Institution: University of Nottingham

Unit of Assessment: 2

Title of case study: Responding to the threat of pandemic influenza

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

Research carried out by the Health Protection and Influenza Research Group (HPIRG), Division of Epidemiology and Public Health, impacted directly on the UK Government's response to the 2009 influenza pandemic, feeding directly into policy-making decisions. The group was appointed as an official WHO Collaborating Centre for pandemic influenza in 2010 and through its related research has "reduced the economic impact on Member States for pandemic preparedness" (quote from reference 7, section 5). In 2011, it secured £7M funding from the US Centers for Disease Control and Prevention (CDC) to lead 'once only' work to determine the modes of influenza transmission using a human challenge model.

2. Underpinning research (indicative maximum 500 words)

a) In late April 2009, as it became rapidly apparent that a pandemic had started, the Department of Health (England) asked Prof Van-Tam, Head of HPIRG, to design, establish and lead the Influenza Clinical Information Network (FLU-CIN) to study the detailed clinical epidemiology of cases of pandemic influenza in UK hospitals. The brief was to establish the network within 4 weeks and begin reporting to the Scientific Advisory Group for Emergencies (SAGE) within 8 weeks. These objectives were achieved by the FLU-CIN coordinating team in Nottingham (Van-Tam – Head of Unit, Enstone – Research Associate, Hashim – Research Associate, Myles – Associate Professor) working in partnership with clinical groups across the length and breadth of the UK to assemble the largest longitudinal cohort of pandemic influenza patients in Europe, from which detailed clinical data were extracted.

b) In May 2009, the NIHR began commissioning a series of 'emergency' research studies to address issues arising during the 2009 pandemic. The HPIRG was awarded direct funding for two of these:

- 'MummyFlu': an estimation of the degree of antibody protection conferred to newborn babies by vaccination of their mothers during pregnancy (2009-10: Puleston (Associate Professor), Van-Tam).
- An estimation of influenza virus transmission parameters through the sampling of patients with pandemic flu and the environment around them (2009-11: Killingley – Clinical Research Fellow, Van-Tam, Enstone)

The HPIRG was a major co-applicant (with Leicester University) on a third:

- A comparative assessment of the serological response in adults to the two pandemic vaccines chosen for deployment by the UK Government. (2009-10: Van-Tam).

c) In the aftermath of the 2009 pandemic, under its new WHO responsibilities, HPIRG designed and led an evaluation to examine whether preparedness activities put in place across Europe and central Asia prior to 2009 aided the pandemic response, (2010-11:Hashim – PhD student, Shaw (Prof Social Sciences), Van-Tam).

d) In addition, over the period 2011 to 2013, WHO Headquarters in Geneva requested and funded HPIRG to undertake four commissioned systematic reviews and meta-analyses on areas of international importance in relation to influenza control:

- Effectiveness in immunocompromised patients (2011: Beck - Lecturer, Hashim, Van-Tam, Enstone)
- Effectiveness of vaccinating healthcare workers to prevent illness in patients (2011: Dolan – seconded Public Health trainee, Van-Tam, Hale – PhD student)
- Effectiveness of antiviral drugs in reducing community transmission (2013: Beck, Okoli – Research Associate, Van-Tam)

- Effectiveness of movement restriction on disease containment (2013: Beck, Mateus – seconded trainee, Van-Tam)

e) It has long been recognised that the mode of influenza transmission is poorly understood and is a significant international problem: authoritative advice on prevention cannot be given to the public and healthcare workers about protective countermeasures (e.g. hand hygiene, face masks, respirators). Having undertaken pioneering pilot work to develop a human challenge model for transmission of influenza, HPIRG formed a major international consortium (EMIT) and was awarded £7M from CDC to continue this work (2011-13: Van-Tam, Enstone, Killingley), which is regarded as globally important and absolutely unique.

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

1. Nguyen-Van-Tam JS, Openshaw PJM, Hashim A, Gadd EM, Lim WS, Semple MG, Read RC, Taylor BL, Brett SJ, McMenamin J, Enstone JE, Armstrong C, Nicholson KG. Risk factors for hospitalisation and poor outcome with pandemic A/H1N1 influenza: United Kingdom first wave (May-September 2009). Thorax, 2010; 65: 645-651. doi:10.1136/thx/2010.135210 (most highly cited paper in Thorax in 2012).
2. Puleston R, Bugg G, Hoschler K, Konje J, Thornton J, Stephenson I, Myles P, Enstone J, Augustine G, Davis Y, Zambon M, Nicholson K, Nguyen-Van-Tam J. Multi-centre observational study of transplacental transmission of influenza antibodies following vaccination with AS03(A)-adjuvanted H1N1 2009 vaccine. PLoS One. 2013;8(1):e47448. doi:10.1371/journal.pone.0047448. PubMed PMID: 23372640; PubMed Central PMCID: PMC3553100.
3. Killingley B, Greatorex J, Cauchemez S, Enstone JE, Curran M, Read RC, Lim WS, Hayward A, Nicholson KG, Nguyen-Van-Tam JS. Virus shedding and environmental deposition of novel A (H1N1) pandemic influenza virus: interim findings. Health Technol Assess. 2010 Oct;14(46):237-354. doi: 10.3310/hta14460-04. PubMed PMID: 20923613 (pdf available on request).
4. Nicholson KG, Abrams KR, Batham S, Clark TW, Hoschler K, Lim WS, Medina MJ, Nguyen-Van-Tam JS, Read RC, Warren FC, Zambon M. Immunogenicity and safety of a two-dose schedule of whole-virion and AS03A-adjuvanted 2009 influenza A (H1N1) vaccines: a randomised, multicentre, age-stratified, head-to-head trial. Lancet Infect Dis. 2011 Feb;11(2):91-101. doi: 10.1016/S1473-3099(10)70296-6. PubMed PMID: 21168369.
5. Hashim A, Jean-Gilles L, Hegermann-Lindencrone M, Shaw I, Brown C, Nguyen-Van-Tam J. Did pandemic preparedness aid the response to pandemic (H1N1) 2009? A qualitative analysis in seven countries within the WHO European Region. J Infect Public Health. 2012 Aug;5(4):286-96. doi: 10.1016/j.jiph.2012.04.001. PubMed PMID: 23021651.
6. Dolan GP, Harris RC, Clarkson M, Sokal R, Morgan G, Mukaigawara M, Horiuchi H, Hale R, Stormont L, Bechard-Evans L, Chao YS, Eremin S, Martins S, Tam JS, Penalver J, Zanuzadana A, Nguyen-Van-Tam JS. Vaccination of health care workers to protect patients at increased risk for acute respiratory disease. Emerg Infect Dis. 2012 Aug;18(8):1225-34. doi: 10.3201/eid1808.111355. PubMed PMID: 22840895; PubMed Central PMCID: PMC3414018.

Major Grants related to the activities in section 2 above:

1. Influenza Clinical Information Network. Awardee: Van-Tam. Sponsor: University of Nottingham. Funder: Department of Health, England. Period of the grant: 9 months (01 April 2010 to 31 Dec 2010). Value: £181,360.50.
2. MummyFlu. Awardees: Van-Tam, Puleston. Sponsor: University of Nottingham. Funder: NIHR. Period of the grant: 21 months (01 April 2009 to 31 Dec 2010). Value: £82,851
3. Virus shedding study. Awardee: Van-Tam, Killingley. Sponsor: University of Nottingham. Funder: NIHR. Period of the grant : 21 months (21 August 2009 to 27 May 2011). Value: £372,225.
4. WHO Evaluation of 2009 pandemic response. Awardee: Van-Tam, Hashim, Shaw. Sponsor: University of Nottingham. Funder: World Health Organization. Period of the grant: 22 months (01 December 2009 to 30 September 2012). Value: £79,088
5. WHO systematic reviews and meta-analyses. Awardee: Van-Tam, Beck, Dolan, Puleston.

Sponsor: University of Nottingham. Funder: World Health Organization. Period of the grant: 11 months (20 December 2010 to 30 November 2011). Value: £12,293

6. EMIT: Evaluation of Modes of Influenza Transmission. Awardee: Van-Tam, Enstone. Sponsor: University of Nottingham. Funder: CDC, Atlanta. Period of the grant: 2 years; October 2011 to September 2013. Value: $10,800,000

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

a) The FLU-CIN delivered its first report to SAGE, on time, less than 8 weeks after planning began. The Chairs of SAGE later wrote: "We greatly appreciated your work as the lead for the hub of the Flu Clinical Information Network as well as your contribution to the sub-group on clinical countermeasures and to research to inform the UK's response". A FLU-CIN report was submitted fortnightly to the UK Government (via SAGE) from June 2009 until February 2010. This provided information on the proportion of otherwise healthy individuals with pandemic influenza requiring critical care, the burden of disease in children, and helped towards the early identification of risk factors for severe outcomes. The data we provided contributed towards UK government policy for the use of antiviral drugs and vaccines to combat the pandemic. In addition, our data fed directly into UK clinical management guidelines formulated by the Pandemic Influenza Clinical and Operational group (PICO). As an example, the minutes of the UK Scientific Advisory Group for Emergencies on 11th January 2010 note: “The FLU-CIN structure had proved a great success in obtaining detailed clinical data about patients hospitalised with the pandemic (H1N1) 2009 virus. Maintaining some sort of legacy structure, that could be activated rapidly in the event of a new pandemic, should be a priority” (see reference 1 below).

b) Regarding the NIHR funded ‘emergency’ influenza studies, these were commissioned and awarded as part of the UK Government’s R&D response to pandemic influenza, and all three were published rapidly in Health Technology Assessment, in line with other NIHR funded work. The ‘MummyFlu’ project delivered critical data that demonstrated that 2009 pandemic vaccines administered to pregnant women in the UK were highly likely to protect newborns via transplacental transfer of passive immunity. This work has contributed towards the UK’s decision to adopt a policy of influenza vaccination for pregnant women from Autumn 2010 onwards. Similarly the work to evaluate the two pandemic vaccines used in adults in the UK during 2009 provided rapid feedback to the UK Government that one (adjuvanted with AS03) was in fact considerably more immunogenic than the other. This work helped inform the UK’s decision to target children with the AS03 adjuvanted vaccine. (see reference 2)

c) The HPIRGs evaluation work for the WHO Regional Office for Europe was the largest piece of post-pandemic evaluative work undertaken by WHO Europe and led to a consultation workshop in Copenhagen in Autumn 2010, and a formal WHO report (see Section 5). The Director of WHO Europe wrote (Foreword): “A principal value of this report is that it applies a standard framework to highlight essential cross-cutting elements of successful pandemic preparedness activities. Moreover, it takes an objective approach to highlight not only the essential elements of successful activities but also the areas on which the pandemic experience suggests future planning must place greater emphasis…Member States, by sharing the experiences gained and lessons learnt throughout the process, have shaped the recommendations in this report, which we at WHO believe is extremely useful for all countries and WHO alike, as we review our pandemic plans”. The findings of our work have been incorporated into a new draft Pandemic preparedness planning guide for Member States of the WHO European Region and the European Union (affecting 900 million citizens) which were published in late 2012. (see references 3 and 4)

d) The HPIRG’s research work for WHO Headquarters in Geneva has comprised of individual (unpaid) consultancy and expert advice as well as four major systematic reviews and meta-analyses on the subject of influenza vaccination in immunocompromised subjects and vaccination of healthcare workers to protect patients. The WHO was so satisfied with the outputs of this work, it wrote “these reviews have been of fundamental importance in supporting WHO’s recommendations…..the impact of this work is significant in terms of the change in policy, which has reduced the economic impact on Member States for pandemic preparedness…” (see references 5, 6, 7 and 8).

e) The recently funded work on influenza transmission (awarded October 2011), results from sustained efforts to develop this area. In terms of the lack of current understanding about modes of transmission of influenza, this knowledge gap has been identified by the US CDC, the UK Government, the European Centre for Disease Prevention and Control (ECDC), the WHO Global Influenza Research Agenda and the Institutes of Medicine as being a high priority unmet need for influenza. The findings will be applicable in every nation of the world in the event of a future pandemic, emphasising the global importance attached to this work. (see references 9 and 10)

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

Reports, reviews, web links or other documented sources of information in the public domain:

1. HM Government report on the function and value of FLU—CIN https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/215871/dh_122754.pdf (see Section on FLU-CIN)
2. Emergency pandemic research reports including two from Nottingham http://www.journalslibrary.nihr.ac.uk/collections/h1n1-pandemic-flu-research (see Volumes 2 & 3)
3. Pandemic assessment report produced by WHO, joint logo with University of Nottingham http://www.euro.who.int/en/what-we-do/health-topics/communicable-diseases/influenza/publications/2010/recommendations-for-good-practice-in-pandemic-preparedness-identified-through-evaluation-of-the-response-to-pandemic-h1n1-2009
4. Changes to pandemic planning in WHO European Region arising from work performed by Nottingham http://www.euro.who.int/en/what-we-do/health-topics/communicable-diseases/influenza/publications/2012/key-changes-to-pandemic-plans-by-member-states-of-the-who-european-region-based-on-lessons-learnt-from-the-2009-pandemic
5. Updated WHO global pandemic plan, including reference to supporting work under taken in Nottingham http://www.who.int/influenza/preparedness/pandemic/GIP_PandemicInfluenzaRiskManagementInterimGuidance_Jun2013.pdf (see reference 51, page 37)
6. Reference to work underway on a new clinical guideline driven by expert reviews, two of which performed in Nottingham http://www.who.int/influenza/resources/documents/clinical_management_2012/en/
7. Statement/letter from Dr Caroline S. Brown, Programme Manager, Influenza & other Respiratory Pathogens, Division of Communicable Diseases, Health Security & Environment, WHO Regional Office for Europe
8. Contact: Nahoko Shindo MD PhD, Medical Officer, WHO Global Influenza Programme
9. External BBC reporting of influenza transmission work http://www.bbc.co.uk/news/health-21773604
10. CDC report on status of influenza transmission and importance of challenge experiments http://www.cdc.gov/influenzatransmissionworkshop2010/