

<b>Institution:</b> University of Cambridge		
<b>Unit of Assessment:</b> 10 Mathematics		
<b>Title of case study:</b> Controlling influenza using mathematics		
<b>Period when the underpinning research was undertaken:</b> August 2000 to 31 March 2020		
<b>Details of staff conducting the underpinning research from the submitting unit:</b>		
<b>Name(s):</b>	<b>Role(s) (e.g. job title):</b>	<b>Period(s) employed by submitting HEI:</b>
Julia Gog	Professor of Mathematical Biology, Faculty of Mathematics	2002-present
Bryan Grenfell	Professor of Population Biology, Department of Zoology	1990-2004
<b>Period when the claimed impact occurred:</b> 2015 to 31 March 2020		
<b>Is this case study continued from a case study submitted in 2014?</b> N		
<p><b>1. Summary of the impact</b> (indicative maximum 100 words)</p> <p>Key to controlling the spread of viral infections such as influenza, are global vaccination policies as well as models to predict how the virus will spread. Professors Julia Gog and Bryan Grenfell have used mathematics to derive impacts in both of these areas, offering:</p> <p>I1) an essential component of a mathematical model used by the World Health Organisation (WHO) to inform influenza vaccine selection, with associated global impacts on public health and the economy,</p> <p>I2) an increase in public engagement with science combined with an increased awareness in the UK of the dangers of an influenza pandemic and of potential strategies to limit spread,</p> <p>I3) a contribution to UK public policy on influenza pandemic preparedness.</p>		
<p><b>2. Underpinning research</b> (indicative maximum 500 words)</p> <p><b>Multi-strain models of seasonal influenza</b></p> <p>Seasonal influenza, a highly contagious acute viral infection, remains one of the world's greatest public health challenges. Gog began modelling the population dynamics of infectious disease where there are multiple strains with Professor Bryan Grenfell whilst at the Department of Zoology (University of Cambridge) and continued to further develop and interpret a model specific to influenza evolution after moving to the Faculty of Mathematics (University of Cambridge) in 2006. The model has the key property of including multiple strains whilst also being computationally and mathematically tractable [R1]. In [R2], key innovations were presented that made the model framework applicable for prediction for seasonal influenza in humans. Most importantly, [R2] developed the mathematical framework to combine two different forms of virus strain fitness: antigenic fitness (dependent on population immune states) and inherent transmission fitness (independent of population state). This model included more complex interplay between antigenic and genetic spaces for strains than anything presented previously. This work also included a number of other important strain modelling innovations: a new way to implement a discrete time strain model; a strain space that is extensible during a simulation; a tractable way to include temporary broad immunity that runs across all strains; and exploration of vaccination strategies. All of these are valuable for practical usage as a predictive model. In [R3], Gog considered how the model could be extended to deal with the emergence of</p>		

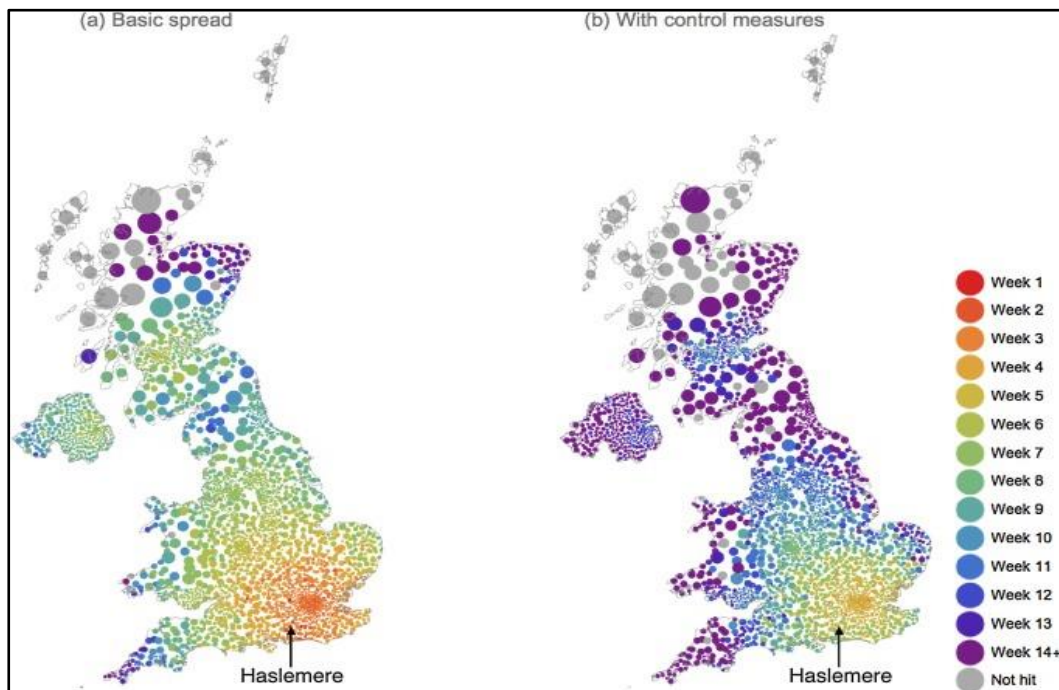
new disease strains, evaluating which elements of modelling frameworks permit flexibility yet maintain biological realism.

All the above properties of the multi-strain model of seasonal influenza mean that it is suitable to being incorporated into a larger framework that can be used to predict the evolution of influenza, in particular the strain of influenza that will be dominant in the next influenza season.

### Insights into pandemic spread dynamics

Predicting the spread of a rarer global outbreak of a deadly influenza virus (pandemic) is essential to informing control strategies and saving potentially millions of lives. As part of long-term collaborations with the US, namely Bryan Grenfell now in Princeton, Lone Simonsen at the George Washington University and Cecile Viboud at the National Institutes of Health, Gog modelled the 2009 H1N1 influenza pandemic in the US, using data from US medical insurance claims [R4, R5]. As well as giving insights into pandemic hubs and short *versus* long distance transmission events, this work highlighted the urgent need for more detailed information on the movement and mixing patterns of host populations.

In September 2017, a collaborative project with the BBC was launched to mark the hundredth anniversary of the 1918 influenza pandemic. The collaboration sought to generate such detailed data on movement that would be of general use to science and hence eventually policy, including pandemic planning in the UK. The result was a ground-breaking citizen science project that produced the biggest ever dataset on how people mix and travel in the UK. Using this national movement data and self-reported contact data from the BBC Pandemic App, Gog and team developed a mathematical model for the spread of influenza, and thereby simulated how a pandemic-like strain of influenza might spread through the United Kingdom [R6]. The town of Haslemere in Surrey was used as the epicentre for the virtual outbreak (Figure 1). They also generated fine-scale age-specific population contact matrices by context and type of contact that can be used to inform prevention and control measures [R7]. The experiment demonstrated among other things that with control measures in place (e.g. hand washing), the spread of influenza throughout the UK could be slowed down significantly.



**Figure 1** Map (a) left indicates the spread of influenza with no control measures in place, and map (b) right with control measures [R6].

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

[R1] Gog, J.R. and Grenfell, B.T. (2002). Dynamics and Selection of Many-Strain Pathogens, *Proceedings of the National Academy of Sciences, USA*, 99, 17209-17214, DOI: [10.1073/pnas.252512799](https://doi.org/10.1073/pnas.252512799)

- [R2] Gog, J.R. (2008). The impact of evolutionary constraints on influenza dynamics, *Vaccine*, 26S, C15-C24, DOI: [10.1016/j.vaccine.2008.04.008](https://doi.org/10.1016/j.vaccine.2008.04.008)
- [R3] Kucharski, A.J., Andreasen V., Gog J.R. (2016). Capturing the dynamics of pathogens with many strains, *J. Math. Biol.*, 72, 1-24, DOI: [10.1007/s00285-015-0873-4](https://doi.org/10.1007/s00285-015-0873-4)
- [R4] Gog, J.R., Ballesteros, S., Viboud, C., Simonsen, L., Bjornstad, O.N., Shaman, J., Chao, D.L., Khan, F. and Grenfell, B.T., (2014). Spatial transmission of 2009 pandemic influenza in the US. *PLoS Comput Biol*, 10(6), p.e1003635, DOI: [10.1371/journal.pcbi.1003635](https://doi.org/10.1371/journal.pcbi.1003635)
- [R5] Kissler S.M., Gog J.R., Viboud C., Charu V., Bjørnstad O.N., Simonsen L., Grenfell B.T. (2019). Geographic transmission hubs of the 2009 influenza pandemic in the United States, *Epidemics*, 26, 86-94, DOI: [10.1016/j.epidem.2018.10.002](https://doi.org/10.1016/j.epidem.2018.10.002)
- [R6] Klepac, P., Kissler, S., Gog, J.R. (2018). Contagion! The BBC Four Pandemic - The model behind the documentary, *Epidemics*, 24, 49-59, DOI: [10.1016/j.epidem.2018.03.003](https://doi.org/10.1016/j.epidem.2018.03.003)
- [R7] Klepac, P., Kucharski, A.J., Conlan, A.J.K., Kissler, S., Tang, M., Fry, H., Gog, J.R. (2020) Contacts in context: large-scale setting-specific social mixing matrices from the BBC Pandemic project, *medRxiv*, DOI: [10.1101/2020.02.16.20023754](https://doi.org/10.1101/2020.02.16.20023754)

Outputs published in peer-reviewed journals.

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

##### **1) An essential component of a mathematical model used by the WHO to inform influenza vaccine selection, with associated global impacts on public health and the economy.**

Vaccination is the principal measure for preventing influenza and reducing its negative impact. Since 1973, the WHO has provided the formal recommendations for the composition of influenza vaccines based on information provided by the WHO Global Influenza Surveillance and Response System (GISRS). Due to the evolution of influenza virus antigens, vaccine effectiveness depends critically on the accurate prediction of which variants will be dominant in the upcoming season.

Following extensive discussions between Gog and Professor Michael Lässig of the University of Cologne in 2011, Grenfell and Gog's multi-strain model [R1, R2, R3] was incorporated as the epidemiological and population dynamics component of a larger model for predicting the evolution of influenza. As Professor Lässig corroborates in [E1],

*"The systematic population dynamics of multiple strains, which is at the heart of Julia's model, proved to be the most informative fitness predictor of influenza strains... this multistrain model is a centerpiece of the mechanistic models that we are using to predict the evolution of influenza."*

These mechanistic models of Łuksza and Lässig, that include Grenfell and Gog's population model component, have been used by the WHO since 2015 to inform seasonal influenza vaccine strain selection, as the Director of the Worldwide Influenza Centre (WIC) confirms below [E2]. The WIC is one of six Collaborating Centres for Influenza in the WHO's GISRS. A major role of the WHO Collaborating Centres is to advise WHO on the composition of seasonal influenza.

*"Predictive modelling for influenza has been transformed in recent years notably so through the work of Prof Michael Lässig and Dr Marta Łuksza [...] These models include as an essential component the model developed by Prof Julia Gog and Prof Bryan Grenfell initially in Cambridge on multi-strain evolutionary models. The Lässig/Łuksza group is one of two modelling groups that have been asked by WHO for input to the WHO influenza Vaccine Composition Meetings (VCM) since 2015, and since 2018 a representative of the Lässig/Łuksza group have been invited to participate directly in these VCMs.[...] It is already clear that the ability to incorporate predictive modelling into important public health decision making through improved recommendations for the composition of influenza vaccines marks a real impact"*

The Centres for Disease Control and Prevention (CDC) hold the most comprehensive data on influenza vaccination reach and significance. In seasons, such as 2017-2018, when the vaccine matched most circulating strains, the influenza vaccine has been shown in recent studies to reduce the risk of influenza illness by between 40% and 60% among the overall population, highlighting the importance of accurately predicting the circulating strains. In the United States 2017-2018 season alone, more than 155,000,000 doses of influenza vaccine were distributed and vaccination averted an estimated 6,200,000 influenza illnesses, 91,000 influenza-associated hospitalizations, and 5,700 influenza-associated deaths [E3].

## **I2) An increase in public engagement with science, stimulating increased public awareness of the dangers of an influenza pandemic and of potential strategies to limit spread**

The ground-breaking citizen science project described in the Underpinning Research section was a form of public engagement that produced impact during the research project itself. Over 86,000 people around the UK took part in the experiment via the BBC Pandemic App, and a television programme on the project entitled "Contagion!" The BBC Four Pandemic" was broadcast in March 2018 [E4], generating large public interest

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The first scientific article derived from the programme data [R6] received a record number of 718 tweets, with 66% being from the general public as of January 2020 [E8].

## **I3) Informing policy via SPI-M**

An influenza pandemic is viewed by the UK government as a major threat to the UK due to both its high likelihood of occurrence and severity of outcome. Gog has been recognised for her key contributions to influenza control by being invited to join the UK government working group on strategic influenza pandemic planning, namely the Scientific Pandemic Influenza Modelling subgroup (SPI-M). The Lead Analyst for Infectious Diseases in the Department of Health and Social Care (DHSC), confirms Gog's key role [E9]:

*"During non-pandemic periods, SPI-M's main role is to advise DHSC on pandemic preparedness policies. A recent example of work in this area is to use complex mathematical modelling to determine the potential impact of vaccines arriving at different times during an influenza pandemic. This will help ministers decide whether or not the UK should spend significant sums of money on a contract to develop and supply such vaccines.[...] As one of the UK's leading influenza modellers, Professor Gog is a key member of the group."*

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

E1) Letter of support, dated 15/07/19, from Professor Michael Lässig, Scientific Coordinator, CRC 1310 Predictability in Evolution, University of Cologne

E2) Letter of support, dated 22/01/20, from the Director of the Crick Worldwide Influenza Centre

E3) CDC webpages: Vaccine Effectiveness (page 2 of 5) and Summary of the 2017-2018 Influenza Season (page 2 of 3) <https://www.cdc.gov/flu/>

E4) BBC webpage on the "Contagion!" The BBC Four Pandemic" programme

<https://www.bbc.co.uk/programmes/p059y0p1>. R7 evidences total number of participants in the experiment via the BBC Pandemic app.

E5) **Text removed for publication**

E6) **Text removed for publication**

E7) **Text removed for publication**

E8) Altmetric webpage giving metrics on [R6], downloaded 24/01/20.

<https://www.altmetric.com/explorer/highlights?q=Contagion%21%20The%20BBC%20Four%20P>

[andemic%20%E2%80%93%20The%20model%20behind%20the%20documentary&show\\_detail  
s=34711620](#)

E9) Letter of Support, dated 20/01/20, from Lead Analyst, Department of Health and Social Care