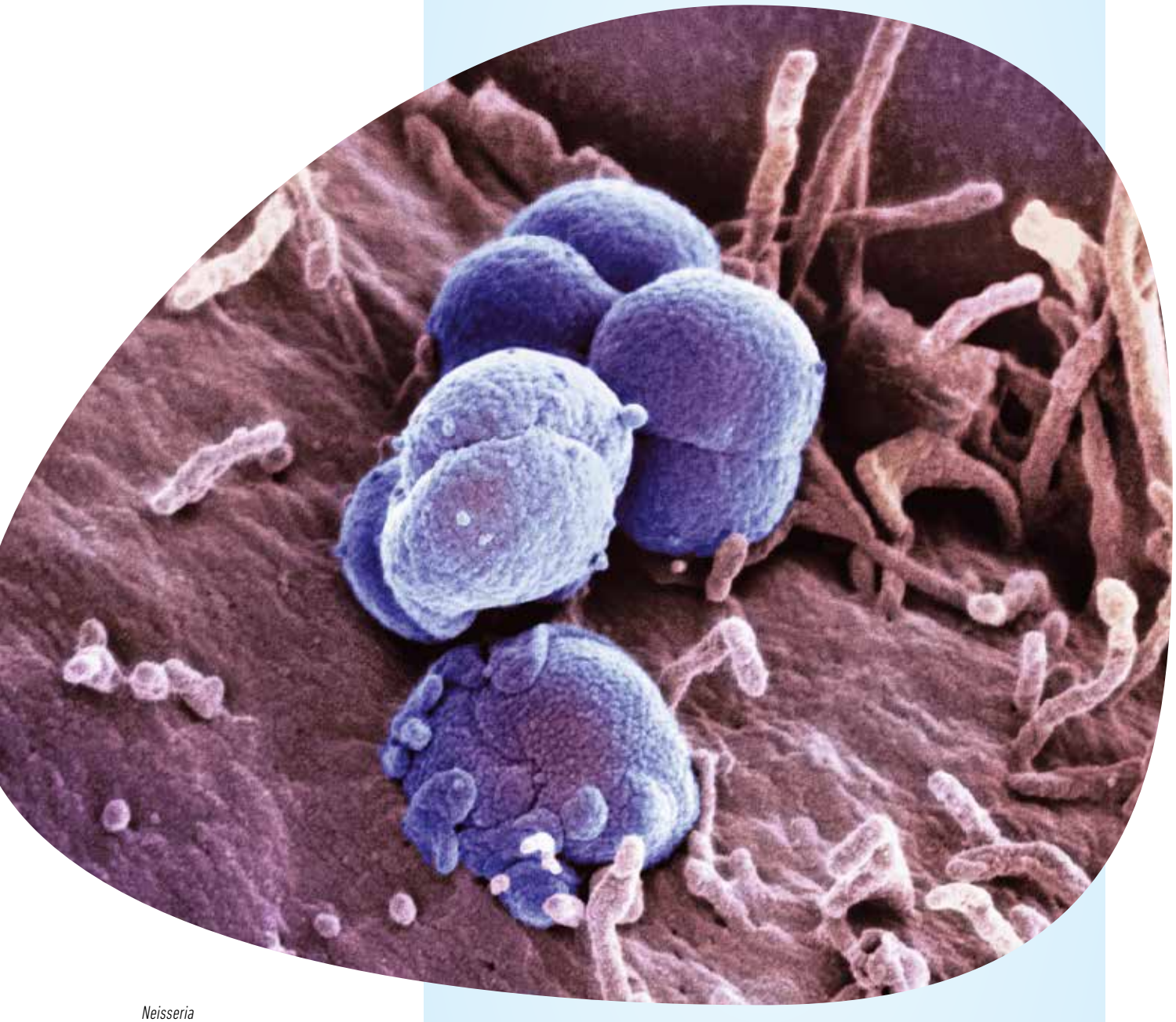
Clinical material is often the most precious resource for research on STIs; we need to maximise the opportunities for its use.[24] Any contracts with the private sector will need to be carefully designed to maintain the flow of samples and data, and apportion ownership in the most equitable ways. There are models from the voluntary sector of how non-contractual links can develop through, for example, joint appointments.

## PATIENT ACTIVISM IN THE RESEARCH PROCESS

The experience of AIDS shows what can be done through well-co-ordinated research to understand and diagnose infectious disease (and develop treatments), as well as the importance of public health campaigns in slowing disease spread.

Patient groups were clearly important in the early days of AIDS research in the 1980s. The Terence Higgins Trust was one of these groups. In many cases, the patient group knew more than the individual physicians and scientists treating the disease. There was, subsequently, extensive collaboration between researchers and patient groups. This patient-driven approach was not always comfortable for the physicians and scientists involved, but proved effective.[25]

HIV may be a model of how we respond to new emerging therapies for STIs, in terms of care provision and follow-up monitoring and research. There are ideas to draw on from the HIV experience in terms of driving research for the STIs today, and these should be explored.



*Neisseria gonorrhoeae* bacteria (blue) infecting a human epithelial cell (purple).

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# TABLES

## TABLE 1. MAJOR STIs IN THE UK

| Infection | Causative organism(s) | Total cases |
|---|---|---|
| Chlamydia | *Chlamydia trachomatis* | 213,398* |
| HIV/AIDS | Human immunodeficiency virus (HIV) | 96,000† |
| Genital warts | Human papilloma virus (HPV) | 90,000‡ |
| Non-specific genital infection | Unknown | 59,942§ |
| Anogenital herpes | Herpes simplex virus (HSV) | 32,021§ |
| Gonorrhoea | *Neisseria gonorrhoeae* | 23,183* |
| Molluscum contagiosum | Molluscum contagiosum virus (MSV) | 11,884§ |
| Trichomoniasis | *Trichomonas vaginalis* | 6,638§ |
| Syphilis | *Treponema pallidum* | 3,226* |
| Chancroid \| Lymphogranuloma venereum \| Donovanosis | *Haemophilus ducreyi* \| *Chlamydia trachomatis* \| *Calymmatobacterium granulomatis* | 414§ |

*These data are UK-wide new cases for 2011. www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317132033760, p. 4.

†Figure is an estimate of the number of people living with HIV in the UK by the end of 2011. www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317137200016, p. 2.

‡These data are UK-wide for 2009. www.gov.uk/government/uploads/system/uploads/attachment_data/file/207669/dh_133346.pdf, p. 3.

§Data available for England only – figures are for new cases in 2012. www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1247816547927, p. 12.

## TABLE 2. STATE OF THE ART IN TREATING STIs

| Infection | Vaccine | Cure | Main problems |
|---|---|---|---|
| HIV | No | No | Antiretroviral resistance, lack of cure, lack of vaccine |
| HPV | Yes | No | Preventative vaccine only, lack of cure, long-term protective value of vaccine unknown, risk of HPV type replacement unknown |
| Gonorrhoea | No | Yes | Severe antibiotic resistance |
| Syphilis | No | Yes | Antibiotic resistance |
| Chlamydia | No | Yes | Antibiotic resistance |

# AUTHORSHIP

The Microbiology Society convened an Expert Panel that met twice in late 2012 and early 2013 to identify the major issues.

Selected members of the Expert Panel then authored the first draft:

- **Dr Tariq Sadiq** wrote the section on rapid diagnostics; **Professor David Livermore** also contributed significantly.
- **Dr Samuel Moses** wrote sections on new therapies, vaccines and microbicides.
- **Dr William Burns** and **Dr Jonathon Stoye** wrote the text on animal and *ex vivo* models, in consultation with **Professor David Taylor-Robinson** (Department of Medicine, Imperial College London).
- **Professor Heather Cubie** contributed material on Scottish research on HPV.
- **Professor Pete Borriello**, **Mrs Dariel Burdass**, **Dr William Burns** and **Dr Benjamin Thompson** drafted all other sections.
- **Professor Tony Barnett** made a significant contribution by asking us to think critically, but constructively, about the research problems we identified.

The combined draft was sent to the entire Expert Panel for comments.

The following individuals and groups also gave valuable advice:

- **British HIV Association**.
- **Professor Jonathan Ross** (on behalf of the British Society for Sexual Health and HIV).
- **Professor Martin Cranage** (Hotung Chair of Molecular Vaccinology, St George's, University of London; Policy Committee Member, Microbiology Society).
- **Dr Kirstine Eastick** (Director, Scottish Bacterial Sexually Transmitted Infections Reference Laboratory).
- **Society for Applied Microbiology**.
- **Dr Desmond Walsh** (Medical Research Council).
- **Dr Andrew Winter** (Consultant in Sexual Health and HIV Medicine, NHS Greater Glasgow and Clyde).

The amended draft was sent to the **Society's Policy Committee** and **Council** for consideration of the report contents and recommendations, and for final commentary and agreement.

The text represents the view of the Expert Panel, the Society's Policy Committee and the Microbiology Society Council.

# EXPERT PANEL MEMBERS

| | |
|---|---|
| **Professor S. Pete Borriello** (Chair) | Editor-in-Chief, *Journal of Medical Microbiology* and *JMM Case Reports* |
| **Professor Nigel L. Brown** | President, Microbiology Society |
| **Professor Tony Barnett** | Professor of the Social Sciences of Infectious Diseases, London School of Hygiene and Tropical Medicine and Honorary Professorial Research Fellow, London School of Economics |
| **Professor Virginia Berridge** | Professor of History & Director, Centre for History in Public Health, London School of Hygiene and Tropical Medicine |
| **Dr Peter Biggins** | Defence Science and Technology Laboratory, Ministry of Defence |
| **Dr Angie Bone** | Formerly Director, National Chlamydia Screening Programme, Public Health England |
| **Professor Heather A. Cubie** | HPV Research Group and Scottish HPV Investigators Network, University of Edinburgh |
| **Ms Andrea Duncan** | Programme Manager, Sexual Health & HIV, Department of Health (Health, Science and Bioethics Division) |
| **Dr Catherine Fleming** | Consultant genitourinary physician, University College Hospital Galway, Ireland |
| **Professor Lucinda Hall** | Professor of Molecular Microbiology & Lead, Centre for Immunology and Infectious Disease, Barts and the London School of Medicine and Dentistry |
| **Professor Catherine Ison** | Director, Sexually Transmitted Bacteria Reference Laboratory, Public Health England; Visiting Professor, School of Public Health, Imperial College London |

| | |
|---|---|
| **Professor David Livermore** | Professor of Medical Microbiology, Norwich Medical School, University of East Anglia; Lead, Antibiotic Resistance, Public Health England |
| **Dr Fiona Lyons** | Consultant genitourinary physician, St James's Hospital, Dublin, Ireland |
| **Dr Samuel Moses** | Consultant Virologist, Public Health England Microbiology Services; Associate Clinical Lecturer, Newcastle University |
| **Mr Martin Murchie** | President, Society of Sexual Health Advisers; Senior Sexual Health Adviser, The Sandyford Initiative, NHS Greater Glasgow & Clyde |
| **Dr Anthony Nardone** | Epidemiologist, Sexual Health Promotion & Evaluation, HIV/STI Department, Public Health England |
| **Dr Tariq Sadiq** | Reader & Honorary Consultant, St George's, University of London |
| **Dr Jonathan Stoye** | Head, Division of Virology, National Institute for Medical Research, Mill Hill |
| **Mr James Taylor** | Senior Health Officer, Stonewall |
| **Dr David Ulaeto** | Defence Science and Technology Laboratory, Ministry of Defence |
| **Mr Paul Ward** | Deputy Chief Executive, Terence Higgins Trust |
| **Professor Robin A. Weiss** | Emeritus Professor, Division of Infection & Immunity, University College London |

# REFERENCES

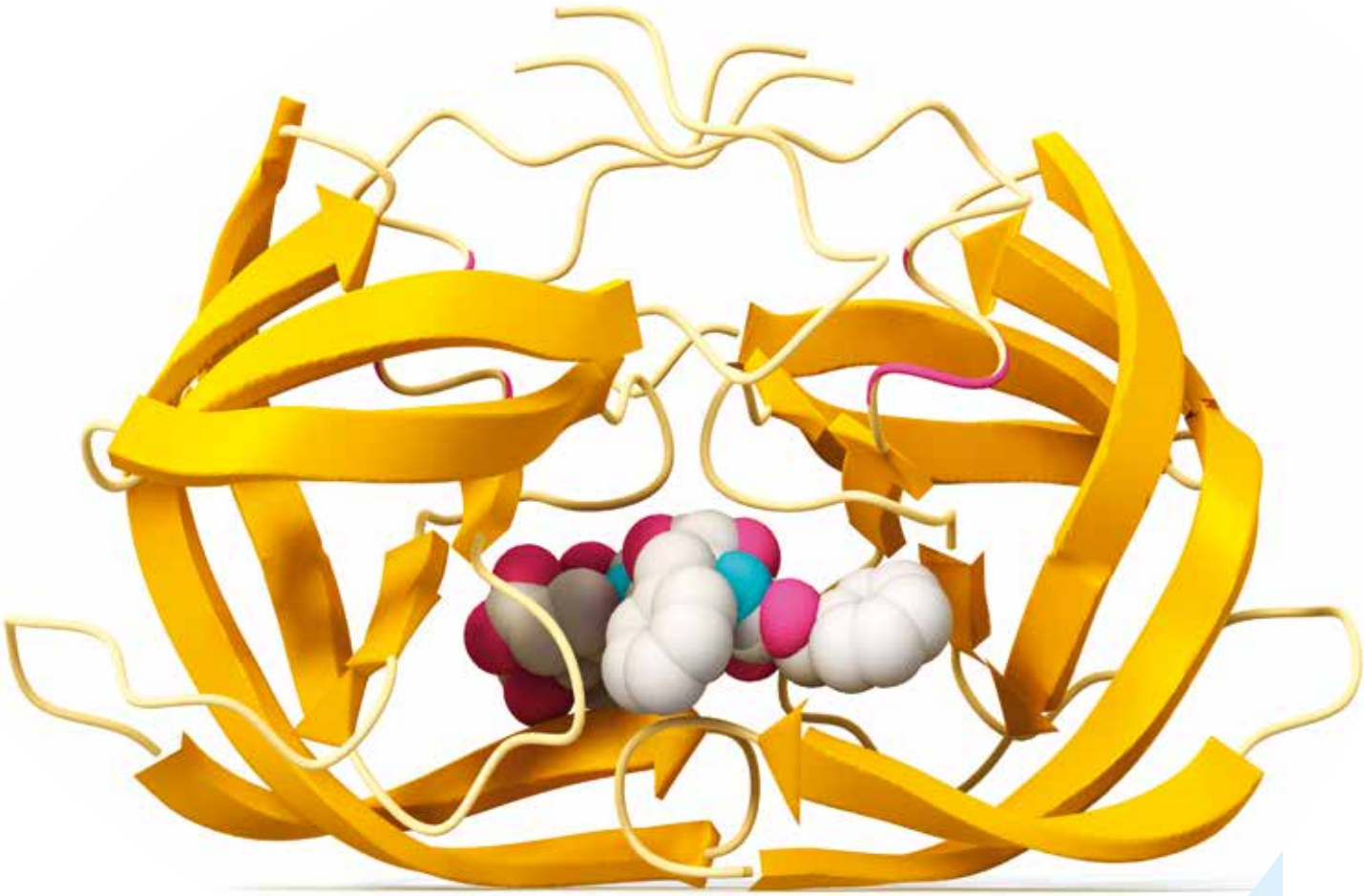

1. *Department of Health Framework for Sexual Health Improvement in England* – published in March 2013. www.gov.uk/government/uploads/system/uploads/attachment_data/file/142592/9287-2900714-TSO-SexualHealthPolicyNW_ACCESSIBLE.pdf
2. Department of Health/Department for Environment, Food and Rural Affairs (2013). *UK Five Year Antimicrobial Resistance Strategy 2013–2018*. www.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf
3. *GRASP 2011 Report: The Gonococcal Resistance to Antimicrobials Surveillance Programme*, Health Protection Agency, September 2012. www.hpa.org.uk/Publications/InfectiousDiseases/HIVAndSTIs/GRASPReports/1209GRASP2011/

   *Annual Report of the Chief Medical Officer, Volume Two, 2011 Infections and the rise of antimicrobial resistance.* www.gov.uk/government/uploads/system/uploads/attachment_data/file/138331/CMO_Annual_Report_Volume_2_2011.pdf
4. **Bignell, C. & Fitzgerald, M., Guideline Development Group, British Association for Sexual Health & HIV UK (2011).** UK national guideline for the management of gonorrhoea in adults, 2011. *Int J STD AIDS* **22(10)**, 541–547.

   **Unemo, M. & Nicholas, R. A. (2012).** Emergence of multidrug-resistant, extensively drug-resistant and untreatable gonorrhoea. *Future Microbiol* **7(12)**, 1401–1422.
5. US Food and Drug Administration, *Antiretroviral drugs used in the treatment of HIV infection*, 8 February 2013. www.fda.gov/ForConsumers/byAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm118915.htm

   **Dabbouseh, N. M. & Jensen, D. M. (2013).** Future therapies for chronic hepatitis C. *Nat Rev Gastroenterol Hepatol* **10(5)**, 268–276.
6. **Coates, A. R. & Halls, G. (2012).** Review: Antibiotics in phase II and III clinical trials. *Handb Exp Pharmacol* **211**, 167–183.
7. Coates & Halls, *ibid.*
8. **Rasmussen, T. A., Tolstrup, M., Winckelmann, A., Ostergaard, L. & Søgaard, O. S. (2013).** Eliminating the latent HIV reservoir by reactivation strategies: advancing to clinical trials. *Hum Vaccin Immunother* **9(4)**, 790–799.
9. Rasmussen *et al.*, *ibid.*
10. Department of Health/Department for Environment, Food and Rural Affairs, *ibid.*
11. **Allen, V. G., Farrell, D. J., Rebbapragada, A., Tan, J., Tijet, N., Perusini, S. J., Towns, L., Lo, S., Low, D. E. & Melano, R. G. (2011).** Molecular analysis of antimicrobial resistance mechanisms in *Neisseria gonorrhoeae* isolates from Ontario, Canada. *Antimicrob Agents Chemother* **55(2)**, 703–712.

12. **Sadiq, S. T., Dave, J. & Butcher, P. D. (2010).** Point-of-care antibiotic susceptibility testing for gonorrhoea: improving therapeutic options and sparing the use of cephalosporins. *Sex Transm Infect* **86(6)**, 445–466.
13. The UK Clinical Research Collaboration (UKCRC) translational infection research initiative consortium, *Electronic self-testing instruments for sexually-transmitted infections*. www.esti2.org.uk
    European Centre for Disease Prevention and Control (2012). *Technical Report: Novel approaches to testing for sexually transmitted infections, including HIV and hepatitis B and C in Europe*. http://ecdc.europa.eu/en/publications/publications/novel_approaches_to_testing_for_stis_.pdf
14. **Lawung, R., Cherdtrakulkiat, R. & Prachayasittikul, V. (2012).** Protocol for a facile multiplex PCR for multi-antimicrobial resistance and Gonococcus detection. *Methods Mol Biol* **903**, 329–341.
15. Oxford Nanopore Technologies Ltd (undated). *Summary*. www.nanoporetech.com/about-us/summary
16. **Bertelli, C. & Greub, G. (2013).** Rapid bacterial genome sequencing: methods and applications in clinical microbiology. *Clin Microbiol Infect* **19(9)**, 803–813.
17. www.gov.uk/government/news/dna-tests-to-revolutionise-fight-against-cancer-and-help-100000-nhs-patients
18. US National Institute of Allergy and Infectious Diseases, 25 April 2013, *Statement: NIH Discontinues Immunizations in HIV Vaccine Study*. www.niaid.nih.gov/news/newsreleases/2013/Pages/HVTN505April2013.aspx
19. For example: Combined Highly Active Anti-Retroviral Microbicides (CHAARM). http://chaarm.eu
20. **Van Damme, L. & Szpir, M. (2012).** Review: Current status of topical antiretroviral chemoprophylaxis. *Curr Opin HIV AIDS* **7(6)**, 520–525.
21. **Carney, F. E. & Taylor-Robinson, D. (1973).** Growth and effect of *Neisseria gonorrhoeae* in organ cultures. *Br J Vener Dis* **49**, 435–440.
    **McGee, Z. A., Johnson, A. P. & Taylor-Robinson, D. (1976).** Human fallopian tubes in organ culture: preparation, maintenance, and quantitation of damage by pathogenic microorganisms. *Infect Immun* **13(2)**, 608–618.
22. **WHO Scientific Group on Treponematoses Research (1966).** *Treponema pallidum*. A bibliographical review of the morphology, culture and survival of *T. pallidum* and associated organisms. Culture of *T. pallidum in vitro*: i. History. *Bull World Health Organ* **35(suppl.)**, 47–54.
23. **Litt, D. J., Palmer, H. M. & Borriello, S. P. (2000).** *Neisseria meningitidis* expressing transferrin binding proteins of *Actinobacillus pleuropneumoniae* can utilise procine transferrin for growth. *Infect Immun* **68**, 550–557.
24. **Health Protection Agency (2005).** *Providing the Evidence Base for Public Health: The Health Protection Agency's Research Strategy 2005–10*, p. 11; para. 6.2. www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1203064757273
25. **Berridge, V. (1996).** *AIDS in the UK: the Making of Policy, 1981–1994*. Oxford: Oxford University Press. Idea captured in Part 1, 1981–1985, 'Policy from below'.



Drug development has prolonged the life of millions of HIV-positive individuals.

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