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| Institution: The University of Edinburgh | | |
| Unit of Assessment: UoA 5 Biological Sciences | | |
| Title of case study: Real-time genetic epidemiology and the Bayesian Evolutionary Analysis Sampling Trees (BEAST) phylogenetics software inform public health responses to minimise damage from Ebola and SARS-CoV-2 outbreaks | | |
| Period when the underpinning research was undertaken: 2007 - 2020 | | |
| Details of staff conducting the underpinning research from the submitting unit: | | |
| Name(s): Prof Andrew Rambaut | Role(s) (e.g. job title): Professor of Molecular Evolution | Period(s) employed by submitting HEI: 2006 – present |
| Period when the claimed impact occurred: 1 st August 2013 – 31st Dec 2020 | | |
| Is this case study continued from a case study submitted in 2014? Y/N NO | | |
| <p>1. Summary of the impact</p> <p>Attribution: Research into viral evolution during epidemics by University of Edinburgh scientist Andrew Rambaut has guided the response to the Ebola Zaire outbreak in Western Africa and the global SARS-CoV-2 (Covid-19) pandemic.</p> <p>Impact on public policy, health and welfare: Rambaut's research into real-time genomic epidemiology, in partnership with his development of improved BEAST software and his involvement in international efforts on viral sequencing have had major impacts on public health policy and service provision.</p> <p>Beneficiaries: Public agencies such as health bodies World Health Organisation, Centre for Disease Control, Science Advisory Group for Emergencies and governments (UK, Guinea, New Zealand) have relied on Rambaut's software and expertise in genomic epidemiology to develop responses to viral outbreaks. Ultimately, the most significant beneficiaries are the national and global populations subject to infectious disease outbreaks in which BEAST and Rambaut's expertise are used to inform the response.</p> <p>Significance and Reach: The BEAST software and Rambaut's research into real time genetic epidemiology have been used to understand the spread of, and to inform the policy and health service response to viral outbreaks worldwide. They are used to determine disease origin and transmission issues in specific situations, and the information is used to inform policy decisions that impact the health of millions.</p> | | |
| <p>2. Underpinning research</p> <p>Rambaut's interest in phylogenetics of viruses started during his Wellcome-funded PhD, via one of the earliest grants on using virus pathogens genomes to reconstruct epidemiology. During the PhD, Rambaut created software for analyzing virus sequences that have been sampled over time on very short time spans. This marked a paradigm shift from phylogenetic analysis on timescales for animal evolution over billions of years to reconstructing the processes that create phylogenetic trees from virus samples over the timescale of an epidemic. Following on from the success of the concept and initial software development, the kernel of BEAST was released in 2003 and has been continually updated ever since. BEAST is software for Bayesian analysis of molecular sequences related by an evolutionary tree. It analyses gene sequence data from viruses to investigate their evolutionary and</p> | | |

epidemiological dynamics. Information about the timing and spatial location of epidemics can be traced and the rate of epidemiological spread can be measured from a relatively small sample of isolates from the population of infected individuals [3.1]. BEAST was used in the 2014 Ebola outbreak in West Africa to determine the pathways of viral spread through communities [3.2].

Specifically, Rambaut's research showed how virus spread from Freetown to multiple districts throughout Sierra Leone and how virus traffic from Freetown established new transmission clusters late in the epidemic [3.3]. It revealed co-circulation of multiple lineages within individual localities as well as cross-border virus traffic between Guinea and Sierra Leone highlighting important gaps in intervention [3.4]. Finally, it revealed that virus can persist in seminal fluid for at least 500 days and remain infectious during the long term persistence [3.5], all of which had significant impact on management of the outbreak.

BEAST, and Rambaut's research into rapid viral evolution have been used (by the Rambaut group and others) extensively throughout the SARS-CoV-2 pandemic to establish epidemiological models. Rambaut established that there were several SARS-CoV-2 lineages and developed a terminology system to support dissemination [3.6].

3. References to the research

[3.1] Bayesian Phylogenetics with BEAUti and the BEAST 1.7. Alexei J. Drummond, Marc A. Suchard, Dong Xie, Andrew Rambaut. *Molecular Biology and Evolution*, Volume 29, Issue 8, 1 August 2012, Pages 1969–1973, <https://doi.org/10.1093/molbev/mss075>

[3.2] Marc A Suchard, Philippe Lemey, Guy Baele, Daniel L Ayres, Alexei J Drummond, Andrew Rambaut. Bayesian phylogenetic and phylodynamic data integration using BEAST 1.10. *Virus Evolution*, Volume 4, Issue 1, 1 January 2018, <https://doi.org/10.1093/ve/vey016>

[3.3] Park, D.J., Dudas, G., Wohl, S., et al. Ebola Virus Epidemiology, Transmission, and Evolution during Seven Months in Sierra Leone (2015) *Cell*, 161 (7), pp. 1516-1526. DOI: <https://doi.org/10.1016/j.cell.2015.06.007>

[3.4] Carroll, M.W., Matthews, D.A., Hiscox, J.A. et al. Temporal and spatial analysis of the 2014-2015 Ebola virus outbreak in West Africa (2015) *Nature*, 524 (7563), pp. 97-101. DOI: <https://doi.org/10.1038/nature14594>

[3.5] Diallo, B., Sissoko, D., Loman, N.J., et al. Resurgence of Ebola Virus Disease in Guinea Linked to a Survivor with Virus Persistence in Seminal Fluid for More Than 500 Days (2016) *Clinical Infectious Diseases*, 63 (10), pp. 1353-1356. DOI: <https://doi.org/10.1093/cid/ciw601>

[3.6] Rambaut, A., Holmes, E.C., O'Toole, Á. et al. A dynamic nomenclature proposal for SARS-CoV-2 lineages to assist genomic epidemiology. *Nat Microbiol* (2020). <https://doi.org/10.1038/s41564-020-0770-5>

4. Details of the impact

Rambaut's work on viral evolution, evidenced by the development of his BEAST software, has guided public response to several viral outbreaks in the REF period. BEAST has been under continued development to ensure that its relevance increases, with improvements to user-friendliness within the review period.

Rambaut has guided the development of policy on sequence sharing globally with the goal of open sharing of viral sequence data, while ensuring appropriate accreditation and ownership of sequence intellectual property [5.1, 5.2]. This hinges on the ARTIC network [5.1, 5.3, and 5.4]: a large Wellcome Trust-funded project that links together diverse viral genome sequencing capabilities throughout the world. Serving as a repository of key protocols and services, ARTIC uses virus sequencing in combination with BEAST to respond to outbreaks in real time (<http://artic.network>). It is frequently used by WHO to provide sequencing capabilities in pandemic and epidemic situations [5.1]

Impact on Health Policy:

While Rambaut's work during the REF period was associated with the response to Influenza, Ebola, Zika and SARS-CoV-2, the majority of impact is associated with the Ebola Pandemic in Sierra Leone, Guinea and Liberia [5.1, 5.2], and COVID-19 [5.1].

The 2014 – 2016 Ebola outbreak in West Africa was of unprecedented magnitude. WHO declared a public health emergency in August 2014 and the epidemic that followed resulted in 28,616 documented cases and 11,310 deaths in 3 countries.

Prior to this outbreak, genomic studies of infectious disease outbreaks were retrospective: 2013 was the first time that genomic data was used in real time to inform policies and infection control in a public health setting [5.1, 5.2]. High throughput next-generation sequencing enabled rapid and in-depth viral genome surveillance during the outbreak. Ian Goodfellow, a collaborator of Rambaut set up a 'lab in a suitcase' (based around the Oxford Nanopore minION sequencer) in Guinea and Sierra Leone to sequence viruses in the field, providing the sequence data that Rambaut's lab then analysed for phylogenetic analysis with a turn-around time of 24-48 hours [5.1, 5.2]. Analyses of the molecular sequence data was performed by Rambaut and informed public health bodies (WHO, CDC) in West Africa at the time of the Ebola epidemic. The data revealed the pathways of viral spread through communities and was used to direct intervention methods to transmission hot spots and to determine the impact of specific interventions [5.1, 5.2].

The analyses using BEAST determined whether a new case of Ebola came from a new hidden transmission chain or a known transmission chain or from an individual infected months previously. The response by public health officials differed depending on this information e.g. contact tracing, running a vaccine trial. As a result of the published analyses [e.g. 3.5], there is now longer term follow up of Ebola survivors and they are counselled with this new information [5.1]. New guidelines from WHO were introduced in January 2016 [5.5].

The **coronavirus** pandemic has had an unprecedented worldwide impact on health and the economy, with 74,763,331 confirmed cases and 1,659,570 deaths as of 17th Dec, 2020. Mitigation strategies to reduce spread and track infections have been heavily reliant on viral genome sequencing. Internationally, much of the policy based around the WHO's response to the virus and the sharing policy adopted by the global community to provide genome sequences allowing tracking of the virus has been directly influenced by Rambaut's work [5.1].

Rambaut's research has had a direct impact on UK and worldwide policy in response to the coronavirus epidemic. Rambaut is a member of the SAGE committee and has been providing evidence to SAGE regarding the transmission rate and consequences of importing the virus into the UK [5.6]. His work was specifically referenced in terms of the UK's policy for border control in response to coronavirus, as described in the Hansard report for the parliament's response to the pandemic [5.7], which describes the development of the international travel restrictions and their impact on national spread of the virus. Rambaut's models of genetic

phylogeny were used in the Imperial College Model for the spread of coronavirus in the UK [5.8].

Internationally, Rambaut's group was the first to demonstrate the rapid spread and evolution of the virus in China, showing that it had been circulating for a shorter time than previously estimated. His work contributed to discrediting the 'lab-origin' theory for coronavirus [5.6]. His work has had substantial international impact: Rambaut's research is specifically mentioned in SitRep 3 from the WHO's Novel Coronavirus (2019-nCoV) task force [5.9]. His work feeds directly into the epidemiology modelling group at the WHO. His research is specifically referenced in three European Centre for Disease Prevention and Control's reports: "Outbreak of acute respiratory syndrome associated with a novel coronavirus, China: first local transmission in the EU/EEA", updates 1-3. His research recommending the classification of coronavirus into distinct phylogenetic lineages [3.6] has been used by ESR in New Zealand to help develop responses to the virus [5.10]. Finally, his leadership of the ARTIC network [5.3, 5.1] resulted in development of internationally accepted protocols for the sequencing of SARS-CoV-2 RNA [5.1].

5. Sources to corroborate the impact

[5.1] Testimonial: Infectious Hazard Management Department, World Health Organization, Geneva, Switzerland

[5.2] Wellcome-DfID report – Data Sharing in Public Health Emergencies: Anthropological and historical perspectives on data sharing during the 2014-2016 Ebola epidemic and the 2016 Yellow fever epidemic – See Page 84 for paragraph on Rambaut's involvement with WHO during Ebola outbreak. <https://www.glopid-r.org/wp-content/uploads/2019/07/data-sharing-in-public-health-emergencies-yellow-fever-and-ebola.pdf>

[5.3] Testimonial: Deputy Director, Head of Research and Development, National Infection Service, Public Health England

[5.4] Artic Network Summary: <https://artic.network/1-about.html>

[5.5] WHO interim advice on the sexual transmission of the Ebola virus disease. 21 January 2016 <https://www.who.int/reproductivehealth/topics/rtis/ebola-virus-semen/en/>

[5.6] SAGE group membership - <https://www.theguardian.com/world/2020/apr/24/coronavirus-whos-who-on-secret-scientific-group-advising-uk-government-sage> (The Guardian, print readership: 1,027,000; circulation 187,000 (April 2020)).

[5.7] Hansard report (Transcript from Hansard) – "Government Decisions on the Border Up To and During Lockdown" refers specifically to Rambaut as source of Figure 3; published 5th August 2020 <https://publications.parliament.uk/pa/cm5801/cmselect/cmhaff/563/56305.htm>

[5.8] Report from Imperial College London COVID-19 Response Team, specifically mentions the BEAST 2.6 software (Page 5), of which Rambaut was a co-author.
<https://doi.org/10.25561/77169>;

[5.9] World Health Organisation Situation Report: WHO Covid-19 SitRep 3, Page 6, Section IV. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200123-sitrep-3-2019-ncov.pdf?sfvrsn=d6d23643_8

[5.10] Tweet from Joep de Ligt ESR, Crown Research Institute, New Zealand,
<https://twitter.com/Joepdl/status/1296310423017254912>