Institution: University of Cambridge

Unit of Assessment: UoA 5

Title of case study: Antigenic Cartography: mapping the flu virus to produce better vaccines

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

Researchers in the University of Cambridge's Department of Zoology have developed a new methodology to analyse pathogen evolution. This 'antigenic cartography' has led to the group becoming integrally involved in the World Health Organisation (WHO) influenza vaccine strain selection process, and has directly contributed to more accurate and appropriate flu vaccine design, with associated international impacts on disease prevention and public health (the flu vaccine is given to ~350 million people annually). The research has directly affected how public health professionals conduct disease surveillance and sampling.

2. Underpinning research (indicative maximum 500 words)

Derek Smith started developing software to build antigenic maps in 1999 whilst at the University of New Mexico and Santa Fe Institute (New Mexico, US). These visually represent the antigenic distance between different strains of a virus, showing the relationships among them, and their rate of evolution. He joined the University of Cambridge Department of Zoology in 2003 (as a Research Associate and group leader, Professor since 2007), and the underpinning computational method developed by Smith (as lead scientist, with expertise in computer science, mathematics and virology) and his collaborators (Alan Lapedes, a physicist at Los Alamos National Laboratory, New Mexico, US; Ron Fouchier, a virologist at Erasmus Medical Centre, Rotterdam, the Netherlands) was published in 2004[1].

By describing and analysing 35 years of influenza virus evolution, the paper resolved the fundamental problems of reliably measuring antigenic differences among pathogens, and substantially increased the resolution at which antigenic differences among influenza viruses could be determined. More importantly, it resolved the paradoxes that had made such data refractory to detailed quantitative analysis, and caused a paradigm shift in how antigenic data are interpreted.

Within two weeks of the 2004 publication, Smith was asked by the World Health Organization to have his group analyse the data generated by the WHO global network of (then) four laboratories that track the influenza virus, and to attend the WHO meeting three months later (September 2004) that would choose the strains to be used in the next global influenza virus vaccine, in order to demonstrate his method's applicability. Since that meeting, Smith's group has been integrally involved in the WHO influenza vaccine strain selection process (see section 4).

In 2008, subsequent antigenic and genetic analyses of HA in influenza isolates undertaken by Smith and Dr Colin Russell (Research Associate then Royal Society University Research Fellow 2006-2013) resolved the long-standing question of where seasonal influenza viruses originate from each year[2]. They found that influenza A(H3N2) viruses (the type of influenza that causes most morbidity and mortality) do not persist in any one country in the world, but in a meta-population structure of epidemics passing among a network of countries in east and south-east Asia, and that epidemics in the rest of the world are seeded each year from this network. This work resolved a decades-old puzzle of how influenza viruses circulate around the world, provided fundamental insights into the combined evolution and epidemiology of influenza viruses, and has had translational impact on influenza surveillance and vaccine strain selection (see section 4).

The method, named 'antigenic cartography' by Smith, has subsequently been used in the first virological characterization of the 2009 influenza pandemic[3] (authorship included five Smith group members and the public health scientists in Mexico and the United States involved in initial detection of the pandemic, with Smith as one of two corresponding authors). In addition to its use in influenza, the group has additionally applied antigenic cartography to influenza viruses in other species, including poultry (2010)[4] and horses (2011)[5], in order to demonstrate virus evolution and aid vaccine selection. In collaboration with Taiwanese academics, Smith has also produced the first antigenic map of enterovirus 71 (2011)[6], an important emergent human infectious disease, particularly in Asia, and is involved in the phase I and II clinical trials of an enterovirus 71 vaccine in Taiwan.

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

1. DJ Smith, AS Lapedes, JC de Jong, TM Bestebroer, GF Rimmelzwaan, ADME Osterhaus, and RAM Fouchier. Mapping the Antigenic and Genetic Evolution of Influenza Virus. *Science* (2004) 305: 371–376 doi: 10.1126/science.1097211
2. Russell CA, TC Jones, IG Barr, NJ Cox, R Garten, V Gregory, I Gust, AW Hampson, AJ Hay, AC Hurt, JC de Jong, AI Klimov, T Kageyama, N Komadina, AS Lapedes, YP Lin, A Mosterin, M Obuchi, T Odagiri, ADME Osterhaus, GF Rimmelzwaan, MW Shaw, E Skepner, K Stohr, M Tashiro, RAM Fouchier, DJ Smith. 2008. The global circulation of seasonal influenza A(H3N2) viruses. *Science* (2008) 320: 340–346 doi: 10.1126/science.1154137
3. Garten RJ, Davis CT, Russell CA, Shu B, Lindstrom S, Balish A, Sessions WM, Xu X, Skepner E, Deyde V, Okomo-Adhiambo M, Gubareva L, Barnes J, Smith CB, Emery SL, Hillman MJ, Rivailler P, Smagala J, de Graaf M, Burke DF, Fouchier RA, Pappas C, Alpuche-Aranda CM, López-Gatell H, Olivera H, López I, Myers CA, Faix D, Blair PJ, Yu C, Keene KM, Dotson PD Jr, Boxrud D, Sambol AR, Abid SH, St George K, Bannerman T, Moore AL, Stringer DJ, Blevins P, Demmler-Harrison GJ, Ginsberg M, Kriner P, Waterman S, Smole S, Guevara HF, Belongia EA, Clark PA, Beatrice ST, Donis R, Katz J, Finelli L, Bridges CB, Shaw M, Jernigan DB, Uyeki TM, Smith DJ, Klimov AI, Cox NJ. Antigenic and Genetic Characteristics of Swine-Origin 2009 A(H1N1) Influenza Viruses Circulating in Humans, *Science* (2009) 325: 197-201. doi 10.1126/science.1176225
4. Fouchier RAM and DJ Smith. Use of antigenic cartography in vaccine seed strain selection. *Avian diseases* (2010) 54: 222-3 doi: 10.1637/8740-032509-ResNote.1
5. Lewis NS, Daly JM, Russell CA, Horton DL, Skepner E, Bryant NA, Burke DF, Rash AS, Wood JL, Chambers TM, Fouchier RA, Mumford JA, Elton DM, Smith DJ. The antigenic and genetic evolution of equine influenza A(H3N8) virus from 1968-2007 *J Virol*. 2011 Sep 21 doi: 10.1128/JVI.05319-11
6. Huang SW, Kiang D, Smith DJ, Wang JR. Evolution of re-emergent virus and its impact on enterovirus 71 epidemics. *Exp Biol Med* (2011) 236:899-908 doi: 10.1258/ebm.2010.010233

Major relevant funding:

- United States National Institutes of Health (NIH) Director's Pioneer Award, for "Antigenic Cartography" to Smith (2005). $2,500,000. These awards are given for "highly innovative – potentially transformative biomedical research with the potential to produce an unusually high impact" (E. Zerhouni, NIH Director 2005) https://commonfund.nih.gov/pioneer/Recipients05.aspx
- Royal Society University Research Fellowship: 'The evolution and epidemiology of antigenically variable pathogens'. Russell (2009-2014). £582,000
- Human Frontier Science Research Project 2008: 'Integrating the antigenic, genetic, and epidemiological analyses of antigenically variable pathogens'. PI: Smith. $1,350,000
- Bill & Melinda Gates Foundation 2009: 'High-throughput identification of influenza virus amino acids responsible for human-to-human transmission'. PI: Smith (sub-grant from University of Wisconsin-Madison). $618,000
- EU Framework Programme 7 2009: 'European Management Platform for Emerging and Re-emerging Infectious Disease Entities'. PI: Smith. Work package of €450,000
- EU Framework Programme 7: 'ANTIGONE—ANTIcipating the Global Onset of Novel Epidemics'. PI: Smith, €160,000

- US National Institutes of Health: 'Investigations to improve annual seasonal influenza vaccination'. PI: Smith. Work package of $499,400

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

Influenza epidemics affect about 10% of the world's population each year (about 600 million people), resulting in ~500,000 deaths. However, the primary vaccine component (the viral surface glycoprotein hemagglutinin (HA)) has a seemingly endless capacity to evolve. Consequently, the vaccine needs to be updated, sometimes annually, to remain effective. Smith's 'antigenic cartography' method is now a key component in this updating process. As a result, the work is having an international impact on disease prevention and public health, as well as informing decisions taken by the WHO.

Impacts on health and welfare: public health has improved; disease prevention has been enhanced

As a mark of the relevance of its work to the international public health arena, in 2012 the Smith laboratory became a "WHO Collaborating Centre for Modelling, Evolution, and Control of Emerging Infectious Diseases"[7,8] at the WHO's request. Collaborating Centres (CCs) are only invited to be designated as such after successfully collaborating with the WHO in jointly planned activities over several years. The title of, and the terms of reference for[9], the CC deliberately state 'infectious diseases' rather than 'influenza' because of the recognised applicability of the method to a wide range of viral and bacterial pathogens. The official WHO designation states 'This Centre is recruited to support WHO programs in Epidemic and Pandemic Alert and Response by providing a suite of computational tools for analysing the evolution of re-emerging and emerging pathogens. Such tools are applicable to all pathogens and are of high value for surveillance, vaccine strain selection, and support of decision making…. The tools provided by the Centre are state-of-the-art, at the forefront of research, and they have proven to be of high value to WHO and laboratories identified by WHO world-wide.'[10]

The Smith group reports to, and attendance at, WHO strain selection meetings (see below) have an obvious direct impact on the efficacy of updated vaccines, and a related significant impact on public health and disease prevention. As a further example, the virus characterized in the Smith group's 2009 publication is still representative of the strains circulating today, and remains the basis for the H1 component of the current vaccine[11].

Impacts on international development: international agencies have been influenced by research

Since 2011, the WHO has orchestrated the Global Influenza Surveillance and Response System (GISRS) to track influenza virus evolution. Teams in over 100 countries worldwide collect and analyse influenza samples, which are funnelled into one of five WHO Collaborating Centres (CCs) for analyses. The data are then passed to Smith's group, which uses antigenic cartography to produce a report on the current worldwide state of the evolution of the virus, and the likely impact of this on vaccine strain selection. Reports (20-100 pages)[12] are compiled by the group for each six monthly meeting of the WHO influenza vaccine strain selection committee (the latest in Feb 2013), and are used alongside related reports from WHO CCs to determine which strains should be included in the next vaccine. Smith and Russell attend each strain selection meeting, composed of about 10 'Temporary Advisors' (including the directors of the five primary WHO CCs and Smith), and 15 'Observers' (including Russell). The Smith group also uses the results to update a WHO internal website showing the latest evolution of the viruses; more than 500 incremental updates are provided 365 days a year on a 24-hour turn around[13]. The website tracks seasonal flu virus evolution and epidemiology in almost real time, and to date Smith's group has analysed more than 100,000 virus samples from over 100 countries.

Publically available WHO documents corroborate the use and utility of antigenic cartography in vaccine strain selection. For example, the Report of the First Global Consultation: WHO Public Health Research Agenda for Influenza (2009), states (p24) that "*antigenic cartography is useful for vaccine strain selection and evolution studies*"[13]. The WHO report 'Recommended viruses for influenza vaccines for use in the 2010-2011 northern hemisphere influenza season' states (p2) "*antigenic cartography is used as an additional analytical tool to visualize and integrate antigenic data*".[14]

Impacts on practitioners and services: practitioners/professionals have used research findings in conducting their work

The work group's work has had an impact on public health and surveillance professionals in a number of ways. Following publication of the 2008 paper (section 3, ref 2) showing that epidemics of influenza A(H3N2) viruses are seeded annually from east and southeast Asia, Keiji Fukuda, Assistant General of the WHO stated in 'Science' that 'it (the paper) shows strengthening surveillance in Asia is crucial.'[15] H3N2 is the most important seasonal flu virus in humans, causing more morbidity and mortality than other human flu viruses; the WHO now focuses surveillance and strain selection for H3 on the region identified in the publication.

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

7. WHO website: http://apps.who.int/whocc/Detail.aspx?cc_ref=UNK-229&cc_city=cambridge&
8. WHO CC website: www.whocc.infectiousdisease.cam.ac.uk
9. http://www.who.int/immunization/sage/3_Recommendation.pdf
10. The WHO CC designation document
11. See for example: http://www.who.int/influenza/vaccines/virus/recommendations/2013_south/en/index.html (southern hemisphere) and http://www.who.int/influenza/vaccines/virus/recommendations/201202_qanda_recommendation.pdf (northern hemisphere)
12. For example: 'Information for the WHO Consultation on the composition of Influenza vaccines for the northern hemisphere. Meeting Report 14-17 Feb 2011' (current reports are confidential to WHO)
13. WHO Collaborating Centres Designation Form: Centre for Pathogen Evolution, Cambridge. See paragraph 1.2
14. www.who.int/influenza/resources/research/2010_11_report_of_the_first_global_consultation_november_2009.pdf
15. "Mapmaker for the World of Influenza" ***Science****,* Vol. 320, No. 5874. 310–311, 2008