Institution: University of Cambridge

Unit of Assessment: 5

Title of case study: New generation seasonal influenza vaccines

Period when the underpinning research was undertaken: 2004 – present

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:
Derek Smith	Professor of Infectious Disease Informatics	Jan 2003 - present

Period when the claimed impact occurred: 1 January 2014 – 31 July 2020

Is this case study continued from a case study submitted in 2014? Y

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

Research from the group of Professor Derek Smith at the University of Cambridge on the evolution of the influenza virus has been an integral part of the WHO influenza vaccine strain selection process since 2004, with Professor Smith sitting as part of the selection committee. Further research since 2012 has led to the possibility to predict the evolution of human seasonal influenza viruses, and to understanding the immunity induced by influenza vaccination. Since 2017, this work has generated a profound change in the vaccine strain selection process by WHO. An estimated 500 million people are now vaccinated annually with strains informed by this work.

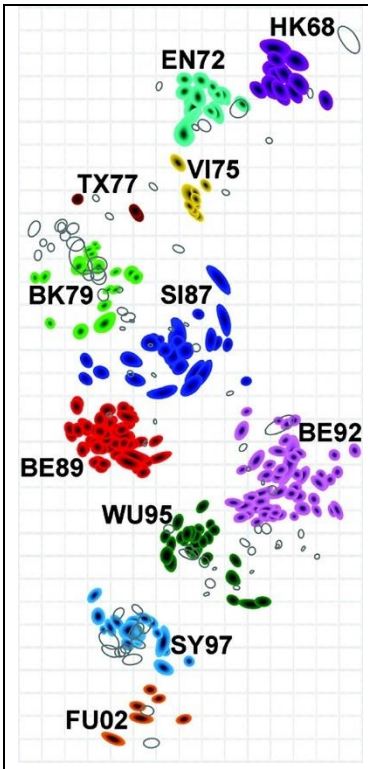
2. Underpinning research (indicative maximum 500 words)

Seasonal influenza is an acute respiratory infection caused by influenza viruses that circulate in all parts of the world. The resulting illness ranges from mild to severe and can cause death. Hospitalization and death occur mainly among high-risk groups, such as pregnant women, children under five, the elderly, individuals with chronic medical conditions and individuals with immunosuppressive conditions. Worldwide, annual epidemics are estimated to result in three to five million cases of severe illness, and 290,000 to 650,000 deaths due to respiratory complications. The most effective way to prevent the disease is vaccination. Safe and somewhat effective vaccines are available and have been used for more than 60 years, with injected inactivated influenza vaccines most commonly used (WHO factsheet, influenza (seasonal), 6 Nov 2018).

The effectiveness of seasonal influenza vaccines fluctuates, but averages ~50%, i.e. in those who are vaccinated the chance of having symptomatic influenza is approximately half that of non-vaccinated people. One known shortfall in vaccine effectiveness is the mismatch that results from evolution of antigens (the parts of the virus that generate an immune response) in the circulating viruses during the eight months between vaccine strain selection and the onset of the influenza season. Such a mismatch occurs in approximately one in three influenza seasons and lowers vaccine efficacy by approximately 20% when it does.

Professor Derek Smith at the University of Cambridge recognized that by understanding the mechanism behind the evolution of seasonal influenza viruses it may be possible to predict its antigenic evolution with reasonable accuracy, potentially enabling antigenically advanced or “evolution proof” vaccines to be deployed. In such a scenario, populations could be vaccinated against strains yet to occur in nature through a process the Cambridge group refers to as immunity management.

Understanding the evolution of seasonal influenza virus



In 2004, Professor Smith published a new bioinformatics method, antigenic cartography, that substantially increased the resolution at which antigenic data could be interpreted [R1]. This method also allows a simple visualization of antigenic evolution, in the form of an "antigenic map" that permits straightforward understanding of antigenic evolution. It can be easily seen, for example, that influenza viruses evolve in a sequence of large steps from one antigenic variant or cluster to another (Figure 1, taken from [R1]).
Antigenic cartography has become widely adopted in the study of antigenically variable pathogens [R1]. Follow-on work [R2, R3] by the Smith group in 2013 showed that these steps, each of which requires an update to the influenza virus vaccine, are typically caused by just a single amino acid (AA) substitution in the viral hemagglutinin protein and are limited to a small area of the protein peripheral to the receptor binding site of the virus [R2].

The implications of these findings are profound. First, it enabled a better understanding of the evolutionary process for seasonal influenza viruses. Second, the evolutionary paths from any starting point are sufficiently constrained that they can be evaluated in a laboratory resulting in surprisingly accurate prediction of seasonal influenza viruses evolution for the first time.

Figure 1 *Antigenic map of influenza A (H3N2) virus from 1968 to 2003 (from [R1])*

Understanding the immune response to influenza vaccination
Published in 2014, Professor Smith's group developed a method to assess and visualize specific antibody protection to influenza in individuals and populations [R4]. Antibody levels to multiple antigenic variants are plotted on an antigenic map to form an antibody landscape or immunity profile. Using antibody landscapes, the Smith group discovered the "backboost" phenomenon: vaccination with an influenza variant boosts antibody levels not only to the variant itself, but also to a wide spectrum of previous and current influenza strains.

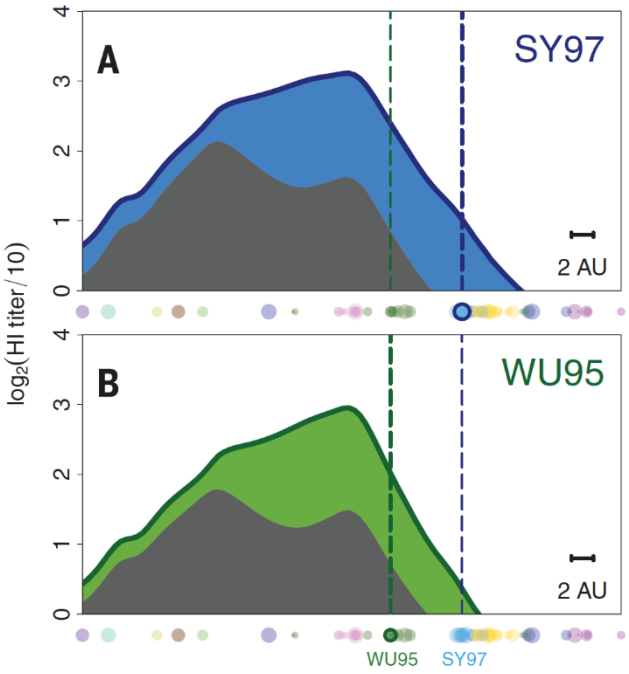


Figure 2 *The grey areas in these figures show antibody landscapes, the immunity level or antibody titre, for various strains representative of approximately 50 years of evolution of the influenza subtype A/H3N2.*

(A) The blue area shows the boost in titres after vaccination with a strain (SY97) from an antigenically more advanced cluster that was not yet circulating widely (in blue).
(B) The green area shows the boost in titres after vaccination with a strain (WU95) from the cluster circulating at the time (in green).

The vertical dotted lines indicate the position of the (blue, SY97) and (green, WU95) wildtype vaccine viruses. As can be seen, the more advanced vaccination provides higher protective titres to strains in both the old and the new cluster.

Using these data, Professor Smith's group proposed vaccination with an antigenically advanced strain, either from nature or predicted using a combination of computational and laboratory experiments, that can avoid the risk of mismatch as it protects against novel and upcoming strains,

and, thanks to the backboost phenomenon described above, also protects against currently or previously circulating strains. This new, ground-breaking knowledge on the evolution of seasonal influenza has been part of an ongoing, in-depth knowledge exchange relationship with the World Health Organisation (WHO), influencing vaccine selection and implementation within the REF reporting period.

This research was conducted by the following members of Prof. Smith's research group: Sam Wilks, Terry Jones, Ana Mosterin, Sarah James, David Burke, David Pattinson, and Sina Tureli.

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

R1. Smith, D. J., Lapedes, Alan S., de Jong, Jan C., Bestebroer, Theo M., Rimmelzwaan, Guus F., Osterhaus, Albert D.M.E. (2004) Mapping the Antigenic and Genetic Evolution of Influenza Virus. ***Science***, 305(5682):371-376. doi:10.1126/science.1097211 *

R2. Björn F. Koel, **David F. Burke**, … **Eugene Skepner**, **Nicola S. Lewis**, … **Colin A. Russell**, … **Derek J. Smith** (2013) Substitutions Near the Receptor Binding Site Determine Major Antigenic Change During Influenza Virus Evolution. ***Science***, 342(6161):976-979. doi:10.1126/science.1244730 *

R3. Chengjun Li, Masato Hatta, **David F. Burke**, … **Colin A. Russell**, **Sarah L. James**, **Eugene Skepner**, … **Derek J. Smith** & Yoshihiro Kawaoka (2016). Selection of antigenically advanced variants of seasonal influenza viruses. ***Nature Microbiology***, 1(6):16058. doi:10.1038/nmicrobiol.2016.58 *

R4. J. Fonville, **S. H. Wilks**, **S. L. James**, … **T. C. Jones**, … **A. Mosterin**, **L. C. Katzelnick**, …, **E. Skepner**, **C. A. Russell**, T… **D. J. Smith** (2014). Antibody landscapes after influenza virus infection or vaccination. ***Science***, 346(6212):996-1000. doi:10.1126/science.1256427 *

*All publications have been subject to peer-review

Details of funding competitively awarded

- Royal Society University Research Fellowship: The evolution and epidemiology of antigenically variable pathogens. (2009-2014). GBP582,000
- Human Frontier Science Research Project (2008) Integrating the antigenic, genetic, and epidemiological analyses of antigenically variable pathogens USD1,350,000
- Bill & Melinda Gates Foundation (2009) 'High-throughput identification of influenza virus amino acids responsible for human-to-human transmission USD618,000
- European Commission Horizon 2020: COMPARE - Collaborative Management Platform for detection and Analysis of Re-emerging and foodborne outbreaks in Europe GBP396,895
- United States National Department of Health and Human Services, Advanced vaccination and immunity management strategies to protect from influenza virus infection. PI of consortium (2015-2021) USD8,010,586

United States National Institutes of Health
2005, Director's Pioneer Award, USD2,500,000
2012-2013, Investigations to improve annual seasonal influenza vaccination, USD499,400
2015-2021, Linking dengue antigenic and genetic variation to individual and population risk, USD351,289
2014 -2021, Centers for Excellence in Influenza Research and Surveillance, USD9,098,822

EU Framework Programme 7
2009-2014 EMPERIE European Management Platform for Emerging and Re-emerging Infectious Disease Entities, EUR450,000
2011-2016 ANTIGONE—ANTIcipating the Global Onset of Novel Epidemics, EUR160,000

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

Worldwide, influenza annually infects on average 10% of the world population (Somes et al., doi: 10.1016/j.vaccine.2018.04.063). Annual epidemics are estimated to result in three to five million cases of severe illness (WHO factsheet, Influenza (seasonal), 6 November 2018) and a study published in 2019 estimated that, in the period 2002-2011, an average of 389,000 respiratory deaths were associated with influenza globally each year for 31 countries representing five WHO regions (Paget *et al.*, doi: 10.7189/jogh.09.020421). The economic impact is over USD25 billion per year in medical costs and lost earnings in the USA alone (Putri *et al.*, 2018, doi: 10.1016/j.vaccine.2018.05.057).

Professor Smith at the University of Cambridge has been a member of the WHO vaccine strain selection committee since the publication of his group's antigenic cartography method in 2004 (R1), and their research has been closely involved in WHO decision-making on influenza vaccines in the REF period.

Reporting to WHO

The Smith group receives all the WHO collaborating centre global data on the evolution of seasonal influenza viruses (approximately 20,000 strains per year) as it is generated; they process these data and return the analyses to the WHO network within 24 hours. Such an update happens about 75 times a year. The Smith group produces six extensive, confidential reports per year (42 for this REF period) on the global evolution of seasonal influenza viruses. These reports are distributed to the WHO and to the nine WHO laboratories in the world primarily responsible for vaccine strain selection, prior to teleconferences and meetings at WHO for choosing the influenza vaccine strain. These nine labs are the official, national state-sponsored reference labs for influenza, and historically were the only participants in vaccine strain selection meetings. Professor Smith was initially invited to attend this meeting in 2004, by virtue of the value his unique research insights provided and has remained on the committee since then. Regarding the Cambridge reports, the Director of the WHO Global Influenza programme states: "These reports integrate the surveillance data and viral characterization from the WHO collaborating centres...in an accessible and accurate form, provide unique insight on the evolution of the viruses for vaccine strain selection purposes, and are an integral part of the vaccine strain selection process." [E1]

Influencing selection of the seasonal influenza vaccine

The work performed by the group of Prof. Smith asks fundamental questions about evolution and host immunity and has applied relevance of interest to the WHO vaccine strain selection committee. The Director of the WHO Global Influenza programme says: "In particular the Cambridge group's work on antigenically advanced vaccines, prediction of evolution and the backboost phenomenon in human immunity are all highly relevant and useful for the vaccine choice. Further, this work has been performed in a highly collaborative way with WHO." [E1]

[Text removed for publication]

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Effect of vaccine strain selection

These decisions enable assessment of the effect of [Text removed for publication] vaccine updates in practice using data from 2018 and 2019. In both cases, serological analysis of vaccinated humans showed that the updated vaccines stimulated a strong response against the new variants against which they were targeted and, importantly, an equally strong backboost response against older strains. The effect of the vaccine is also captured in estimates of vaccine effectiveness (VE). Such estimates are only regularly measured by a small number of countries, and only for those subtypes of influenza that circulate in sufficient numbers. Previous variants to the vaccine strain remained dominant in Canada in season 2019/20 (fortunately, Canada is the country that estimates VE most extensively). Vaccine effectiveness against these older strains was substantially higher (62%) than that seen in the previous six years in North America when a classical matched vaccine choice had been made (figure 3 below, data from E2, E3, E4).

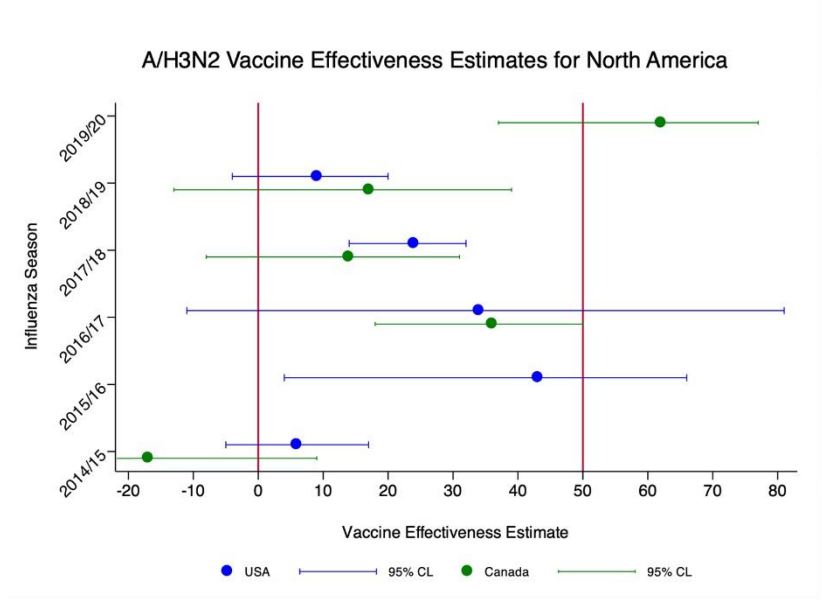

Figure 3 *Seasonal VE estimates for A/H3N2 for North America for seasons 2014/15 - 2019/20. VE estimates for the USA (in blue) are from the US Flu Vaccine Effectiveness Networks, estimates for Canada (in green) are from the Canadian Sentinel Practitioner Surveillance Network.*

The Director of the WHO Global Influenza Programme says that [Text removed for publication]

The close involvement of Prof. Smith in WHO vaccine selection, and the integration of advice based on new results from his group regarding the evolution of the influenza pathogen, has been highly influential in management of this seasonal illness. The Director of the WHO Global Influenza programme says: [Text removed for publication] [E1]

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

E1. Testimonial from Director of the WHO Global Influenza programme
E2. Canadian Sentinel Practitioner Surveillance Network (SPSN) influenza vaccine effectiveness estimates
E3. US Seasonal Influenza Vaccine Effectiveness, 2019-2020
E4. US Past Seasons Vaccine Effectiveness Estimates