Institution: University of Aberdeen		
Unit of Assessment: 10 (Mathematical Sciences)		
Title of case study: Application of mathematical models for public health protection against infectious diseases		
Period when the underpinning research was undertaken: 2008-2020		
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:**
Francisco Perez-Reche	Senior Lecturer in Physics	2013-present
Norval Strachan	Professor in Physics	1998-present
Ken Forbes	Professor in Medical Sciences	1989-2019
Period when the claimed impact occurred: 2016-2020		
Is this case study continued from a case study submitted in 2014? N		

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

The Institute of Pure and Applied Mathematics (IPAM), with the Department of Physics and School of Medicine, Medical Sciences and Nutrition developed and applied mathematical models to tackle infectious diseases in the UK and EU. Specifically:

- Our machine learning research underpinned action on human campylobacteriosis and informed professional debate on the source of human listeriosis in the UK and EU.
- We used compartmental models to determine progress of the COVID19 epidemic, understand role of asymptomatic cases in local outbreaks and predict outbreaks in higher education institutions. This informed the actions of public health teams.

Our research and advice contributed to food safety standards and embedding of risk assessment practice in the UK and EU.

2. Underpinning research (indicative maximum 500 words)

The Aberdeen team, led by Dr Perez-Reche (Maths - expertise in machine learning and compartmental models), Prof Strachan (Physics - expertise in Monte Carlo techniques and quantitative risk assessment) and Prof Forbes (Medical Sciences – molecular epidemiology) have collaborated to develop and apply mathematical methods to describe the transmission and risk of infectious diseases (group website: https://bit.ly/2P9Iaho).

2.1 Machine learning methods

Campylobacter is the most common cause of bacterial food poisoning in the world, with the European Centre for Disease Control reporting 250,161 cases in 2017. However, there is an estimated 9-fold under-reporting rate, resulting in 500,000 cases per annum in the UK alone. Using a source attribution model, based on machine learning methods for classification, the team identified shop-bought chicken meat as the main source of human campylobacteriosis [3]. This research has continued during the current REF period focussing on the Grampian region of Scotland, now incorporating whole genome sequencing using our state of art machine learning approach [5]. It was found that there was commonality of strains from chickens and human cases providing robust evidence that humans are contracting campylobacteriosis from retail chickens [P1].

Listeria causes around 2,500 infections and 250 deaths per year in the EU. In 2014, the Aberdeen team, based on its *Campylobacter* expertise, together with Statens Serum Institute (SSI), French Agency for Food Safety (ANSES) and Public Health England (PHE), were commissioned by the

European Food Safety Authority (EFSA) [P2, S4, S5] to assess the value of utilising whole-genome sequencing (WGS) in determining the source of human listeriosis. Aberdeen's open source machine learning method [5] was utilised to analyse the massive datasets involved. The method, which relies on the Hamming distance between genomes to estimate the probability that a pathogen originates from a certain source, outperformed previous methods in terms of computational time for both *Listeria* and *Campylobacter*. Indeed, analyses take seconds rather than days [5]. The Aberdeen team identified that the main source of listeriosis was food of bovine origin but there were also contributions from other food animals, including fish [S4, S5].

2.2 Compartmental models

In April 2020, novel compartmental models were developed that incorporated both reported and unreported infectious individuals in the COVID-19 outbreak [4]. These models were used to analyse strategies to suppress the virus in exemplar countries. The research [4] provided evidence to confirm that: (i) more than 50% of infectious individuals were not tested for infection at the early stages of the epidemic, (ii) reducing the underlying transmission of untested cases was crucial to suppress the virus, and (iii) establishing herd immunity was not feasible during the early months of the epidemic.

In September 2020, the team used data on the incidence of COVID19 from across the world, together with student and staff numbers at UK HEIs in a stochastic mathematical model to predict that 81% of the UK HEIs had more than a 50% chance of having at least one COVID-19 case arriving on campus at the beginning of the academic year [6]. Predictions for the number of cases expected at each campus were also provided. Based on these estimates, it was suggested that universities had to plan for COVID-19 cases to arrive on campus and facilitate mitigations to reduce the spread of disease particularly during the first two weeks of term.

Furthermore, vaccination, as an anthropogenic mechanism for achieving herd immunity, was studied by extending the explosive percolation paradigm to develop “explosive immunisation”: a new method to inform targeted immunisation that enables the burden of epidemics to be minimised by vaccinating as few people as possible [2, P4]. The method assigns a score to each individual to quantify their contribution to the chance of a large epidemic if they are not immunised. Explosive immunisation targets individuals with a high score, who are called ‘superblockers’. These are typically well-connected individuals who move between different communities and whose immunisation abruptly decreases the possibility of an epidemic. It is because of this sudden decrease of the probability for an epidemic that the method was called explosive immunisation.

2.3 Monte Carlo modelling for food safety risk assessment and spread of infectious disease

The Aberdeen team have applied Quantitative risk assessment (QRA) to food safety challenges since 2008. QRA is a mathematical methodology employing Monte Carlo simulation that estimates the risk of disease following consumption of contaminated food. In collaboration with the Dutch National Institute for Public Health (RIVM), they developed dose-response models, a key component of QRA, for *E. coli* O157 under Bayesian frameworks utilising human outbreak data [1, P3]. The team discovered that there is considerable heterogeneity across the virulence of *E. coli* O157 strains but that ingestion of 100-200 bacteria is sufficient for 50% of infected people to fall ill, posing a considerable health risk to consumers. Funded by the research councils [P5], the Aberdeen team used these models in QRAs of *E. coli* O157 from beef-burgers [P6], private water supplies and direct contact with infected animals.

3. References to the research (indicative maximum of six references)

References

[1] PFM Teunis, ID Ogden, **NJC Strachan.** (2008). Hierarchical dose response of E. coli O157:H7 from human outbreaks incorporating heterogeneity in exposure. *Epidemiology & Infection* 136(6), 761-770. doi: 10.1017/S0950268807008771

[2] P Clusella, P Grassberger, **FJ Perez-Reche**, et al. (2016). Immunization and Targeted Destruction of Networks using Explosive Percolation *Phys. Rev. Lett*. 117(20), 208301. doi: https://doi.org/10.1103/PhysRevLett.117.208301

[3] Sheppard SK, Dallas JF, **Strachan NJC**, Macrae M, McCarthy ND, Falush D, Ogden ID, Maiden, MCJ, **Forbes KJ**. (2009). Campylobacter Genotyping to Determine the Source of Human Infection. Clinical Infectious Diseases, 48:1072-1078. doi: https://doi.org/10.1086/597402

[4] **F Perez-Reche, KJ Forbes, NJC Strachan.** (2020). Importance of untested infectious individuals for the suppression of COVID-19 epidemics. *medRxiv* doi: https://doi.org/10.1101/2020.04.13.20064022

[5] **FJ Perez-Reche,** O Rotariu, BS Lopes**, KJ Forbes,** and **NJC Strachan.** (2020). Mining whole genome sequence data to efficiently attribute individuals to source populations. *Sci. Rep*. 10, 1214. doi: https://doi.org/10.1038/s41598-020-68740-6

[6] **FJ Perez-Reche, NJC Strachan.** (2020). Estimating the number of COVID-19 cases being introduced into UK Higher Education Institutions during Autumn 2020. *medRxiv* doi: https://doi.org/10.1101/2020.09.02.20186676

Evidence of the Quality of the Research

Papers 1-3; 5 were published in peer-reviewed journals of international standing (4 and 6 are currently under review in internationally recognised journals). This research is deemed to be of at least 2* and is underpinned by the following sources of peer-reviewed research funding.

Grants:

[P1] **Forbes, Strachan** Employing source attribution and molecular epidemiology to measure the impact of interventions on human campylobacteriosis in Scotland. Food Standards Scotland (2012-2017; GBP738,881.52).

[P2] **Strachan**, **Forbes** and **Perez-Reche**. Listeria whole genome sequencing. EFSA. (10/2014-06/2017; GBP53,900) (part of a EUR420,000 project with the Danish Statens Serum Institut (SSI), French Agency for Food, Environmental and Occupational Health and Safety (ANSES) and Public Health England (PHE)).

[P3] **Forbes** and **Strachan**. Next Generation Sequencing of *E. coli* O157 isolates from humans, food and the environment. FSAS & the University of Aberdeen*.* (2012-2013; GBP11,000).

[P4] **Perez-Reche**, et al. Complex percolation for epidemics on networks and applications of mutual information. Leverhulme Trust (2015-2016; GBP18,300).

[P5] K Killham, **N Strachan**, et al. Reducing *E. coli* O157 risk in rural communities. ESRC (2007-2010;GBP697,095) FEC.

[P6] **Strachan**. Expert opinion on preparation of rare beef burgers. Aberdeen City Council. (2016; GBP2323).

[P7] **Strachan**. Providing lectures for a risk assessment course. EU BTSF (2015-2018; EUR6000).

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

4.1 Impact of Machine Learning Research

4.1.1 Research underpinned action on Campylobacter in the UK and EU

The source attribution research on campylobacteriosis [3, 5] underpinned a joint campaign by UK food authorities and industry, which resulted in the successful reduction of Campylobacter levels in retail chicken. This is evidenced by the reduced prevalence of birds with >1000 cfu/g from 18.4% to 5.8% between 2014- 2019 and hence improved food safety for consumers across the UK (FSA *Campylobacter* Data Gathering Survey, 2019) [S1].

The Aberdeen team (Strachan) provided the European Food Safety Authority (EFSA) with evidence (as a member of the Working Group on Campylobacter in broiler meat – source attribution) of the extent to which meat derived from retail chickens contributes to human campylobacteriosis [S2, included for context]. EFSA, as a result of this and in combination with its risk assessment work, issued advice on reduction of *Campylobacter* in retail meat production in 2011 [S3, included for context]. On 23rd August 2017 the EU commission regulation (EU) 2017/1495 [S4] was published which stipulated the levels at which *Campylobacter* may be present in chicken carcases. Para 5 of this document quotes the EFSA opinion [S2, included for context] which as mentioned above is underpinned by the Aberdeen studies. This regulation came into force across the EU in January 2018. Hence, the Aberdeen studies have been central to the provision of underpinning evidence for food safety regulation across the 27 member states of the European Union.

4.1.2 Informed professional debate on the source of human Listeriosis in the EU

The team's work on *Listeria* source attribution for EFSA raised awareness of potential shortcomings in standard risk assessment methodology that pointed to fish products as the main source of listeriosis in the EU [S6]. Our work [S5] found products of bovine origin as the main source of human listeriosis leading to acknowledgement by EFSA that further work needs to be undertaken using a broader dataset, in order to ascertain additional sources of contamination. Based on this contribution, a team member was invited to present the *Listeria* work to the USDA – Food Safety Inspection Service in Washington, DC, as part of the debate on the potential role of WGS for health protection [S7].

4.2 Compartmental models have informed the actions of public health teams in responding to the COVID19 pandemic and the public's understanding of spread of the virus

In 2020, the Aberdeen team used their compartmental models for COVID-19 [4, 6] to provide advice to Public Health teams in Scotland in three ways (see testimonial [S8]).

(i) In April 2020, the Aberdeen team provided estimates for the time dependent reproduction number, *R*, for Scotland as a whole and at the level of individual Health Boards. At the time when these estimates were provided, in the early part of the pandemic, the Scottish Government were not in a position to provide the Public Health teams of the NHS Health Boards with estimates of this important epidemiological measure. The timely estimates from the Aberdeen team helped inform the Health Boards of the progress of the pandemic and underpin the response.

(ii) The prediction generated by the Aberdeen team of the percentage of asymptomatic infected people [4] underpinned the scientific basis for the findings of the Public Health team investigation into the outbreak of COVID-19 in a vessel that arrived into a Scottish harbour in April 2020.

(iii) The predictions of the Aberdeen team of outbreaks in UK higher education institutions [6] proved to be prescient and were made available to Public Health teams in Scotland, thereby raising the awareness of the need for response in educational settings to reduce transmission of this disease.

The team's research on COVID-19 [4, 6] and explosive immunisation [2] received considerable interest from the media and public, both nationally and internationally in different forms, including 1 TV and 3 radio interviews, over 30 newspaper and online articles and 5 public events, with attendees of 50-70 people per event. Overall, the media audience is estimated to be of the order of a million individuals (press coverage details: https://bit.ly/3qSrFUZ).

4.3 Research and advice contributed to food safety standards and embedding of risk assessment practice in the UK and EU

Prof Strachan was Chief Scientific Adviser to Food Standards Scotland (FSS) from 2016-2020. He led the development of a science strategy for the organisation in which risk assessment was embedded and presented it at an open meeting of the FSS board [S9i]. He provided advice on risk assessment to FSS on Shiga toxin producing *E. coli* (STEC) in unpasteurised cheese; contributed to a public information statement on STEC [S9ii] and gave a seminar to the FSS Board describing uncertainty and the application of the precautionary principle in the risk analysis process.

The Aberdeen team was commissioned by BTSF (the Better Training for Safer Food training initiative from the European Commission) to teach the dose-response modelling section of the

QRA course, based on their research, to staff from competent authorities (e.g., food authorities) across Europe. Four courses were taught (in Berlin (March, 2015), Prague (May, 2017), Lisbon (March, 2017) and Tallinn (May, 2015)) to approximately 20 attendees each [P7] [S10].

The Aberdeen team provided advice to Aberdeen City Council on the safety of the cooking of beef burgers in 2016 [S11i, ii] based on risk assessment research. The advice resulted in the prohibition of the sale of rare burgers in Scotland. In 2018, a member of the Aberdeen team acted as an expert witness in the court case of South Lanarkshire Council versus Errington Cheese Ltd [S11iii], providing key evidence based on Aberdeen's dose-response work on *E. coli* O157 for the judgement.

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

[S1] Food Standards Agency (2019) Campylobacter Data Gathering Survey https://bit.ly/3qTAQV4

[S2 (context)] EFSA Panel on Biological Hazards. Scientific Opinion on Quantification of the risk posed by broiler meat to human campylobacteriosis in the EU. EFSA Journal 2010: 8(1): 1437. https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2010.1437.

[S3 (context)] EFSA press article on advice on reduction in *Campylobacter* counts in chicken meat at www.efsa.europa.eu/en/press/news/110407 and actual advice at https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2011.2105.

[S4] Commission Regulation (EU) 2017/1495 of 23 August 2017 amending regulation (EC) No 2073/2005 as regards *Campylobacter* in broiler carcasses. Official Journal of the European Union L218/1, 24.8.2017. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R1495&from=EN.

[S5] EM Nielsen, ..., F Perez-Reche, K Forbes, N Strachan (2017). Closing gaps for performing a risk assessment on Listeria monocytogenes in ready-to-eat (RTE) foods: activity 3, the comparison of isolates from different EFSA Supporting Publications 14 (2), 1151E

[S6] EFSA Scientific Opinion (2017, 2018)
https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5134;
https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/sp.efsa.2017.EN-1151

[S7] USDA-Food Safety Inspection Services Presentation (2017); Presentation given in Washington, DC, to encourage the use of combining WGS and risk assessment. Agenda: https://bit.ly/37LI0mL; Presentation slides: https://bit.ly/3pRMf6C

[S8] Testimonial (email) from consultant in Public Health Medicine (NHS Fife) on the impact of University of Aberdeen advice on the response to the COVID-19 epidemic in Scotland (2020).

[S9 (group)] (i) FSS Science, Evidence and Information Strategy (2017): Board Meeting - _Papers - March -Science Evidence and Information 1.pdf (foodstandards.gov.scot); (ii) FSS Public Information Statement on STEC: https://bit.ly/3aT5yYO

[S10] Testimonial from Leader of the biological hazard board, Norwegian Scientific Committee for Food and Environment

[S11 (group)] (i) Expert report for the Aberdeen City Council (2016) www.aberdeencity.gov.uk/sites/default/files/EIR_16_0779_ScientificAssessment_Redacted.pdf; (ii) Testimonial from Aberdeen City Council (2020); (iii) Expert witness in the South Lanarkshire Council versus Errington Cheese Ltd case (2018) https://www.casemine.com/judgement/uk/5b45d0a82c94e029f7d70a15