Institution: University of Cambridge		
Unit of Assessment: UOA1		
Title of case study: Rapid 'in the field' diagnostics and genomics at the heart of a viral epidemic: containing the 2013-2016 Ebola crisis.		
Period when the underpinning research was undertaken: May 2013- Jan 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:**
Professor Ian Goodfellow	Professor of Virology and Deputy Head of the Department of Pathology	2012 – present
Dr Luke Meredith	Postdoctoral research associate	2015 – July 2020
Period when the claimed impact occurred: Nov 2014 – present		
Is this case study continued from a case study submitted in 2014? N		

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

The 2013-2016 Ebola epidemic presented a global health crisis in which >28,500 cases were recorded, >11,000 patients died, and countries in West Africa and beyond united to contain the disease. This response was impaired initially by slow diagnostics and a lack of necessary laboratory infrastructure, allowing the epidemic to spread. Goodfellow led an international team that established an 'in field' lab for rapid Ebola diagnosis and the first genetic sequencing facility in Sierra Leone. This effort processed >25,000 samples in the field, reduced diagnosis time from 7 days to 4-6 hours and directly informed the WHO response strategy. As a direct result, the spread of Ebola was tracked and minimized allowing containment of disease sources, ultimately ending the epidemic. Goodfellow and colleagues continue to provide training on viral sequencing in affected regions, published protocols on rapid sequencing that have been disseminated worldwide, and have built capacity in Sierra Leone through a diagnostic laboratory that continues to provide employment to approximately 40 local staff, supporting local public health.

2. Underpinning research (indicative maximum 500 words)

Ebola is a negative-sense RNA virus and one of the deadliest pathogens known to man. It causes Ebola haemorrhagic fever which is fatal in 50% of cases. It can be transmitted between humans or from animals to humans. Goodfellow is an expert in the biology, transmission and genome analysis of RNA viruses. His research showed that genetic sequencing and phylogenetic analysis can be used to track the spread of norovirus between patients in hospital [1]. Consequently, he was invited by Public Health England and the World Health Organisation (WHO) to apply his research and expertise to enable large scale, real-time viral genomic sequencing to tackle the 2013-2016 Ebola virus epidemic in Africa.

Real-time phylogenetic tracing of Ebola: Working alongside collaborators from the Wellcome Sanger Institute in Cambridge and the Universities of Edinburgh and Birmingham, the Cambridge University team sequenced and analysed >1,200 Ebola virus positive patient samples, generating >600 complete genomes. This represented >1/3 of all the Ebola genomes produced during the epidemic. This data was used to track infection sources and clusters with the specific aim of containing and ending the epidemic. Real-time viral surveillance and phylogenetic analysis of viral genomes identified the sources of new disease clusters, enabling rapid epidemiological tracing and providing public health teams with key data to contain and end the epidemic [2]. Critically, these data also showed for the first time that Ebola virus can persist in the breastmilk of asymptomatic mothers and be transmitted to breastfed children [2].

Tracking patterns of disease spread: As a key member of the international response team, Goodfellow and his collaborators tested the association of geography, climate and demography with viral movement among administrative regions. This work inferred a classic 'gravity' model, with intense dispersal between larger and closer populations. In particular, this work showed that the Ebola virus tends to spread between locations that are less than 70 km apart. The larger the origin/destination population, the greater the viral spread. Importantly, this work revealed that once

the virus has dispersed internationally, border closures were not effective at reducing further spread [3].

Understanding the aftermath: Two months after the WHO declared the end of the epidemic in Sierra Leone, a new case of the disease emerged. This new diagnosis had enormous implications for the international response, potentially requiring the reestablishment of containment activities. However, sequencing work performed by the team led by Goodfellow, proved that this case involved a persisting 2014 strain, transmitted most likely via a chronically infected individual rather than a resurgence of the strain responsible for recent epidemic [4]. Goodfellow and his team were also responsible for sequencing samples from a new cluster that emerged 2.5 months after the Ebola epidemic was declared over in Guinea. Similarly, this work also enabled verification that the source of transmission was *via* an asymptomatic individual with persistent infection. His seminal fluid was still infectious 470 days post infection. This work showed for the first time that Ebola can persist four times longer than initially thought and that virus evolution rates are slow during persistence [5].

Understanding treatment: TKM-130803 was developed as a potential treatment of Ebola. Goodfellow was part of the clinical trials team that tested the efficacy of the drug in 14 adults with severe Ebola virus disease. Goodfellow and his team, including Meredith, were responsible for the viral load analysis, viral sequencing and the subsequent pharmacokinetic analysis of the TKM-130 in patient samples. The drug proved ineffective, demonstrating the need for further novel therapy development [6, 7].

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] *Scott JT…**Goodfellow I**, Horby P, RAPIDE-TKM trial team. Next-generation whole genome sequencing identifies the direction of norovirus transmission in linked patients (2013) *Clin. Infect. Dis.* 57(3):407–14

[2] *Arias A…**Meredith,L**… Kellam P† **Goodfellow I**†, Cotten M† Rapid outbreak sequencing of Ebola virus in Sierra Leone identifies transmission chains linked to sporadic cases (2016) *Virus Evol*. 22;2(1):1–10. (†- corresponding authors)

[3] *Dudas G…**Meredith, L**… **Goodfellow I,**...et al Lemey P, Rambaut A. Virus genomes reveal factors that spread and sustained the Ebola epidemic. (2017) *Nature*. 0;544(7650):309–15,

[4] *Alpren C… Interagency Investigation Team [includes **Goodfellow,I**].Notes from The Field: Ebola Virus Disease Cluster - Northern Sierra Leone, January 2016. (2016) *MMWR Morb Mortal Wkly Rep*. 65(26):681–2

[5] *Diallo B…**Goodfellow I, Meredith LW**… Duraffour S. Resurgence of Ebola Virus Disease in Guinea Linked to a Survivor With Virus Persistence in Seminal Fluid for More Than 500 Days. (2016) *Clin. Infect. Dis.* 15;63(10):1353–6, 2016.

[6] *Dunning J…**Goodfellow I**…Horby PW; RAPIDE-TKM trial team.. Experimental Treatment of Ebola Virus Disease with TKM-130803: A Single-Arm Phase 2 Clinical Trial. Seidlein von L, (2016) *PLoS Med*. 13(4):e1001997

[7] *Scott JT…**Meredith, L**…**Goodfellow I,** Horby P; RAPIDE-TKM trial team (2020). Pharmacokinetics of TKM-130803 in Sierra Leonean patients with Ebola virus disease: plasma concentrations exceed target levels, with drug accumulation in the most severe patients. *EBioMedicine*, Feb;52:102601.

Competitive funding received:
Wellcome Trust Enhancement Award (March 2015-Feb 2017), 'Characterization of Ebola Virus diversity during the EVD outbreak in Sierra Leone'; GBP396,808 Ref: 097997/Z/11/A
Wellcome Trust Collaborative Award (October 2017-September 2022), 'Putting genomic surveillance at the heart of viral epidemic response' (ARTIC project),~GBP3,000,000 (~GBP482,639 to University of Cambridge) Ref: 206298/B/17/Z
Wellcome Trust Provision for Public Engagement (April 2018-March 2021) 'Infectious science engagement activities in post- Ebola Sierra Leone', GBP144,350 Ref: 207498/Z/17/A.

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

Ebola is spread by direct human-human or animal-human contact and on average kills more than 50% of patients who contract the disease. During the 2013-2016 Ebola outbreak in Guinea, Liberia and Sierra Leone, >28,500 cases were recorded and >11,000 patients died. The WHO declared the outbreak a 'Public Health Emergency of International Concern', reserved only for events with a risk of international spread or that require an international response. In November 2014, Goodfellow led an international team that set up one of the first rapid diagnostic laboratories for Ebola treatment and holding centres in Sierra Leone.

Impact on the health and wellbeing of people

Accurate, rapid diagnosis of Ebola: Makeni, in northern Sierra Leone, was a hotspot for new Ebola cases. However, at the start of the epidemic the lack of rapid diagnosis and laboratory infrastructure allowed the disease to spread at an unprecedented rate. During this time, Ebola infected patients and suspected cases were quarantined together with increased opportunity for transmission. By establishing the first Ebola diagnostic laboratory in Northern Sierra Leone, Goodfellow reduced the 'in the field' diagnosis time from up to seven days down to 4 - 6 hours for patients at the treatment centre and ~24 hours for samples received from surrounding districts [A]. During its operation, the mobile diagnostic laboratory processed more than 25,000 patient samples [A,B], diagnosing more than 20,000 patients [A]. Their work provided the scientific basis for the WHO coordinated quarantine and treatment response for the 325 patients who tested positive for Ebola at the Makeni treatment centre [B]. Critically, the rapidity of the diagnosis also allowed non-infected patients, who would ordinarily be co-quarantined and potentially infected by diseased patients – to be discharged, directly reducing mortality and Ebola transmission rates. 40 individuals survived their infections. In addition, this process detected cases of unrelated but treatable infectious diseases, including over 750 patients with malaria who were provided with appropriate therapy [A].

Improving public understanding of infectious diseases: During the Ebola outbreak, rumors often hampered control efforts, prompting Goodfellow to establish a public engagement programme in 2016 to increase understanding of infectious diseases and how to protect oneself. The programme employs three people and has engaged >4,000 students at >50 schools across Sierra Leone. By simulating real-time outbreaks students are prompted to identify the pathogen and the chain of transmission by comparing genetic sequences to reference ones, highlighting the need for expediency in implementing control measures. During the Covid-19 pandemic the team have continued to engage local students with information on the pandemic and how to protect themselves and their families. The programme has also benefitted those employed by it: one member of the engagement team subsequently obtained a fully funded scholarship to undertake a degree programme in Japan, and another completed a degree in Public Health [C].

Impact on practitioners and the delivery of professional services

Impact on disease control policy: Little is known about how Ebola emerges, evolves and spreads, severely hampering the efforts of medical and public health staff to manage epidemics. By establishing the first 'in the field' genetic sequencing facility in Sierra Leone – Ebola Outbreak Sequencing Service (EOSS) – Goodfellow and collaborators at the University of Edinburgh provided the WHO with reports on clusters of infection, unmasking sources of 'cryptic' Ebola cases [A]. This was the first time WHO had supported the deployment of genomic sequencing during an Ebola outbreak and at the time, this laboratory was the only in-country sequencing capacity available. Their results directly informed the local government, Centres for Disease Control and WHO quarantine, road block and surveillance policies. For example, following development of Ebola in a 13-month old baby who had been quarantined for the standard 21 days, the WHO were considering increasing the quarantine period across the region, fearful that this case reflected an increase in the Ebola incubation period [A]. This would have had major workforce, resource and containment implications for the response effort. However, sequencing at the EOSS established that the Ebola transmission route in this case was via breastmilk in an otherwise clinically healthy mother [2]. Reassured by these results, the WHO maintained the existing 21-day quarantine period [A], and this research informed WHO guidelines for breastfeeding women in the context of

Ebola virus disease [D]. A Technical Officer from the WHO Health Emergencies Programme stated: *"Professor Goodfellow arrived in Sierra Leone in 2014, and his research expertise was invaluable in establishing and running the Ebola diagnostic laboratory in Makeni. The diagnostic laboratory served the 100 bed Ebola treatment centre (ETC) in Makeni at which it was based, as well as the surrounding district. During its operation, the laboratory processed more than 25,000 patient samples…The mobile laboratory established by Professor Goodfellow led to the diagnosis of >20,000 patients. Their work had a significant impact on improving the laboratory response by decreasing the diagnosis time of patients…The Ebola Outbreak Sequencing Service (EOSS), established by Professor Goodfellow in 2015 provided further crucial data to the WHO, allowing us to identify sources of sporadic cases of Ebola during the tail-end of the epidemic. This was the first time WHO had supported the deployment of genomic sequencing during an Ebola outbreak and at the time, this laboratory was the only in-country sequencing capacity available….The UniMak Infectious Disease Research Laboratory (IDRL) established by Professor Goodfellow at the University of Makeni and the training they have given staff, has also provided much needed local expertise, allowing Sierra Leone to react quickly in response to any new, sporadic Ebola cases…Professor Goodfellow's contribution formed a crucial role in helping to bring the epidemic in Sierra Leone to a close and his ongoing work at the UniMak IDRL has allowed us to maintain effective local disease surveillance since."* [A].

Preparedness for future epidemics: It is highly likely that future epidemics of Ebola will occur. Therefore, to enhance epidemic preparedness in the wider region, in 2017 Goodfellow joined with collaborators from the University of Edinburgh, Birmingham and Oxford, KU Leuven, UCLA and the Fred Hutchinson Cancer Centre to form the Wellcome Trust funded ARTIC Network, aiming to develop real-time genomic surveillance in field settings. This collaboration has led to the delivery of training workshops and sequencing protocols that have had a profound impact on public health. For example, in December 2018 Goodfellow acted as a tutor on a five-day workshop attended by 21 researchers and staff from public health laboratories in 13 countries, including Botswana, Kenya, Ghana, Nigeria, Tanzania and Zimbabwe. Separately, in December 2019, Goodfellow visited the national laboratory in the Democratic Republic of the Congo (*Institut National pour la Recherche Biomédicale*, INRB) to provide training on virus genome sequencing as part of the ongoing efforts to control the Ebola epidemic [E]. The team trained by Goodfellow and colleagues from the University of Birmingham have since deployed their lab to North Kivu, where it is now providing real-time sequencing support to the DRC outbreak [E]. Goodfellow and colleagues continue to provide support remotely as the work is being undertaken by scientists from INRB. The open source 'blueprints' the ARTIC team developed to enable the setting up of diagnostic sequencing services in resource limited settings have since been used by researchers in Glasgow to respond to outbreaks of Rabies virus in Kenya, Tanzania and the Philippines [F]. This experience resulted in the rapid provision of an optimised protocol for sequencing the pandemic SARS-CoV-2 virus, used by labs in Hangzhou CDC in China, and subsequently by labs across 4 continents [F].

Impact on commerce and the economy

During the 2013-2016 epidemic, Goodfellow also worked with the University of Makeni to establish a permanent Infectious Disease Research Laboratory (UniMak-IDRL) within Sierra Leone; thereby training local staff to provide diagnostics and state-of-the-art research methods. The UniMak-IDRL was already serving as the host lab for the EOSS by the end of the 2013-2016 epidemic and has since played a key role in researching, diagnosing and monitoring Ebola for the world. Since opening in September 2014, the UniMak-IDRL has [C]:

- Provided employment to approximately 40 local staff as a direct result of lab activities.
- Received external funding of >USD3,000,000 from multiple international donors.
- Coordinated regional training biosafety and epidemic preparedness training courses for the WHO and US Centre for Disease Control.
- Expanded the UniMak School of Public Health from 12 students/year in 2014 to 72 students/year in 2019. 280 students are currently enrolled. The best students train in the UniMak-IDRL with a view to supporting and growing local public health expertise. Graduates have gone on to successful careers as laboratory technicians and managers, and nursing managers.

The outcomes of these capacity building activities at the IDRL have resulted in:

- On 14th January 2016, following a 42-day period where no new cases were identified, the WHO declared the Ebola epidemic in Sierra Leone over. The same day, a postmortem sample tested positive, raising concerns around the possible origin, whether this was a new imported case or a part of an unmonitored chain of transmission which would necessitate the immediate re-escalation of control measures, taking up valuable resources. The national IDRL lab staff were able to sequence the virus within 48 hours and determine that it was most likely linked to the persistence of Ebola virus in the individual's sexual partner [A,C].
- The laboratory played a key role in the characterisation of an outbreak for African Swine Fever virus (ASFV) in November 2019, allowing for earlier introduction of prevention and control measures [G].
- The facilitation of ongoing clinical trials in the treatment and prevention of Ebola: the EboVac vaccination trial and the TKM Ebola therapeutic trial which started during the epidemic [6, 7] and [C,G].

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

[A] Testimonial from Technical Officer, WHO.
[B] Logue CH *et al.* 2017 Case study: design and implementation of training for scientists deploying to Ebola diagnostic field laboratories in Sierra Leone: October 2014 to February 2016. Phil. Trans. R. Soc. B 372: 20160299, page 8
[C] Testimonial from VC of UniMak on the impact of the lab on the local community and public engagement programme.
[D] Guidelines for the management of pregnant and breastfeeding women in the context of Ebola virus disease. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO., cites [2] pages 16-18.
[E] ARTIC Network Training: (i) ARTIC Network Real-time virus genome sequencing training workshop report (ii) Tweets showing training at *Institut National pour la Recherche Biomédicale*, December 2019 (iii) WHO, Ebola virus disease – Democratic Republic of the Congo, Disease outbreak news: Update, 30 April 2020
[F] ARTIC Network Blueprints to support setting up diagnostic sequencing services in resource limited settings (i) Brunker K, Jaswant G, Thumbi SM *et al.* Rapid in-country sequencing of whole virus genomes to inform rabies elimination programmes [version 2; peer review: 3 approved] Wellcome Open Res 2020, 5:3;. (ii) Oxford Nanopore Technologies, 'ARTIC Network provides protocol for rapid, accurate sequencing of novel coronavirus (nCoV-2019): first genomes released' 10th February 2020
[G] UNIMAK Infectious Disease Research Laboratory (i) *Food and Agriculture Organization of the United Nations* Sierra Leone confirms African Swine Fever outbreak, 13th December 2019; (ii) Update on IDRL 17th December 2016, Unimak.edu website