H7N9, like H5N1 – re-exposes weaknesses in pandemic vaccine development

LONDON, UK----3th March 2014----ExpertREACT. Although spreading faster, H7N9 appears deadly but less so than H5N1. Like H5, poor immunogenicity of H7 could hamper vaccine development exposing weaknesses despite our advances in production systems. Universal vaccines remain key

Like its older cousin H5N1 first observed in 2003, the recent A (H7N9) avian influenza virus emerged from the avian/human interface in China **(1)**. Before March 2013 H7N9 had not previously been seen in either animals or people once again demonstrating the huge fluidity and unpredictable nature of the influenza virus. Antigenically, H7N9 viruses are different from seasonal influenza viruses infecting humans. The HA gene is most similar to that of A(H7N3) viruses detected in ducks in Eastern China whereas the NA gene is most similar to N9 NA genes from viruses circulating recently in domestic ducks in China and Korea.

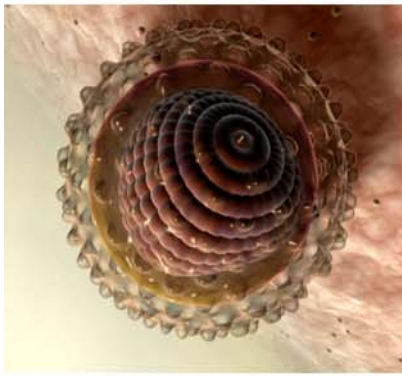
Although also associated with high morbidity/mortality, H7N9 does not appear to transmit easily from person to person, and sustained human-to-human transmission has not been reported. After less than a year from its first reports there have already been greater than 300 cases of H7N9 occurring in two distinct waves. As of 28 January 2014, the case fatality rate of all confirmed cases was 22%, but many cases are still hospitalized. Of all cases, 67% were male with the median age of reported cases being 58 years and that of fatal cases, 66 years **(2)**.

In comparison to H7N9, the accumulation rate of H5N1 cases has been far slower with the same amount of cases taking 4 to 5 years to be recorded **(3)**. From 2003 to the present day 650 cases of H5N1 have now been recorded with 386 deaths (59% mortality). H5N1 presently appears more lethal than H7N9 consistent with the inverse relationship between transmissibility and mortality. Although it is still early, H7N9 has only been observed in 2 countries, China and Malaysia whereas the established H5N1 virus is now observed in 16 countries. It is highly likely that H7N9 will spread to poultry of neighboring countries. Further spread of H7N9 may enhance its pandemic potential.

The emergence of H5N1 spurred enormous investment in influenza vaccine production capabilities enabling the international community to respond more effectively to an influenza pandemic. In order to strengthen the US influenza vaccine supply, notably the US HHS has awarded over $1 billion in contracts to manufacturers to develop cell-based technology **(4)**. This was in addition to investments in other areas e.g. recombinant protein technology, strengthening egg supply and antigen sparing technologies i.e. adjuvantation.

Despite some manufacturer attrition, the investment in cell-based technology has seemingly paid off. During the 2009 H1N1 pandemic a number of cell-based vaccines were available such as Novartis' Celtura™ and Baxter's Celvapan™. Indeed, Novartis also received approval from HHS's Food and Drug Administration (FDA) for its cell-based seasonal influenza vaccine Flucelvax, which it supplied to the 2013-2014 influenza seasons albeit, had much lower quantities than egg-based equivalents **(5)**.

Investments in cell culture, manufacturing again may also support our defence against H7N9. In August 2013 Novartis vaccines initiated a phase 1 clinical study to evaluate the safety and immunogenicity of four different doses of H7N9 vaccination in adults between the ages of 18 years and 65 years (NCT01928472). Importantly, company is again utilizing their cell based technology with and without an adjuvant. In November 2013, the company announced positive clinical results stating the vaccine was now in large-scale production highlighting the rapid response capability of their cell culture system.



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Other players such as GSK (Phase II), Novavax, National Institute of Allergy and Infectious Diseases (NIAID), Sanofi/NIH are also developing H7N9 vaccines, but appear to be using egg-based systems with both inactivated and live-attenuated approaches. In China, the origin of the H7N9 outbreak, Officials with Shanghai Public Health Clinical Center have stated that their genetically-engineered vaccine passed the preliminary animal tests of laboratory mice **(6).** Chinese-based Sinovac also submitted a Clinical Trial Application(CTA) with the China Food and Drug Administration(CFDA) to commence human clinical trials for its H7N9 vaccine in late January 2014 **(7).** In Taiwan, Adimmune Corp will begin a second phase of human trials for its H7N9 vaccine in March **(8).**

All vaccine manufacturers face similar challenges as they did with H5N1 in that H7 vaccines are poorly immunogenic and, given a lack of population immunity to H7, it is predicted that the amount of antigen (90mcg) and number of doses (~2) would severely impact the timeframe of a widespread immunisation campaign. For all of the talk regarding the speed of a pandemic response and the advantage of one particular production system over another, it is clear that it is the nature of pre-existing immunity to the particular influenza virus that sets the pace. Pre-existing immunity to H1 viruses was an advantage in 2009.

Recent progress on universal influenza vaccines, for example, Biondvax's M-001, which could theoretically provide protection against all pandemic strains still appears the most promising way forward to deal with the unexpected.

***Top 5 companies:** GSK Biologicals, Sanofi Pasteur, Merck & Co, Pfizer (Wyeth) and Novartis Vaccines and Diagnostics

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