

Impact Objectives

- Through the development of a low-cost same-day whole-genome-sequencing (WGS) service, offer faster diagnosis of infections and subsequently more targeted care
- Identify and gain a greater understanding of how antibiotic resistance can emerge and spread, so as to stop standard practices today, such as surgery and chemotherapy, from becoming too risky to undergo
- Apply cutting-edge scientific techniques, for example DNA technology, to speed up the diagnosis and ultimately improve the prognosis of patients suffering from infections such as TB, MRSA and pneumonia

Improving public health through targeted care

Professor Derrick Crook discusses his work to improve patient care that centres on transforming how infections are analysed and treated



Could you begin by introducing yourself?

I am a professor of Microbiology and NHS consultant

microbiologist, and academic molecular microbiologist with extensive experience in developing and optimising processing work flows for microorganism whole-genome-sequencing (WGS).

I lead the current National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) theme, as well as a Health Protection Research Unit. I also coordinate the Modernising Medical Microbiology (MMM) Consortium, which involves more than 60 multidisciplinary researchers.

I led the BRC team that has produced the first automated whole-genome-sequencing (WGS) Illumina short read based solution for clinical use, which is being implemented for mycobacterial diagnostics nationally by Public Health England.

I also lead a University of Oxford collaboration with Oxford Nanopore Technologies to optimise the processing of samples containing pathogens for sequencing on their platforms, including direct from samples.

How did you come to work in the field of infections?

Growing up on a farm in Africa meant I saw

the impact of infections around me. This generated a long-term interest in the biological processes of infections and global health.

Could you discuss the key objectives of the Modernising Medical Microbiology (MMM) research group?

We are improving diagnostics processes so care for patients can become more targeted and effective. This is important not just for individual patient care, but also for public health, in preserving antibiotic effectiveness against infections.

We aim to understand where the reservoirs of pathogens are, so we can better target interventions.

Can you tell us about your efforts to formulate a low-cost same-day whole-genome-sequencing (WGS) service?

This is a simplification of the diagnostic microbiology laboratories that have the potential to bring high-quality diagnostic services to high, medium and low income countries. The application of this has profound implications for the management of infectious diseases globally. Faster diagnosis of infections can help to target therapy and could allow more effective antibiotic treatment.

How is your work centred on predicting antimicrobial resistance progressing?

Our work is developing remarkably well with tuberculosis (TB) and HIV; however, most

other pathogens are still in their infancy. We aim to predict resistance by using WGS faster and possibly more accurately than current phenotypic methods. It is absolutely vital to deploy it as a clinical diagnostic service to improve outcomes for patients.

Antimicrobial resistance is an extremely critical issue. The impact of resistance is not just that we may find it increasingly hard to treat infections, but that many medical interventions that are taken for granted today, such as surgery and chemotherapy, become more of a risk.

What success have you seen in your efforts surrounding TB?

The successful culmination of our work is the first national rollout of a WGS service in diagnostic use by a public health body globally – an event heavily covered by both the UK and international media. The implementation of WGS in mycobacteria diagnosis has a real benefit to the patient, as turn-around-time is only seven days compared to between four and 12 previously for speciation and resistance only.

As the report includes relatedness, possible transmission or outbreaks can be investigated and interrupted much earlier and with greater specificity than with previous methods. Because all specificity, resistance testing and relatedness can be determined in one test rather than lots of different ones, there are costs savings in re-agents and time for Public Health England (PHE).

Resistance is futile: overcoming antibiotic resistance

The Modernising Medical Microbiology (MMM) research group at the University of Oxford, UK, is investigating trends in the incidence of infections and who is contracting them. The ultimate, infinitely beneficial goal, is to improve healthcare and health outcomes

Antibiotic resistance is a terrifying phenomenon that is becoming increasingly pervasive, with a number of pathogens outwitting medicine and spreading, in spite of best efforts to stop this. More knowledge is required about how bugs are transmitted around hospitals in order to design improved interventions that can prevent this transmission and save lives.

Derrick Crook, Professor of Microbiology, Consultant Microbiologist/Infectious Disease, Group Head/PI and Consultant Physician at the University of Oxford in the UK, is head of a research group entitled Modernising Medical Microbiology (MMM) that is seeking to revolutionise how infections are analysed and treated, with the long-term goal of improving patient care.

Crook is working alongside Professor of Medical Statistics and Epidemiology Sarah Walker and Professor of Medicine Tim Peto, among others. Crook gives an insight into the value of collaboration to the project: 'Most of our work involves collaboration with groups in the UK and abroad. This gives us confidence that our findings could be applicable globally,' he says. 'We also benefit from expertise and discussion from other groups on planning, execution and interpretation of the results of our projects.'

The work is funded by: the Oxford BRC Infection Theme and the Modernising Medical Microbiology UK Clinical Research Consortium (UK-CRC), Wellcome Trust, Medical Research Council (MRC), Bill & Melinda Gates Foundation, Oxford Biomedical Research Centre, Natural Environment Research Council (NERC), Department of Health (DoH) and the National Institute for Health Research, and encompasses a plethora of projects.

These include: the Comprehensive Resistance Prediction for Tuberculosis: an International Consortium (CRYPTIC) project, which is seeking to speed up diagnosis of tuberculosis (TB); the environmental REsistome: confluence of Human and Animal Biota in antibiotic resistance spread (REHAB), which is looking

in detail on a genetic level at bacteria in farm animals, human/animal sewage, sewage treatment works and rivers, to work out the complex network of transmission of important antibiotic-resistant bacteria and antibiotic resistance genes; Infections in Oxfordshire Research Database (IORD), which is seeking to improve the management of infection in UK hospitals; Antibiotic Review Kit (ARK) Programme, which is aiming to safely reduce antibiotic use in hospitals; National Institute of Health Research (NIHR) Health Protection Research Unit, which is developing new ways to detect, monitor, investigate and reduce the occurrence of healthcare-associated infections and antimicrobial resistance in the NHS; Health Innovation Challenge Fund (HICF), which is working to demonstrate locally-based genome sequencing operating in a network of routine UK NHS service laboratories at Oxford, Brighton, Birmingham and Leeds; whole-genome association studies that are attempting to pin down genetic variants associated with phenotypes such as increased virulence or mortality in various study species; and the MMM Transmission Study, which is the group's first project that is using a bug's genetic code to work out whether and how it is being passed from person to person.

INVESTIGATING TRENDS

An important element of the group's work is to investigate trends in the incidence of infections and who is contracting them. 'We have identified that the diagnosis of pneumonia is increasing, but further work is on-going to determine why this may be happening,' Crook explains. The team wishes to modernise the way infections are analysed and diagnosed by using cutting-edge scientific techniques; for example, using DNA technology to more quickly diagnose cases of TB. The group is also striving to transform how the treatment of patients is studied. To do this, the researchers are using large databases of hospital electronic information in order to identify trends in how infections behave and thus analyse how patient care can be improved. The group is using techniques, including DNA analysis of bacteria and viruses, to better understand how infections

spread, how to treat them, and how to prevent them in the future. The researchers are also exploring how antibiotic resistance occurs and how this can be prevented.

The infections the researchers are focusing on are: *Staphylococcus aureus* (including MRSA); *Clostridium difficile* (C. diff); *Mycobacterium tuberculosis* (TB); and the Enterobacteriaceae family (*Escherichia coli*, *Klebsiella* species and others). 'Our group is examining samples from Enterobacteriaceae from different sources to work out how these bacteria are able to become resistant to many different antibiotics,' Crook explains. 'The DNA that confers resistance is associated with plasmids and transposons, small pieces of DNA that move between different bacteria. We are at an early stage of investigating the bacteria, the plasmids and the transposons to understand how this happens.'

OVERCOMING CHALLENGES

The team's work on TB involved collaboration with the National Mycobacterium Reference service (NMRS) in Birmingham, UK, which provides TB screening and diagnosis for 39 other laboratories. 'All positive sputum samples submitted to the RCM were processed by standard diagnostic methods (Hain or phenotyping by culture) and WGS from April 2015 to March 2016,' the team explains. 'All WGS generated were analysed by the semi-automated analysis pipeline (COMPASS) developed by the MMM group. Development of COMPASS includes generation of a suitable report in conjunction with medical doctors and we work closely with Public Health epidemiology teams to produce visualisation tools for the detection of transmission events.'

There are challenges related to NHS workflows of processing samples and the threat this poses to effective treatment, which the team is seeking to overcome through its research. By decreasing the time taken to diagnose infections, treatment could be improved. 'There are issues of processing samples that are a function of slow methodologies of current diagnostic tests,' Crook explains.



‘The unlimited use of antibiotics in food production and healthcare has created an environment where bacteria with resistance survive better’

When it comes to antibiotic resistance, the team is striving to identify and understand how resistance can emerge and spread. This is where the researchers’ efforts are currently focused, rather than on working on therapeutic solutions to this. ‘Since the early introduction of antibiotics, we have been aware of the emergence of resistance (as often noted, it was mentioned by Alexander Fleming in his Noble prize speech),’ highlights Crook. ‘The unlimited use of antibiotics in food production and healthcare has created an environment where bacteria with resistance survive better. Resistance is an unintended consequence of the usage of antibiotics.’

IMPROVING PRACTICES

Further challenges the team has encountered include achieving robust validation and also

dealing with a lack of software solutions for large-scale processing of diagnostic samples. The group is currently at an early phase of development and implementation, but has high hopes for the work: ‘Currently we are still learning, and it is being used as a research tool, but this will progressively develop over the next decade,’ Crook explains.

Looking ahead, the group looks set to radically transform the outlook for healthcare, particularly in the arena of infectious diseases, and is succeeding in demonstrating that UK-based science can lead to improvements in the treatment of patients. The programme of work is leading the way in this field and could dramatically improve the fields of microbiology and infectious disease in years to come.

Project Insights

FUNDING

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