Influenza: a world of discoveries, outbreaks and controversy

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Abstract

Working in an area such as influenza is a free ticket into science communication, a pathway aided amply by the amazing evolutionary powers of the virus; regular outbreaks keep the media engaged and the audience keen. Everyone has heard of flu, and they probably already have an opinion: ‘I don’t take the vaccine, it gives me the flu anyway.’ ‘Didn’t the government waste loads of money on that Tamiflu drug that doesn’t work?’ ‘I’ve never had flu because I eat a banana every day and sleep with a boiled onion when I’ve sat next to someone on the train who was coughing.’ Such muddled messages and folklore fallacies could be very damaging unless we as scientists stand up and correct them. In addition, there are wider ethical debates around sharing data from clinical trials and the acceptable limits of scientific research to which we must all contribute.

There will be another influenza pandemic, but knowing when, or predicting how bad it will be, is difficult. Birds are the source of all natural influenza viruses, including those that cause human pandemics. Influenza viruses can cross from wild birds into domesticated species such as chickens and pigs. Once in poultry, the virus can evolve to become highly pathogenic, resulting in rapid death of the infected animals, taking out whole sheds of animals in less than a day. This is devastating for the poultry farmers, as the imposed control strategy is to cull the entire remaining stock. (I have been asked ‘Will there be enough turkeys for Christmas?’! Currently a novel avian influenza, H5N8, with some genes derived from the better known H5N1 bird flu viruses, is spreading extensively through the migratory pathways travelled by wild birds and making frequent incursions to domestic poultry in Europe including the UK. After showing some interest in the meaning of Protection and Surveillance Zones imposed to contain these outbreaks, what the mainstream media want to know is, how dangerous are such viruses for people exposed to the affected chickens, turkeys or ducks and how likely are they to spread more widely and infect the general public? To answer this question we need to understand the host range barrier; put simply: what is the difference between humans and chickens that means that most avian influenza viruses do not infect people and, if they do, they do not transmit amongst us [1]? Scientists working in this area got into hot water in 2012. They were trying to understand why the infamous H5N1 bird flu, a virus fatal for chickens and the majority of the 800 or so infected humans, does not transmit onwards from infected people to others. If it did, it would probably spark a serious outbreak because most people in the world have no pre-existing immunity to this strain. The assumption was that certain genetic changes could adapt the H5N1 virus to support transmission through the air between people, but the nature of those changes was unknown. In a series of now highly controversial ‘gain of function’ (GoF) experiments, two groups working in labs in the USA and Netherlands generated mutant viruses that could transmit between ferrets, an accepted animal model for human to human transmission [2, 3]. They gained new information about the importance of temperature and pH stability for survival of contagious influenza that may also help us to enhance the longevity and efficacy of vaccine viruses. However, when the results were announced rather dramatically at a conference they sparked the ‘wrong’ sort of press and drew attention to these experiments in a way that aggravated members of the lay public and of the scientific community who had not previously been acquainted with this style of molecular virology. Some scientists found these experiments unacceptable, arguing the risks of such artificial viruses escaping from the lab to spark a human-created pandemic did not outweigh the benefits brought by the increased knowledge about the virus [4]. At one point GoF opponents even proposed that the details of the experiments were redacted, not to be shared with the scientific community let alone the public, for fear that terrorists could create their own transmissible viruses for nefarious use. At the 2014 Microbiology Society’s Peter Wildy Prize lecture at the annual conference, the Virus Division hosted a debate on this important issue, and it is a subject every scientist should consider. Indeed, this topic makes great teaching material, to encourage undergraduate science students to consider where the limits of acceptable science lie, whether redaction is
an acceptable option and how science is regulated. These events have now changed forever how funding and publication of this type of science is handled. In January 2017 the White House Office for Science and Technology Policy published new guidelines for oversight of this type of research following on from the publication of the US government-commissioned Gryphon report in 2016. Closer to home, many Microbiology Society members will have already encountered questionnaires when submitting or reviewing a manuscript that ask whether the science under review involves creation of materials or information that fall into the Dual Use Research of Concern category. In the event of future media interest in this area, the responsible steps taken by funders and publishers will allow us to reassure the public that appropriate ‘self’ regulation is being adopted.

Another ‘hot topic’ for science communication is the matter of vaccines. There is a topical influenza vaccine story to introduce this subject; the UK is currently embarking on an exciting new approach to influenza vaccination, namely vaccinating children. Prior to 2013, UK policy was to only vaccinate elderly and at-risk people with the inactivated influenza vaccine. Introduction of influenza vaccines for children was informed by the epidemiology of the last influenza pandemic in 2009. Then, rather than H5N1 that had up to that time been considered the most likely pandemic threat, it was a ‘swine’ flu that took us by surprise and adapted for transmission between people. During the early part of the summer, influenza case numbers were escalating across the country. But then, in the third week in July, numbers began to plummet, and they stayed low until September. This timing correlates almost perfectly with the summer school holidays and, combined with some previous modelling about childhood vaccination, was the final snippet of evidence that prompted the new UK policy. Early data in geographical areas where the scheme has been piloted already look very encouraging [5]. Not only was there less influenza illness in the primary age school children who received vaccine, but indirect effects were seen across the whole community with significantly fewer deaths due to respiratory illness compared to areas where the scheme has not yet been introduced. The whole success story could be a wonderful way to teach the general importance of vaccine coverage and herd immunity for reducing or eliminating infectious disease… the children are not being given the vaccine because they themselves are at huge risk of severe flu, they are being asked to take it as an altruistic effort to lower total influenza circulation in the community because this will reduce illness and hospitalizations in those who are more vulnerable, such as the elderly and immunocompromised. And yet, just last summer, 2016, there came a ‘fly in the ointment’ impacting on this success story. The vaccines advisory body for the USA, known as ACIP, recommended that live attenuated influenza virus (LAIV) no longer be used in American children (www.cdc.gov/media/releases/2016/s0622-laiv-flu.html). Currently intense research efforts are trying to get to the bottom of the discrepancy between US vaccine efficacy data that prompted this backwards move and data from the other countries where LAIV is used that are much more encouraging.

Not only is this story a great way to engage children, because it actually is all about them, it is also a great opportunity to explain to the lay public the difference between different types of vaccine we use today. The vaccine we are giving to children is not an injection but a simple squirt up the nose with a ‘live’ virus that is ‘cold adapted’, meaning it can replicate to a limited degree in nasal passages as they are cooled by the air we breathe, but it cannot penetrate to the deeper lung and cause illness because it is unable to replicate at our normal body core temperature of 37°C. Most people who know about flu vaccine think of the other type of inactivated vaccine given to those at risk of a severe influenza outcome such as the elderly. Every year the Department of Health is frustrated by the poor uptake of this vaccine particularly in healthcare workers but also in vulnerable groups, over 65s, asthmatics, etc. One reason often given is, that ‘it gives you flu; you feel terrible after the injection and that’s not worth it’. Plausible explanations for this unfortunate myth that has perpetuated might be the timing of influenza vaccination at the start of the winter colds and flu season leading to coincidental respiratory infections around that time, and that some vaccine components might lead to reactions around the injection site. Communicating these alternative interpretations to the public can allay their doubts. However, we also need to keep repeating that this is an inactivated vaccine – an inert injection of a fragment of the virus (largely the haemagglutinin spike protein, HA). You cannot get flu from an injection of inactivated vaccine!

No matter what type of vaccine we attempt to generate and distribute in the face of an emerging pandemic, it is inevitable that part of our pandemic response will rely on antiviral drugs [6], and once again clear and concise communication is required to ensure public trust in this approach. The Tamiflu controversy exemplifies this: governments have stockpiled the antiviral drug Tamiflu in order to have at least one mitigation option to control the virus in the early phase. Between 2006 and 2013, the UK government spent £424 million stockpiling Tamiflu and £136 million on the other licensed neuraminidase inhibitor (NAI), Relenza. However, some people strongly voiced the opinion that this was a waste of money, and maintained that there was inadequate scientific information to justify the spend. AllTrials is a campaign group spearheaded by the clinician, academic and journalist Ben Goldacre and popularized by the British Medical Journal. AllTrials use Tamiflu as one of their ‘poster children’ examples to argue that big pharma should be ‘forced’ to make public all the data they obtain during clinical trials, not only the data that were submitted to regulators for licensure. In 2013, Roche and GSK, manufacturers of the NAI class of drugs to which Tamiflu and Relenza belong, were persuaded by campaigners to release their trials data and several groups analysed them. The Cochrane group published their findings amongst much publicity, announcing that these antiviral drugs decreased the
length of influenza symptoms by less than 1 day (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008965.pub4/abstract;jsessionid=D0952B85723A29FF11B3087DB5F71938.f03). They argued that this small effect did not justify the money spent, nor offset the occasional side effects of nausea that were reported during trials. They even tried to suggest in their report that the drugs did not work against influenza virus itself. To those of us who work in the influenza research arena and have handled these drugs, this did not ring true and so it was important to speak out for the other side. This is easy to do because of the Science Media Centre (SMC; http://www.sciencemediacentre.org/). They can help scientists reach journalists, by enrolling as an expert and responding to enquiries whenever science relevant to their own expertise comes to the media’s attention. SMC arrange press briefings at key moments, for example during the early days of an outbreak of flu, Ebola or Zika, or when reports are published such as that commissioned by the UK government from the Academy of Medical Sciences and Wellcome Trust on the Tamiflu situation (http://www.acmedsci.ac.uk/file-download/38069-561595082cd83.pdf). These briefings marry up the journalists who are trying to get the science in their story correctly reported with the expert scientists who are hoping to make sure the reporting is accurate.

A message I provided to SMC about the Tamiflu controversy was as follows:

Treating influenza is a challenge. For most people it is an acute disease, lasting less than 1 week. In the respiratory tract, peak virus replication occurs in the first days after a person gets infected, but they might not feel ill straight away. Severe influenza disease is usually associated with higher virus replication so it has always made sense that a drug that targets the virus might also help to control symptoms. But getting the drug to the patient in time is difficult because often patients present late, some days after the virus replication has peaked. This difficulty in timing may explain why often these drugs have a bigger effect when given prophylactically (before the person even catches the virus) than as treatments. In other words, it is not that the drugs do not work, it is just difficult to use them to their best effect. Most of the trials on the NAI drugs that were re-analysed by the Cochrane group were conducted on previously healthy adults, infected with a seasonal influenza virus. Although 1 day shortening of symptoms does not sound like a lot, in an illness that lasts only 6 days, it is quite an improvement. The situation in a pandemic is very different: more previously healthy people suffer severe influenza, and raised influenza awareness means they are more likely to present early. The first wave of the 2009 pandemic was boosted by the ‘worried well’, a large group presenting to their GPs with flu-like symptoms in whom influenza is not laboratory confirmed. One can fairly extrapolate that the rather moderate beneficial effects of NAs during seasonal influenza in the 1990s and early 2000s [7] would translate into more apparent positive benefits during a severe and widespread outbreak. Indeed, published retrospective observational studies overwhelmingly support a beneficial effect for early treatment with NAIs in hospitalized patients, including pregnant women, during the swine flu pandemic in 2009/2010 [8]. This suggests that stockpiling of these drugs was prudent.

If another pandemic came tomorrow, and the government had no drug with which to treat thousands of influenza-infected patients, there would be a public outcry. Meanwhile the scientific lesson to draw from the Tamiflu controversy is that speed is of the essence in treating acute viral infections with antivirals. Even if tomorrow we developed a better new anti-influenza virus drug (and all sorts of academic research are justified on this basis!), we lack the ability to administer it effectively: we do not have a sensitive rapid diagnostic for influenza, so we cannot tell who should receive antivirals and who would not benefit. In an outbreak that might last months and where manpower and antivirals might be scarce, this becomes key.

Academics can easily get buried in their intricate and specialist scientific universes. But by engaging in science communication and teaching young people, who generally ask interested and interesting questions, you are forced to think more widely about your subject and then the gaps in our knowledge and capabilities become apparent as gaping holes. Perhaps ultimately this is the best reason for engaging in communication activities.

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References