Institution: Imperial College London

Unit of Assessment: 02 Public Health, Health Services and Primary Care

Title of case study: Evidence to Inform Policy Formulation for Influenza Pandemic Planning and Response

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

The work of Professor Ferguson and colleagues at Imperial College on modelling the effect of different intervention measures on the spread and health impact of a new influenza pandemic has substantially shaped UK and international public policy-making over the last 7 years. Prior to 2009, this work shaped UK policy on antiviral and pre-pandemic vaccine stockpiling and use, and on the potential use of school closure and border restrictions during a pandemic. During the 2009 H1N1 pandemic, real-time research provided the first estimates of key epidemiological parameters of the new pandemic virus, demonstrating the low-to-moderate severity and lower than typical transmissibility. In the UK, US and other countries, these data informed public policy decisions to pull back from use of economically costly interventions (such as reactive school closure or antiviral prophylaxis) and focus on targeted use of vaccination as the principal pandemic mitigation measure.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor Neil Ferguson, Professor of Mathematical Biology (2000-present)
Dr Simon Cauchemez, Reader in Statistical Infectious Disease Epidemiology (2005-present)
Professor Christophe Fraser, Professor of Theoretical Epidemiology (2000-present)

From 2004, and building on extensive experience in modelling both seasonal influenza and emerging infections (e.g. SARS and H5N1 avian flu), Professor Ferguson led an extensive research programme to improve understanding of the epidemiology of pandemic influenza and the evidence base for interventions to mitigate the impacts of influenza pandemics. This research:

a) Analysed data collected in historical influenza pandemics (1-5) to improve our epidemiological understanding of pandemics and the effectiveness of interventions (notably school closure [5] and other non-pharmaceutical interventions [4]). This work, undertaken from 2004-2009, provided some of the first reliable estimates of the transmissibility of pandemic influenza, demonstrating that the reproduction number, *R*, of the 3 twentieth century pandemics lay in the range 1.6-2.0, and thus that control measures needed only to have relatively moderate effects to achieve substantial reductions in the rate of spread and overall impact of a pandemic. Analysis of historical records of the 1918 'Spanish flu' H1N1 pandemic in the US highlighted that public health measures could substantially slow spread (4), while detailed statistical analysis of seasonal influenza transmission patterns in contemporary France (5) provided the first quantitative estimates of the role of schools in both seasonal and pandemic influenza transmission, suggesting that school closure as a public health measure might have a substantial impact on peak incidence in a pandemic (and thus healthcare demand) but more moderate impacts on overall attack rates.

b) Developed, in 2004, the first continental-scale epidemic simulator to examine the potential impact of multiple interventions on the transmission of pandemic influenza. The feasibility of containing a lethal pandemic at source was examined (1), together with a wide range of potential mitigation strategies (2). This work highlighted that the timescale of spread of a pandemic would make it unlikely that pandemic vaccine would be available in the first wave of transmission, meaning it would be necessary to rely on layered combinations of antiviral use and non-pharmaceutical interventions to achieve substantial mitigation of a severe influenza pandemic. Professor Ferguson developed a simulation platform to inform pandemic planning which combined epidemiological information on influenza transmission dynamics with data derived from clinical trials and observational studies on the impact of vaccines, antivirals and public health measures on influenza disease burden and transmission. This platform allowed

flexible modelling of the likely impacts of different combinations of interventions on the speed of spread and overall attack rate of an unfolding pandemic. Logistical constraints could be specified, and resource requirements (e.g. antiviral stockpile sizes) assessed. The work concluded that if a severe pandemic (e.g. caused by H5N1) was detected within the first few generations of human-to-human transmission, it might be feasible to achieve containment of spread through the intensive use of antiviral prophylaxis, quarantine, school and workplace closure and travel restrictions (1). However, once an outbreak exceeded a few hundred cases, containment was predicted to be very unlikely to succeed (1), and use of more sustainable layered interventions to mitigate pandemic impact was indicated (2). Related work by Professor Ferguson and colleagues demonstrated that the use of international travel bans would be unlikely to have a major impact on the global spread of a pandemic (3).

c) Analysed surveillance data collected in the first few weeks of the 2009 H1N1 pandemic to provide the first estimates of pandemic transmissibility and severity (6). This work was undertaken in collaboration with colleagues in the World Health Organisation (WHO) and the Mexican Ministry of Health. It concluded that the transmissibility of the 2009 pandemic was less than the previous 3 pandemics, and that severity was at worst moderate, with a 1918-like high severity scenario being able to be excluded. Throughout the pandemic, the MRC Centre for Outbreak Analysis and Modelling at Imperial analysed surveillance data for WHO and multiple governments (notably UK, US and China), to improve situational awareness and decision-making.

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

(1) Ferguson, N.M., Cummings, D.A., Cauchemez, S., Fraser, C., Riley, S., Meeyai, A., Iamsirithaworn, S., Burke, D.S. (2005). Strategies for containing an emerging influenza pandemic in Southeast Asia. *Nature*, 437, 209-214. DOI. Times cited: 702 (as at 4th November 2013 on ISI Web of Science). Journal Impact Factor: 38.59

(2) Ferguson, N.M., Cummings, D.A., Fraser, C., Cajka, J.C., Cooley, P.C., Burke, D.S. (2006). Strategies for mitigating an influenza pandemic. *Nature*, 442, 448-452. DOI. Times cited: 669 (as at 4th November 2013 on ISI Web of Science). Journal Impact Factor: 38.59

(3) Hollingsworth, T.D., Ferguson, N.M., Anderson, R.M. (2006). Will travel restrictions control the international spread of pandemic influenza? *Nat Med*, 12, 497-499. DOI. Times cited: 53 (as at 4th November 2013 on ISI Web of Science). Journal Impact Factor: 24.3

(4) Bootsma, M.C.J., Ferguson, N.M. (2007). The effect of public health measures on the 1918 influenza pandemic in US cities. PNAS, 104, 7588-7593. DOI. Times cited: 123 (as at 4th November 2013 on ISI Web of Science). Journal Impact Factor: 9.73

(5) Cauchemez, S., Valleron, A.J., Boëlle, P.Y., Flahault, A., Ferguson, N.M. (2008). Estimating the impact of school closure on influenza transmission from Sentinel data. *Nature*, 452, 750-754. DOI. Times cited: 167 (as at 4th November 2013 on ISI Web of Science). Journal Impact Factor: 38.59

(6) Fraser, C., Donnelly, C.A., Cauchemez, S., Hanage, W.P., Van Kerkhove, M.D., Hollingsworth, T.D., Griffin, J., Baggaley, R.F., et al. (2009). Pandemic Potential of a Strain of Influenza A (H1N1): Early Findings. *Science*, 324, 1557-1561. DOI. Times cited: 714 (as at 4th November 2013 on ISI Web of Science). Journal Impact Factor: 31.02

Key funding:

- National Institutes of Health (NIGMS MIDAS initiative; 2004-2009; $470,000). Principal Investigator (PI), N. Ferguson, Mathematical Models in the study of Infectious Disease spread and control
- European Commission (FP6; 2005-2008; €1,400,000), PI N. Ferguson, Mathematical modelling of emerging and deliberately released pathogens ('INFTRANS')
- Bill & Melinda Gates Foundation (2008-2013; £2,400,000), PI N. Ferguson, Vaccine Modelling Initiative.
- Medical Research Council (MRC; 2008-2013; £2,100,000), PI N. Ferguson, MRC Centre for Outbreak Analysis and Modelling.

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

Impacts include: health and welfare, public policy and services, international development
Main Beneficiaries include: Governments, WHO

Prior to the references 1 and 2 above, there was virtually no quantitative evidence base for planning for influenza pandemic containment or mitigation. The research of Professor Ferguson and colleagues at Imperial supported UK and international pandemic preparedness policy, notably in (a) influencing the size of antiviral stockpile purchased and policies on treatment and prophylaxis, (b) policies on the use of travel restrictions and school closure for pandemic mitigation. It also supported WHO planning for pandemic containment. Work during the pandemic provided estimates of pandemic severity and transmissibility and informed government policies about the appropriate level of interventions to introduce in the UK, US and globally.

Impact on policy formulation for influenza pandemic planning:
The research showed that for containment of an emergent severe pandemic to be feasible, the outbreak would need to be detected when cases numbers were still limited (<~100). This research finding directly influenced the 2009 WHO guidelines for pandemic surveillance [1, page 3], building on the earlier WHO protocol for pandemic containment [2, pages 2, 4, and 23]. Professor Ferguson actively advised WHO directly during the formulation of these and other guidelines.

Research on pandemic mitigation and the impact of travel restrictions informed UK policy decisions on pandemic planning – most notably, providing evidence to support stockpiling antiviral drugs and for their use for treatment and prophylaxis, in recommendations that travel restrictions would have a limited role in mitigation, and in recommendations around the potential use of school closure as a public health measure. Much of this evidence was synthesised via the Dept. of Health (DH) UK Scientific Pandemic Influenza Advisory Committee (SPI) Modelling subgroup evidence summaries, [3A cites research references 1 and 2, plus unpublished work for DH on antiviral prophylaxis, while source 3B cites most of the research listed above]. In turn, these modelling evidence summaries informed national planning assumptions and policy on travel restrictions, antiviral stockpiling and use and school closure. The recent (2011) UK Pandemic Preparedness strategy [4] cites Imperial College work on travel restrictions (page 38), work on the use of antivirals for prophylaxis (page 41), and analysis of the 2009 pandemic (page 11). Additional corroboration on the influence of the MRC Centre's work is available from DH.

The research also informed pandemic planning in Europe (e.g. European Centre for Disease Prevention and Control [ECDC] 2009 antiviral recommendations [5; ref 19, cited on pages 5, 11, 17 and 19]) and the United States (US Homeland Security Council Key Elements of Departmental Pandemic Influenza Operational Plans 2008 [6; references 31 and 32]. Interestingly, while plans in Europe and the US were both heavily informed by Professor Ferguson's research (and role on multiple advisory panels), the resulting policies differed in emphasis: in the EU, more focus was placed on the stockpiling and use of antivirals, while in the US, emphasis was placed on the potential for intensive use of non-pharmaceutical interventions (e.g. school closure) to achieve pandemic mitigation. Additional corroboration on the impact of this work on US policy is available from DHHS in the US.

The work of the MRC Centre for Outbreak Analysis and modelling continues to have a lasting impact on policy for pandemic planning. The 2013 WHO guidance for Pandemic Influenza Risk Management cites 5 papers from Centre staff [7, reference 31, 32, 39, 40, 53 in References section on page 34 and citations throughout text].

Impact on public policy-making in response to the 2009 H1N1 pandemic:
During the 2009 H1N1 pandemic, the MRC Centre at Imperial provided real-time analyses for WHO and multiple governments (notably the UK and US, but also including Mexico and China). Professor Ferguson acted as advisor to the WHO Emergency Committee throughout the 2009 H1N1 pandemic, and was also a member of the WHO Ad Hoc Policy Strategic Advisory Group of Experts Working Group on influenza A (H1N1) vaccines. He was a member of the UK Scientific Advisory Group for Emergencies (SAGE; and the modelling subgroup) and the US CDC's 'Team B'

advisory group.

Much of the real-time research undertaken was published after the pandemic, but influenced policy formulation at the time. The single most influential piece of work was the initial assessment of the pandemic (research reference 6), which played a substantial role in (a) informing the WHO decision to move from pandemic phase 4 to 5; (b) reassuring policymakers that the H1N1 pandemic was no 'severe', and therefore default UK, US and WHO policy which had been formulated to mitigate a severe pandemic (e.g. arising from H5N1) could be appropriately modified (e.g. cessation of the UK 'containment' phase and of using school closure in the US, policies on use of vaccines).

Much of the UK modelling advice was summarised in updates published throughout the pandemic by the 'SPI-M-O' advisory group [8]: these summaries are referred to in multiple UK SAGE and DH policy documents, and in the 'Lessons learned' inquiry reports following the pandemic (e.g. the Hine review). However, the nature of both research and policy-making in an emergency means the impact of the MRC Centre's research is most easily corroborated by the individuals listed under 'Sources' below.

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

[1] WHO report "Global Surveillance during an Influenza Pandemic" (2009). Archived on 8/11/13

[2] A. WHO Interim Protocol: Rapid operations to contain the initial emergence of pandemic influenza. Archived on 8/11/13

[3] UK Scientific Pandemic Influenza Advisory Committee (SPI) Modelling subgroup evidence summaries. A. February 2008 version: http://webarchive.nationalarchives.gov.uk/20080728093434/http://advisorybodies.doh.gov.uk/spi/modelling.htm; (archived on 8/11/13) B. June 2013 version: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/208264/SPI-M_Modelling_Summary_13_06_13.pdf (archived on 8/1/13)

[4] UK Influenza Pandemic Preparedness Strategy 2011. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_131040.pdf. Archived on 8/11/13

[5] ECDC Interim Guidance (2009) on Public health use of influenza antivirals during influenza pandemics. http://www.ecdc.europa.eu/en/publications/publications/0907_gui_public_health_use_of_influenza_antivirals_during_influenza_pandemic.pdf. Archived on 8/11/13

[6] US National Strategy for Pandemic Influenza Implementation Plan, Key Elements of Departmental Pandemic Influenza Operational Plans (2008). http://www.flu.gov/planning-preparedness/federal/operationalplans.html# Archived on 8/11/13

[7] Pandemic Influenza Risk Management: WHO Interim Guidance (2013). http://www.who.int/influenza/preparedness/pandemic/GIP_PandemicInfluenzaRiskManagementInterimGuidance_Jun2013.pdf Archived on 8/11/13

[8] SPI-M-O and the 2009 H1N1 Pandemic – document archive. http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/ab/SPI/DH_118862 (archived 8/11/13)

Contact to corroborate impact on UK policy: Senior Principal Analyst, Department of Health, Health Protection Analytical Team
Contact to corroborate impact on WHO policy: Assistant Director-General – Health Security and Environment, World Health Organisation
Contact to corroborate impact on US policy: Chief Medical Officer and Deputy Director, Biomedical Advanced Research and Development Authority (HHS/ASPR/BARDA)