Institution: University of Cambridge		
Unit of Assessment: UOA1		
Title of case study: Generating pathogen genomes for public health benefit.		
Period when the underpinning research was undertaken: 2012 to December 2020		
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:**
Sharon Peacock	Professor of Public Health and Microbiology	2009-2015 2019-present
Ewan Harrison	Senior Research Associate	2014-2018 2019 – present
Ian Goodfellow	Professor of Virology and Deputy Head of the Department of Pathology	2012-present
Period when the claimed impact occurred: August 2013 – December 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact (indicative maximum 100 words)

Sequencing of the SARS-CoV-2 genome has detected new variants that may alter disease severity, transmissibility and vaccine efficacy. This capability has proved critical to guide government decision making for disease control and vaccine roll-out during the COVID-19 pandemic. Based on a decade of translational research that established the public health impact of pathogen sequencing, in late February 2020, Peacock predicted the importance of detecting SARS-CoV-2 genetic changes to control the COVID-19 pandemic. In early March 2020, she initiated and led the development of the COVID-19 Genomics UK Consortium (COG-UK), which she directs. As of December 2020, COG-UK has generated over 160,000 SARS-CoV-2 genomes, made available globally through open access databases, which are being used actively in public health decisions. This work has led directly to a further GBP12,200,000 award to Peacock from the Testing Innovation Fund to increase sequencing capacity by COG-UK, and the announcement of a new national genomic healthcare strategy.

2. Underpinning research (indicative maximum 500 words)

Peacock is internationally recognised for her work demonstrating the utility of pathogen whole genome sequencing (WGS) to benefit of public health. Her research and experience in this field has underpinned the development the COVID-19 Genomics UK Consortium (COG-UK).

Whole genome sequencing to understand outbreaks of hospital associated pathogens: In 2012, Peacock was one of the first to use pathogen WGS to understand the basis of a clinical infectious disease scenario – a methicillin-resistant *Staphylococcus aureus* (MRSA) outbreak in a neonatal intensive care unit. This work confirmed that WGS can distinguish microorganisms responsible for an outbreak, from closely related microorganisms that are not. This was a major breakthrough since hospital-adapted MRSA cannot be distinguished from related bacteria using conventional methods [1].

Building on these data, in 2013 Peacock led a study to determine whether pathogen sequencing could prospectively (rather than retrospectively) inform clinical decision-making. The team used MRSA WGS to identify and control the source of a 6-month MRSA outbreak in a special care baby unit; thereby providing the first evidence that bacterial sequencing could impact on patient care in real-time [2].

Peacock subsequently proposed a new paradigm in infection control in which systematic sequencing in the absence of any epidemiological information could serve as an early warning system for infection outbreaks; thereby, guiding targeted investigation and intervention to control the infection. To test this, she sequenced MRSA isolates collected from 1,465 people not known to be linked to an outbreak. By integrating these genetic data with epidemiological data, she identified 173 outbreaks, containing between two and 44 cases, involving a total of 598 people (41%) [3]. This study provided the first comprehensive picture of MRSA transmission in a large

population and revealed the power of proactive WGS to identify cryptic outbreaks. Many of these outbreaks had continued for months or even years, including a protracted outbreak in a GP surgery in which one person acquired MRSA and later died from MRSA septicaemia. These findings highlighted the imperative for prospective pathogen sequencing, rather than waiting for a suspected outbreak, and represented a paradigm shift for hospital infection control.

To evaluate the cost effectiveness of this 'sequence first' approach, Peacock deployed a model that compared 'MRSA sequencing plus current practice' *versus* 'current practice alone' for outbreak investigation. This work demonstrated that routine, proactive MRSA sequencing was cost effective, reducing total MRSA acquisitions in hospitalised patients in the year following their index admission [4]. In addition to her work with MRSA, Peacock was one of the first to apply clinical sequencing to investigate outbreaks of other multidrug-resistant bacteria, including carbapenemase-resistant gram-negative bacilli (in 2013) [5] and vancomycin-resistant *Enterococcus faecium* (in 2020) [6].

Detection of antibiotic resistance using sequencing technologies: In 2013, Peacock described one of the first clinical applications of DNA sequencing to characterise antibiotic resistance in liquid cultures of *Mycobacterium tuberculosis* (TB). This study genotyped susceptibility to 39 antibiotics, highlighting the value of sequencing to dramatically accelerate TB diagnosis and targeted prescribing [7].

COVID-19 and SARS-CoV-2 sequencing: In late February 2020, when there were just a handful of known COVID-19 cases in the UK, Peacock proposed that detecting genetic changes in the SARS-CoV-2 genome would be important to facilitate disease control. In early March 2020, Peacock initiated and led the development of the COVID-19 Genomics UK Consortium (COG-UK), which she now directs. The consortium includes 16 sequencing hubs (the majority in academic institutions), all four public health agencies of the UK, and the Wellcome Sanger Institute. Together with other investigators in COG-UK, Goodfellow and Peacock used >25,000 SARS-CoV-2 WGS to investigate the rapid global dispersal and increasing frequency of the SARS-CoV-2 spike protein variant D614G. This study supported the notion that the D614G variant has a selective infection advantage and higher viral load (in younger patients) but is not associated with an increase in COVID-19 mortality or clinical severity [8].

3. References to the research (indicative maximum of six references)
Evidence of research quality: *Research published in peer-review journals. Research was supported by competitively won grants.

[1] *Köser CU…**Peacock SJ.** Rapid whole-genome sequencing for investigation of a neonatal MRSA outbreak. *New Engl J Med*. 2012;363:2267-2275.
[2] *Harris SR…**Peacock SJ.** Whole-genome sequencing for analysis of an outbreak of meticillin-resistant *Staphylococcus aureus*: a descriptive study. *Lancet Infect Dis*. 2013;13:130-6.
[3] *Coll F, **Harrison E**…Peacock SJ**.** Longitudinal genomic surveillance of MRSA in the UK reveals transmission patterns in hospitals and the community. *Science Transl Med*. 2017;9(413).
[4] *Dymond A…**Peacock SJ.** Genomic surveillance of methicillin-resistant *Staphylococcus aureus*: a mathematical early modelling study of cost effectiveness. *Clin Infect Dis*. 2020;70(8):1613-1619.
[5] *Reuter S…**Peacock SJ.** Rapid bacterial whole-genome sequencing to enhance diagnostic and public health microbiology. *JAMA Intern Med*. 2013;173:1397-404.
[6] *Gouliouris T…**Peacock SJ.** Acquisition and Transmission Networks of *Enterococcus faecium* Revealed by Whole Genome Sequencing: A Longitudinal Cohort Study. *Nature Microbiol*. 2021;6(1):103-111. Epub 2020 Oct 26.
[7] *Köser CU…**Peacock SJ**. Whole-genome sequencing for rapid susceptibility testing of M. tuberculosis. *N Engl J Med*. 2013 Jul 18;369(3):290-2.
[8] *Volz E…**COG-UK inc. Goodfellow I (Peacock SJ)**…Connor T. Evaluating the Effects of SARS-CoV-2 Spike Mutation D614G on Transmissibility and Pathogenicity. *Cell*. 2021 Jan 7;184(1):64-75.e11. doi: 10.1016/j.cell.2020.11.020. Epub 2020 Nov 19.

Competitive funding received

Department of Health and Social Care, Testing Innovation Fund. GBP12,200,000. (2 Nov 200 – 31 Mar 2021). Extension of COVID-19 genomics capabilities in the UK. Co-lead: Peacock.
UKRI/Wellcome/HMT COVID-19 Fighting Fund (1 April 2020 to current). COVID-19 genomics UK consortium (COG-UK) for rapid development of a national capability for covid-19 sequencing for public health benefit. GBP20,000,000. PI: Peacock.
Health Innovation Challenge Fund (2014-2021). 'Translating whole genome sequence technology into diagnostic and public health microbiology.' GBP4,461,919. PI: Peacock.
UKCRC (UK Clinical Research Collaboration) Translational Infection Research Initiative Phase 2 Consortium Grant (2011-2016). 'Development, evaluation and translation of next-generation sequencing tools to track MRSA transmission pathways and enhance infection control'. GBP3,223,710. PI: Peacock.

4. Details of the impact (indicative maximum 750 words)

Peacock's work applying WGS to infection control has had a profound impact on UK and international policy, placing the UK at the forefront of genomic pathogen sequencing. By establishing and leading COG-UK, she has demonstrated the power of viral WGS to guide disease control and minimise harm to people [A]. COG-UK has positioned the UK as world leaders in COVID-19 genomics, and in September 2020, the Secretary of State for Health and Social Care announced the launch of a new national genomic healthcare strategy, 'Genome UK', the development of which will be based on, and informed by, COG-UK [A].

Impact on practitioners and the delivery of professional services

Establishing routine sequencing services for infection control: Between January and March 2013, Peacock chaired the working group that made recommendations on infectious disease sequencing for the 100,000 Genomes Project in the UK [B]. This led to recommendation for the sequencing of *Mycobacterium tuberculosis* (TB), Hepatitis C, and deep sequencing of HIV to detect drug resistant variants which emerge during treatment. The 2013 report also proposed the need for a devolved network of pathogen sequencing laboratories. As a direct result of these recommendations by Peacock and the committee, in 2017 Public Health England (PHE) announced the launch of a National Mycobacterial Reference Whole Genome Sequencing service [B]. Since its launch, WGS has been performed on culture confirmed TB from 6,479 individuals (1,151 in 2017; 2,693 in 2018; 2,635 in 2019). This information has been used to determine appropriate treatment regimens, and identify clusters of infection [B]. HIV (since 2017) and Hepatitis C (since 2018) sequencing are also now offered through PHE's Antiviral Unit [B].

SARS-CoV-2 sequencing: In March 2020 in response to the COVID-19 pandemic, Peacock obtained GBP20,000,000 to establish COG-UK, overseeing the legal, ethical and governance framework. COG-UK has developed the methods for SARS-CoV-2 sequencing and software tools for data interpretation and integration, including methods for real-time mutation and outbreak detection [C]. These research tools and all genome data generated have been deposited to open access repositories including GISAID (to which 1,000 institutions deposit data and 7,500 researchers participate) and MRC-CLIMB (which serves over 300 research groups across at least 85 research institutions in the UK) [C]. By the end of December 2020, COG-UK had generated more than 200,000 UK SARS-CoV-2 genomes [C] – around 45% of all SARS-CoV-2 genomes sequenced worldwide. These data are actively utilised each day by the four UK Public Health Agencies and government to monitor the spread and evolution of the virus. In November 2020 Sir Patrick Vallance (the UK Chief Scientific Officer) noted the critical role played by COG-UK stating: "*On behalf of the Government, I wanted to acknowledge the scientists and technicians of COG-UK. By mapping over 90,000 genomes you've helped us better understand the virus, identified routes of introduction and transmission, and paved the way for improved treatments and vaccines."* [C]. This unprecedented effort – not previously performed for any pathogen, anywhere in the world – has placed the UK at the forefront of pathogen genomics.

Impact on policy and the health and wellbeing of people

Infection control during the COVID-19 pandemic: In December 2020, COG-UK enabled the discovery of a new, more transmissible SARS-CoV-2 variant (lineage B1.1.7, termed VOI

202012/01 by Public Health England) [D], associated with an outbreak of COVID-19 in Kent that spread rapidly across the UK and beyond. This work informed directly a major change in government policy aimed at saving lives and protecting the NHS: (i) on 19th December 2020, new Tier 4 measures were introduced for 6,000,000 people in the South East of England and London; (ii) previously sanctioned 5-day Christmas 'bubbles' were restricted to Tier 3 or below areas, only on Christmas day; (iii) on Boxing Day 2020, a further 20,000,000 people were brought into Tier 4 [D]. The identification of the new variant also resulted in the closure of borders to the UK by almost all of the EU member states as well as suspension of flights from the UK to India, Iran, and Canada [D].

Prospective tracking of SARS-CoV-2 variants: During the first and second waves of the pandemic, COG-UK identified the origins of viral importations into the UK [E]. These data showed that during the first wave, more than 1,000 introductions occurred between February and March from Spain, Italy and France. Furthermore, studies in Scotland and Wales showed that viral lineages became largely extinct during the first lockdown, with second waves being driven by new introductions [E]. These data refuted the alternative hypotheses that the virus had been important solely from SE Asia or that there existed a single index case. This work contributed to UK government policy discussions relating to border control and viral sequencing from people arriving in the UK from overseas [E].

COG-UK data was also critical for modelling dispersal of the new VOI 202012/01 variant, informing directly the government's New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) assessment of viral transmission [E] Similar work allowed assessment of the transmissibility of the D614G variant which subsequently became ubiquitous around the world [E]. Modelling methods developed by COG-UK for studying these variants remain instrumental for real-time assessment of the pandemic.

Impact on future genomic sequencing services for infection control: In recognition of the crucial role of COG-UK in the response to the COVID-19 pandemic, in November 2020 Peacock secured GBP12,200,000 of additional funds (Testing Innovation Fund) to increase sequencing capacity from 10,000 to 20,000 viral genomes per week by March 2021. She is also supporting the planning, training and handover of a new nationwide sequencing network which will be embedded in the NHS and public health agencies. This national network will sequence SARS-CoV-2 and other pathogens (e.g., TB) to detect and control future infection outbreaks, representing a lasting legacy of the COG-UK for the UK [F].

Impact on public awareness and understanding: Peacock has led numerous events using COG-UK data to educate that public (e.g. *Science Showcase*, an open access recording viewed 57,234 times by 18th December 2020 [G]). Peacock has also participated in Science Media Centre events, producing numerous articles on pathogen sequencing for leading news outlets including the BBC and The Guardian – a commenter on the latter noted: *'We can be really grateful that Britain has such expertise in genome sequencing. The article above provides real insight as to the purpose and benefits of the work of the Genomics UK consortium and others.'* [G].

Policy relating to control of other pathogens: In 2016, Peacock led chapter nine (Pathogen Genomics) of the Annual Report of the Chief Medical Officer on Genomics (Generation Genome) [H]. This chapter articulated the many benefits of sequencing of bacteria and viruses, and specifically its importance controlling epidemics and pandemics, citing case studies including Foot and Mouth and Ebola. This text continued to raise the profile of pathogen sequencing for disease control. A review written by Peacock was also included by a WHO Global Antimicrobial Resistance Surveillance System (GLASS) report as evidence for the use of WGS in the surveillance of antimicrobial resistance [I].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[A] **COG-UK and genomics networks:** (i) COG-UK website; (ii) UK Government Press Release announcing 'Genome UK' strategy, 26 September 2020; (iii) GENOME UK: The future of healthcare, 2020 (pp. 24-25).

[B] **Establishing routine sequencing services for infection control:** (i) Science Priorities for 100,000 Genomes Project (Appendix 3, pp. 15–24); (ii) Gov.UK press release 'England world leaders in the use of whole genome sequencing to diagnose TB', 28 March 2017 (iii) Public Health England: Tuberculosis in England Annual Report 2020 (pp. 46–53); (iv) Antiviral unit (AVU): reference services, Public Health England.

[C] **COVID-19 and SARS-CoV-2 sequencing:** (i) COG-UK Open Access data and protocols, p.7; (ii) GISAID and MRC-CLIMB data; (iii) Summary report: COG-UK geographic coverage of SARS-CoV-2 sample sequencing, Table 1 (iv) Testimonial from UK Chief Scientific Officer, November 2020.

[D] **Infection control during the COVID-19 pandemic:** (i) Transmission of SARS-CoV-2 Lineage B.1.1.7 in England: Insights from linking epidemiological and genetic data; (ii) UK Government Speech Prime Minister's statement on coronavirus (COVID-19): 19 December 2020 (pp. 52–3); (iii) BBC News, 'Coronavirus: EU urges countries to lift UK travel bans' 22 December 2020 (iv) UK Government News Story: Confirmed cases of COVID-19 variants identified in UK (p. 58).

[E] **Tracking of SARS-CoV-2 variants**: (i) du Plessis L, … **the COVID-19 Genomics UK (COG-UK) Consortium**... Pybus OG. Genetic lineage dynamics of the SARS-CoV-2 epidemic in the UK /Establishment & dynamics of SARS-CoV-2 outbreak lineages in the UK. Science 2021; eabf2946 DOI: 10.1126/science.abf2946. (ii) da Silva Filipe A, … **COVID-19 Genomics UK (COG-UK) Consortium**, Holden MTG, Robertson DL, Templeton K, Thomson EC. Genomic epidemiology reveals multiple introductions of SARS-CoV-2 from mainland Europe into Scotland. Nature Microbiology 2021; Jan;6(1):112-122 doi: 10.1038/s41564-020-00838-z (iii) House of Commons Home Affairs Committee: 'Home Office preparedness for COVID-19 (coronavirus): management of the borders', 30 July 2020, pp.24-26 (iv) Minutes of NERVTAG meeting on SARS-CoV-2 variant under investigation VUI-202012/01, 18 December 2020 (v) Volz E…**COG-UK inc. Goodfellow I (Peacock SJ)**…Connor T. Evaluating the Effects of SARS-CoV-2 Spike Mutation D614G on Transmissibility and Pathogenicity. *Cell*. 2021 Jan 7;184(1):64-75.e11. doi: 10.1016/j.cell.2020.11.020. Epub 2020 Nov 19

[F] Gov.uk Press release: '£12.2 million boost for genomic surveillance to help stop transmission of COVID-19' 16 November 2020

[G] **Public communication:** (i) First Science Showcase, COG UK website, 18th December 2020(ii) Here's what we know about the new variant of coronavirus, The Guardian, 22nd December 2020

[H] Annual Report of the Chief Medical Officer 2016: Generation Genome

[I] World Health Organization. (2020). GLASS whole-genome sequencing for surveillance of antimicrobial resistance. World Health Organization.