Institution: University of Oxford

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Pathogen whole-genome sequencing transforms healthcare-associated infection and outbreak management

Period when the underpinning research was undertaken: Aug 2010 - Oct 2018

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
David Eyre	*Infectious Diseases Consultant;* Academic Clinical Lecturer; Research Fellow	*Aug 2013 - Mar 2014 (Category C, NHS OUH);* 2014 – 2018; 2018 – present
Derrick Crook	*Consultant in Infectious Diseases and Clinical Microbiology*	*1996 – present (Category C, NHS OUH)*
Tim Peto	*Consultant Physician*	*1988 – present (Category C, NHS OUH)*
(Ann) Sarah Walker	Professor of Medical Statistics and Epidemiology	Dec 2012 – present
Kate Dingle	Senior Scientist	Aug 2002 – present

Period when the claimed impact occurred: Aug 2013 – Nov 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

University of Oxford researchers have developed world-leading approaches for exploiting whole-genome sequencing (WGS) combined with epidemiological data to monitor and control infection. They gained new understanding of the spread of the lethal pathogens *Clostridioides difficile*, *Candida auris*, *Mycobacterium chimera* and multidrug-resistant *Neisseria gonorrhoeae.* University of Oxford methods are now applied nationally for rapid tracking of transmission, stopping outbreak spread through evidence-based infection prevention measures. Internationally, the research has changed clinical practice, reducing infection rates to save lives and reduce healthcare burdens. Examples of stopping healthcare acquired infections include: reducing *C. difficile* infection, morbidity, and mortality through reduced antibiotic use; eradicating environmental persistence of the super-fungus *C. auris;* and elimination of fatal *M. chimera* infection in cardiac bypass surgery.

2. Underpinning research

Eyre, Walker, Peto, Crook and colleagues at the University of Oxford pioneered combining microbial WGS with clinical and epidemiological data, to track and trace life-threatening infections, particularly in healthcare settings. These powerful strategies have uncovered the sources and routes of transmission in major outbreaks.

In 2012, the University of Oxford team was among the first to demonstrate the power of WGS to enable early outbreak detection and transmission tracing of healthcare-associated infections [1]. They sequenced 26 methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridioides difficile* (formerly *Clostridium difficile*) isolates and measured the genetic relatedness, enabling outbreak identification and finding a previously undetected source of transmission. This proof-of-principle study of rapid WGS showed the potential of this approach to transform identification of transmission of healthcare-associated infections. The group subsequently developed and applied this approach to other settings and pathogens.

C. difficile has diverse routes of transmission

Prior to the University of Oxford research, it was believed that most *C. difficile* infections are acquired from other cases within a hospital environment (nosocomial transmission), so transmission from symptomatic patients has been the focus of prevention guidelines. However, their study performing WGS on over 1,200 consecutive *C. difficile* isolates from cases in Oxfordshire linked to their ward movement data over 3.6 years demonstrated that only a minority of cases are acquired from other unwell cases in hospital [2]. Another study led by Eyre showed

both local transmission of healthcare-adapted lineages and European-wide transmission via other routes.

Antibiotic restriction reduces C. difficile incidence

C. difficile infections have fallen markedly in England, but remained high elsewhere in Europe and North America; understanding the reasons for the decline in England can inform control of infection worldwide. To identify the reasons, the University of Oxford researchers combined WGS and antimicrobial prescribing data, and found that the decrease in *C. difficile* in England can be explained exclusively by falls in strains resistant to fluoroquinolone antibiotics, while the incidence of fluoroquinolone-susceptible strains remained unchanged [3]. This suggested that restrictions in fluoroquinolone use were key in reducing rates of *C. difficile* infection [3].

Candida auris can be transmitted via re-usable equipment

Candida auris is an emerging multi-drug resistant yeast, first reported in 2009, that can cause life-threatening infection in critical care settings. By combining environmental and patient sampling with WGS and routinely collected healthcare data, Eyre and colleagues were able to link one of the largest *C. auris* outbreaks to date worldwide (70 patients colonized or infected with *C. auris* between February 2015 and August 2017, in Oxford University Hospitals NHS Foundation Trust) to re-useable patient equipment (skin-surface temperature probes) for the first time [4]. This study also demonstrated the utility of software developed by Eyre and colleagues for analysing and interpreting pathogen WGS data.

Outbreak of Mycobacterium chimera-linked infection from heater-cooler units

In 2015, an alert was issued by the European Centre for Disease Prevention and Control (ECDC) that heater-cooler units (HCUs) used during cardiac bypass surgery were a likely source of disseminated infection caused by *M. chimera*. As part of the UK national incident investigation led by Public Health England (PHE), the University of Oxford researchers led the design of a case-control genome sequence analysis that pinpointed the infection source as HCUs in the UK and Europe [5]. Genomic data was processed by Crook, Peto and colleagues, and high-resolution phylogenetic typing by the University of Oxford team defined cases, providing precision for quantifying the risk for and outcome of infection. Crook also contributed to collaborative molecular epidemiological investigation of this outbreak in Europe and the US.

Tracking multi-drug resistant gonorrhoea

The University of Oxford researchers developed methods and metrics (including software) to track the spread of *Neissiera gonorrhoeae* and to identify antimicrobial resistance directly from sequencing data [6]. They demonstrated that these WGS-based tools can trace local, national, or international transmission, and be used to track antimicrobial resistance.

3. References to the research (University of Oxford employees in bold, students in italics)

1. *Eyre DW*…**Peto TEA**, **Walker AS**, **Crook DW** (2012). *[17/20 authors at University of Oxford]* A pilot study of rapid benchtop sequencing of *Staphylococcus aureus* and *Clostridium difficile* for outbreak detection and surveillance. BMJ Open 2:e001124. DOI:10.1136/bmjopen-2012-001124. Citations: 261 (Google Scholar 02-2021)
2. *Eyre DW*...**Peto TEA, Walker AS** (2013). *[19/20 authors at University of Oxford]* Diverse sources of *C. difficile* infection identified on Whole Genome Sequencing. *N Eng J Med* 369:1195-1205. DOI:10.1056/NEJMoa1216064. Citations: 582 (Google Scholar 02-2021)
3. **Dingle KE,** Didelot X, **Quan TP, Eyre DW**… **Peto TEA, Walker AS, Crook DW** (2017). *[15/28 authors at University of Oxford]* Effects of control interventions on *Clostridium difficile* infection in England: an observational study. *Lancet Inf Dis* 17:411-421. DOI:10.1016/S1473-3099(16)30514-X. Citations: 219 (Google Scholar 02-2021)
4. **Eyre DW**…**Walker AS, Peto TEA, Crook DW**, Jeffrey KJM (2018*) [9/22 authors at University of Oxford]*. A *Candida auris* outbreak and its control in an intensive care setting. *N Eng J Med* 379:1322-1331. DOI:10.1056/NEJMoa1714373. Citations: 166 (Google Scholar 02-2021)
5. Chand M…**Peto TE, Crook D**, Zambon M, Phin N (2017). *[4/41 authors at University of Oxford]* Insidious Risk of Severe *Mycobacterium chimaera* Infection in Cardiac Surgery Patients. *Clin Inf Dis* 64:335-42. DOI:10.1093/cid/ciw754. Citations: 109 (Google Scholar 02-2021)

6. **De Silva D**…**Crook DW, Peto TEA, Walker AS,** Paul J, **Eyre DW (**2016). *[6/18 authors at University of Oxford]* Whole-genome sequencing to determine *Neisseria gonorrhoeae* transmission: an observational study. *Lancet Inf Dis* 16:1295-1303: DOI:10.1016/S1473-3099(16)30157-8. Citations: 122 (Google Scholar 02-2021)

Funding included: 'Modernising Medical Microbiology' to the University of Oxford, PI Crook, 2009-14: GBP2,588,140 (MRC, G0800778); GBP2,829,138 (Wellcome Trust, 087646/Z/08/Z).

4. Details of the impact

Pathogen sequencing-based approaches widely adopted in public health

The University of Oxford research showed the utility and validity of generating, analysing and interpreting data from pathogen WGS to uncover the underlying drivers of outbreaks, enabling effective interventions [e.g. 1, 2, 4, 6]. Their methods now underpin routine pathogen WGS in healthcare organisations and public health agencies. Since their original demonstration of the power of WGS to address healthcare-associated infections [1], pathogen WGS has expanded rapidly, with more than 20,000 *C. difficile* and 78,000 *S. aureus* genomes sequenced (deposited in NCBI short-read archive, Nov 2020).

Crook was PHE Director of the National Infection Service 2015-2019 and the University of Oxford team worked closely with PHE to address specific outbreaks [e.g. 5, 6], and to develop national strategies, bioinformatic tools and methods [building on 4 and 6] for routine analysis of pathogen sequence data to reduce outbreaks, particularly in healthcare settings (for example, for *C.difficile*, [A]). Embedding WGS in PHE labs and optimizing the use of WGS-based information is now Strategic Priority 7 of the PHE Infectious Diseases Strategy 2020-25 (published Sep 2019, [B]).

This research has also contributed to implementation of WGS for outbreak control by public health bodies internationally. For example, an Associate Director for Science at the US Centers for Disease Control and Prevention (CDC) stated that the University of Oxford research informed CDC policy and procedures, guided the field in how to establish and implement WGS bioinformatics, and *"their greatest impact is in leading the application of advanced genomics for HAIs [healthcare acquired infections]"* [Ci]. Further, the Associate Director of Clinical Microbiology at the University of Virginia, US, stated: "*research and researchers at University of Oxford…have been integral to our ability to assist the entire United States with [nosocomial] outbreak investigation"* [Cii]. An example from Virginia is that a WGS investigation based on University of Oxford methods informed redesign of hospital plumbing, dramatically reducing spread of antibiotic resistant bacteria, reducing new patient infections with carbapenem resistant isolates from 70 to 15 per year, since 2016 [Cii]. In Australia, research by Crook and colleagues "*strongly influenced the implementation of genomics into routine diagnostic testing and public health laboratory surveillance in NSW [New South Wales],…reflected in the development and implementation of the NSW Health Genomics Strategy (June 2017) and the Australian National Microbial Genomics Framework 2019-2022*", according to a lead for public health microbiology in NSW [D].

Reducing healthcare associated C. difficile infections

C. difficile is the biggest cause of infectious diarrhoea in hospitalised patients and can lead to serious infections, with mortality of up to 25% in frail patients. It presents a worldwide problem, causing an estimated 500,000 infections and 29,000 deaths in the US in 2012, and more than 170,000 cases in Europe. The estimated annual attributable cost in the US is USD6,300,000,000.

Redesign of national surveillance for *C. difficile*: Following the University of Oxford discovery [2] that sources other than symptomatic patients are the source of most *C. difficile* infections in endemic settings with routine infection control, PHE designed a new WGS-based national surveillance system for *C. difficile,* substantially based on University of Oxford research [A]. This is the world's first structured national surveillance programme for *C. difficile* based on WGS. Sentinel hospitals were chosen based on University of Oxford analysis of national patient admission and transfer data. The system was approved and scheduled for implementation in 2020, but delayed until 2021 due to the COVID-19 pandemic [A]. The system is in the business plan of PHE for Healthcare Associated Infections (current, Dec 2020) [A], to provide all acute NHS trusts in England (approximately 150) with access to WGS and process approximately 12,000 *C. difficile* samples per year. According to the PHE lead on *C. difficile* the new system is "*a more cost-effective and future-resilient surveillance system to track known and provide an early warning of emergent C. difficile clones and types"* [A], as well as extending global knowledge of how to

diagnose, report and characterise a key infection that is a health service quality performance indicator in many countries, including the UK and US [A].

Widespread adoption of antimicrobial restriction to control *C. difficile* infection: The demonstration that fluoroquinolone restriction was associated with marked falls in incidence of *C. difficile* infection [3] has led to widespread adoption of polices to restrict fluoroquinolone use internationally. This research [3] influenced US public health and clinical leaders to focus on fluoroquinolones [Ci], and the 2017 update by the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America of the Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children cites several studies by Crook and colleagues and recommends restriction of fluoroquinolones [E]. The 2018 guidelines of the European Society of Clinical Microbiology and Infectious Disease recommend "*Restriction of antibiotic agents/classes is effective in reducing CDI rates*" [F], and cites University of Oxford research (including [2, 3]). *C.difficile* infections in the US reduced by approximately 22% from 2017 to 2019, which is likely due to a combination of infection control measures and altered antibiotic prescribing [Ci].

An illustrative example of benefits to healthcare providers is Betsi Cadwaladr University Health Board in Wales, which had one of the highest rates of *C. difficile* infection in the UK. A 2016 WGS investigation by Public Health Wales [G], collaborating with Eyre and colleagues [based on 3], found evidence of antibiotic use being a key driver in patterns of *C. difficile* infection. The report recommended prioritisation of antimicrobial stewardship across primary and secondary care [G]. A spokesperson from the health board was quoted by *The Pharmaceutical Journal* in 2019 [H] as stating that the Board had achieved a 38.7% decrease in *C. difficile* infections comparing 2017/18 to 2018/19, which they partly attributed to a decrease in the antibiotic prescription rate (12.6% decrease in primary care, April 2016-March 2019). The median cost of treating a patient with *C. difficile* infection is GBP7,500, compared to GBP2,800 for patients with other medical conditions, so a decrease in cases provides immediate cost-savings to the healthcare provider, as well as decreasing the high risk of mortality in frail patients.

Improved clinical practice to remove sources of infection

Better infection control measures for *C. auris*: *C. auris* is an emerging multidrug resistant fungus, with healthcare-associated outbreaks detected in at least 30 countries. *C. auris* infection occurs predominantly in patients in high-dependency settings, with high mortality rates – up to 50% – and presenting major treatment challenges due to antifungal resistance and transmission within healthcare units. The University of Oxford discovery that re-useable equipment, including temperature probes, can be a major route for spread and persistence of this pathogen [4] had the immediate impact of stopping the Oxford hospital outbreak in August 2017. Previous infection control measures had no significant effects until removal of the temperature probes from the affected neurosciences intensive care unit. This was the first time an outbreak of *C. auris* had been ended with a clear understanding of the cause, and resulted in the immediate benefit of no further cases from an outbreak that had infected 70 highly vulnerable patients.

This discovery of the infection risk associated with multi-use equipment led to changes in healthcare guidelines. PHE updated *C. auris* guidelines in August 2017 (Ii), specifically referring to reusable equipment such as temperature probes, and there have been no major outbreaks since these changes in practice (Iii). The cost of controlling one previous outbreak was reported as more than GBP1,000,000 (Iii), so preventing outbreaks provides major cost-savings for healthcare and public health bodies. In the US, the University of Oxford research [4] informed CDC guidance on environmental cleaning for *C. auris* prevention [Ci]. CDC guidelines were updated in 2018 to specifically mention disinfection to avoid the risk of transmission via mobile equipment including temperature probes [Ji]. In South Africa, *C. auris* has been detected in approximately 100 hospitals and has caused large outbreaks. To address this, the Federation of Infectious Diseases Societies of Southern Africa issued new guidelines in 2019 [Jii], extensively recommending single-use equipment and disinfection of reusable equipment, citing [4].

Safer cardiac bypass surgery: From 2013 to 2017 in Europe, Australia and the US, more than 100 cases of severe *M.chimaera*-linked infections were reported, associated with cardiac surgery using HCUs, with high morbidity and mortality (9 of 18 patients (50%) in the UK died). Infection was estimated to occur in 1 in 100-1000 patients undergoing surgery with HCUs. Research [including 5] provided certainty about the source, which empowered the case for redesign of the equipment. Robust interventions led to the termination of the outbreak, through withdrawal of the

implicated HCU and major improvements in HCU design by the company [Ki]. The International Society for Cardiovascular Infectious Diseases issued guidelines (Nov 2019) on prevention of *M. chimera* infection following cardiac surgery [Kii], citing this research [5]. No cases of *M. chimera* infection have been found in patients who had open heart surgery in the UK since 2016, showing that accurate identification of the outbreak source led to elimination of this dangerous infection.

Enabling effective public health responses to multidrug resistant gonorrhoea

The World Health Organisation (WHO) reports there were approximately 87,000,000 new cases of gonorrhoea in 2016, and it results in substantial morbidity and economic cost worldwide. Spread of drug-resistant gonorrhoea strains is a major problem and can occur quickly in high-risk populations. Since there are few treatment options, rapid investigation and prevention of outbreaks is essential. In 2018, the WGS methods developed by Eyre and colleagues [6] were adopted by PHE and public health bodies in Australia to conduct rapid investigations into extensively drug-resistant gonorrhoea, enabling tracing of sources and transmission and targeted public health intervention [Li, ii]. For example, two UK cases were traced to Ibiza, Spain, prompting a rapid local and international response to prevent spread [Lii, iii]. According to the WHO [Liv], the rapid contact tracing and public health messaging undertaken by PHE based on this work, resulted in low risk of further transmission in the UK, thus preventing further near-untreatable infections. Also, based on this research, in 2019 the ECDC called on EU/EEA member states to strengthen surveillance, testing and tracing (Liii), and the University of Oxford research (e.g. [6]) has contributed to the implementation of WGS for gonorrhoea surveillance by the WHO [M].

5. Sources to corroborate the impact

A. Letter from PHE Lead on *C. difficile* infection (Dec 2020), describing contribution of University of Oxford research to WGS-based national surveillance system.

B. PHE Infectious Diseases Strategy 2020-2025, published Sep 2020, stating WGS strategy and referring to partnership with University of Oxford, p14 and p15.

C. Letters from: i) Associate Director for Science in the Division of Healthcare Quality Promotion at the CDC, (Dec 2020), detailing contribution of University of Oxford research to CDC policy and actions; ii) Associate Director of Clinical Microbiology and of Medicine and Pathology, University of Virginia, (Nov 2020), detailing contributions to outbreak control in the US.

D. Letter from lead at Centre for Infectious Diseases & Microbiology Laboratory Services, NSW, Australia (Nov 2020), stating contribution of Crook's research to implementation of WGS.

E. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America. Page e5 and references 91, 92, 250, 325.

F. European Society of Clinical Microbiology and Infectious Diseases: Guidance document for prevention of *Clostridium difficile* infection in acute healthcare settings (2018). p1053, and references 31, 32, 33, 57 and 184 in Appendix. DOI: 10.1016/j.cmi.2018.02.020

G. Public Health Wales study report "Enhanced surveillance and response to reduce *Clostridium difficile* infection within North Wales", Sep 2016.

H. The Pharmaceutical Journal, news report 21 Aug 2019, describing reduction in *C difficile* cases in North Wales after reductions in antibiotic prescribing.

I. PHE guidance on *C. auris*: i) August 2017 guidance on management and infection prevention; ii) presentation by PHE National Incident Coordinator for *C. auris*, March 2019.

J. Guidelines for the prevention of *C. auris* infections: i) US CDC, online; ii) Federation of Infectious Diseases Societies of Southern Africa. S Afr J Infect Dis. 2019;34, a163.

K. Changes in design and guidelines for HCUs used in cardiac surgery: i) Medical device correction letter from the manufacturer, LivaNova, Oct 2018; ii) International Society for Cardiovascular Infectious Diseases guidelines (Nov 2019).

L. Investigations of *N. gonorrhoeae* cases: i) in UK and Australia, Jennison *et al. Euro Surveill*. 2019 DOI:10.2807/1560-7917.ES.2019.24.8.1900118; ii) Eyre *et al*. *Euro Surveill*. 2019 DOI:10.2807/1560-7917.ES.2019.24.10.1900147; iii) ECDC comment on Eyre et al. *Euro Surveill*, April 2019; iv) WHO news on gonococcal infection, Jan 2019.

M. Corroborator 1: Director, WHO Collaborating Centre for Gonorrhoea, may be contacted to corroborate contribution of University of Oxford research to WHO implementation of WGS.