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Combating bird flu

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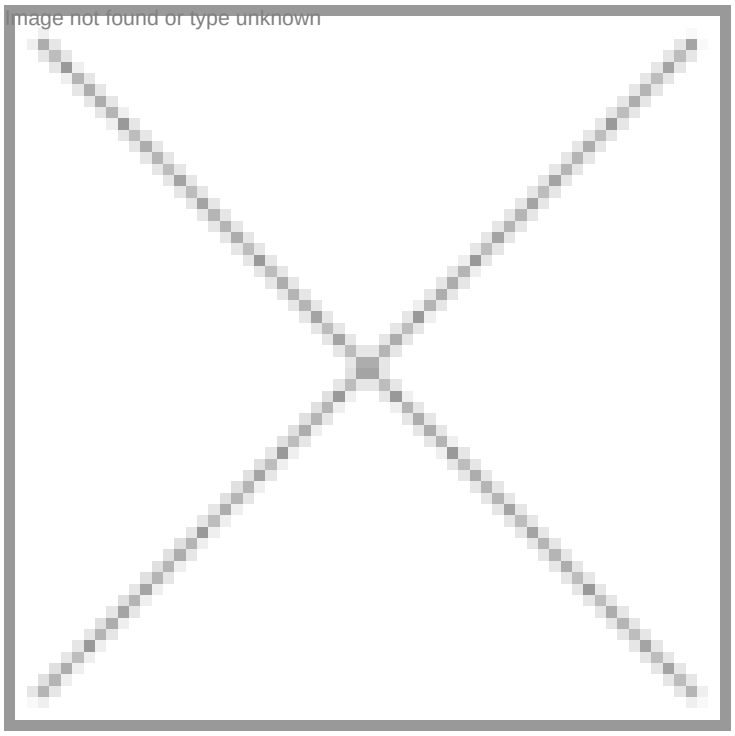
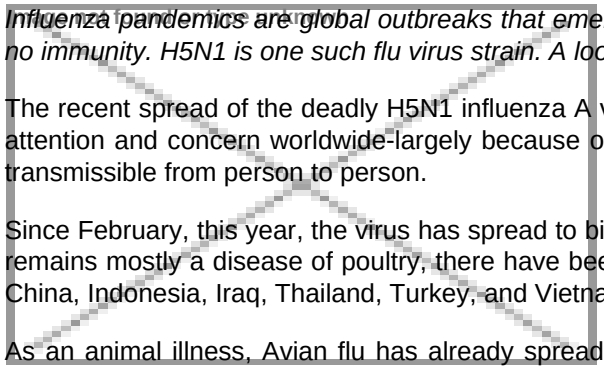


Combating bird flu

Influenza pandemics are global



Influenza pandemics are global outbreaks that emerge infrequently and involve strains of virus to which humans have little or no immunity. H5N1 is one such flu virus strain. A look at the efforts being made to combat and contain this virus.

The recent spread of the deadly H5N1 influenza A virus among birds in Asia, Europe, and Africa has been the focus of much attention and concern worldwide-largely because of the danger that the virus will mutate into a form that will become easily transmissible from person to person.

Since February, this year, the virus has spread to birds in many countries in Africa, Asia, Europe and the Middle East. While it remains mostly a disease of poultry, there have been 176 confirmed human cases since the beginning of 2005 in Cambodia, China, Indonesia, Iraq, Thailand, Turkey, and Vietnam, 98 of which have been fatal.

As an animal illness, Avian flu has already spread like wild fire. India, Afghanistan and Myanmar have also confirmed that recent outbreaks of bird flu in their countries were of the deadly H5N1 strain. In the European Union, Slovakia became the eighth state to confirm outbreaks of bird flu with Greece, France, Slovenia, Italy, Austria, Hungary and Germany also infected.

It is believed that global influenza pandemics as opposed to annual recurrences of seasonal flu tend to strike periodically. In the 20th century, there were pandemics in 1918, 1957 and 1968. According to the WHO, bird flu could potentially cause more deaths than those from the global flu pandemics. As the H5N1 virus is airborne, it is easier to transmit and much more

contagious than HIV/AIDS, WHO officials have stated.

Research efforts

The current approach of tackling the avian influenza is two-pronged-via antiviral drugs and vaccines. The circulating H5N1 strains are susceptible to two antiviral drugs-Oseltamivir (sold as Tamiflu by Roche) and Zanamivir (sold as Relenza by Glaxo SmithKline). These are being stockpiled for use as a prophylactic against any potential influenza pandemic. Scientists are presently researching on how these can be effectively used while companies are simultaneously developing other antivirals and working on mechanisms to further enhance the efficacy of the existing drugs.

Vaccination, the first line of defense to minimize suffering and death from influenza, offers a lot of hope. However, there is currently no vaccine available to protect humans against avian influenza. And at present, little knowledge exists to guide formulation of a vaccine that is both effective and economizes on the use of antigen-the component of the vaccine that elicits the immune response. Nevertheless companies and governments are developing vaccines against avian influenza and clinical trials are underway to test different formulations.

Antiviral drugs in the making

The WHO and governments around the world are stockpiling antiviral drugs-Tamiflu and its rival Relenza. These are being used to treat patients with H5N1, although the WHO has recommended more studies to determine how bird flu patients can be best treated with it. Till now, no direct clinical trial evidence has shown that the medicine is effective in treating people infected with the H5N1 avian influenza virus as no such studies have been conducted.

The currently circulating H5N1 influenza viruses have shown resistance to two older, inexpensive antiviral drugs, rimantadine and amantadine. Scientists are studying how the H5N1 viruses became resistant to these older drugs and carefully watching for any signs of resistance to the newer drugs.

On its part, Switzerland-based Roche is scaling up the production of Tamiflu. It is planning to use 15 partners, including Sanofi-Aventis and Clariant to increase production of Tamiflu by 33 percent, to 400 million treatments annually by the end of 2006.

Besides ramping up the manufacturing capacity, Roche is also focusing on the antiviral drug research front. It is developing models to rapidly predict the response of the emerging new viruses to Tamiflu and has started studies to predict the optimum dose and duration of Tamiflu against the different H5N1 subtypes. The company is also monitoring the resistance of the deadly virus to Tamiflu.

Meanwhile other companies are also developing antivirals against avian flu. The US-based BioCryst Pharmaceuticals has an alternate drug to Tamiflu entering advanced clinical trials. This Birmingham, Alabama based company was given fast track clearance by FDA when its drug Peramivir was shown to be highly effective against the H5N1 infection during clinical trials in mid-January 2006.

Peramivir, a neuraminidase inhibitor, is part of a new class of antiviral agents that work by inhibiting viral neuraminidase, an enzyme essential for the influenza virus to replicate and infect its hosts. This month BioCryst has initiated a phase I clinical trial of Peramivir to determine the pharmacokinetics and safety of single and multiple doses of the drug.

Another US-based company Hemispherx Biopharma, involved in the clinical development and production of new drug entities for the treatment of viral and immune-based chronic disorders, has unveiled the results of laboratory testing that shows its two investigational immunotherapeutics, Ampligen and Alferon, are potentially useful against the avian flu virus. The pre-clinical research indicated that Ampligen, a specifically configured double-stranded RNA, can provide cross-protection against avian flu viral mutations as well as boost the effectiveness of Tamiflu and Relenza, the only two drugs formally recognized for combating bird flu, upto 100 times.

In fact looking at the urgent need to develop flu vaccines/drugs, a US-based venture firm, Kleiner Perkins has set up a special $200 million fund to invest in companies developing products to battle the influenza infection, other infectious diseases and products that will form part of the biodefense preparations of countries. It is called the Pandemic and Bio Defense Fund.

Vaccine research

The WHO has been spearheading the global efforts towards a vaccine against avian influenza. It has developed a H5N1 pandemic vaccine prototype strain, which is publicly available for the development of a suitable vaccine. The WHO has also

encouraged companies to test vaccine formulations that include an adjuvant. This substance boosts the immune response and could allow adequate protection at lower quantities of antigen.

Although the WHO has developed a prototype strain, due to the frequent genetic changes in the virus, the prototype will have to change as the virus changes. In fact it is believed that the virus strain that causes bird flu outbreaks in Africa, Europe, and the Middle East this year is different from an earlier version.

To substantiate this further, the WHO Global Influenza Program has found that certain genes of many newly isolated viruses from animals and humans are genetically distinguishable from the H5N1 pandemic vaccine prototype strains selected in 2004. Since then, the WHO Reference Laboratories have started developing several new recombinant H5N1 prototype vaccine strains representative of different genetic sub-groups of viruses. Recently a H5N1 recombinant vaccine strain from A/Indonesia/5/2005 has been developed.

Chinese poultry vaccine

Various countries are also making strong individual efforts to develop both human and poultry vaccines. China, a nation severely affected by this malady, has developed a vaccine, which it claims not only protects its massive poultry population against bird flu but also against another poultry killer known as Newcastle disease. The vaccine, which was developed by the Harbin Veterinary Research Institute in the north-eastern part of the country, is the world's first live vaccine against bird flu and Newcastle disease. Scientists at the Harbin Institute spent four years developing the new vaccine, which may be used in combination with other vaccines. By March this year, about 2.967 billion doses of avian flu vaccine had been allocated across the country. Scientists claim that the lab tests and field tests had proved the effectiveness of the vaccine despite mutation of the bird flu virus.

Now the scientists are hopeful that the techniques used in researching and producing this vaccine will also help them develop a vaccine to protect humans against bird flu.

At the same time a Chinese company, Sinovac Biotech, which has successfully developed a SARS vaccine in 2003, announced that the China State Food and Drug Administration (SFDA) has approved commencement of human clinical trials for its Pandemic Influenza (H5N1, bird flu) Vaccine ("prototype"). The SFDA fast-tracked its application in one month. The National Institute for the Control of Pharmaceutical and Biological Products, the regulatory arm of SFDA for drug and biological products validation, has closely monitored and tested Sinovac's vaccine throughout the preclinical phase. Sinovac plans to initiate clinical trials as soon as possible. Due to this vaccine's uniqueness, the clinical trial process will be modified slightly, from three phases, to only two stages. Once initiated, it is expected to take about three months to complete preliminary testing for the first clinical stage.

US government efforts

In FY 2006, American President George Bush approved an unprecedented amount of resources to fund vaccine research, development, and procurement. That funding is supporting research on faster and more efficient ways to produce vaccine as well as ways to extend a given supply of vaccine. In addition to vaccines, there is also research into effective antivirals, seeking medications that can effectively reduce the severity of an influenza attack.

Presently the US Congress has allocated a $3.3-billion budget to combat avian flu. And more than half the US bird flu budget, $1.781 billion, will go to developing new vaccines, while $731 million would be spent on drugs such as Roche's and Gilead Sciences' Tamiflu and GlaxoSmithKline's Relenza. The federal government is aiming to stockpile 26 million courses of the antivirals by the end of the year.

In view of the fact that the virus is mutating and there is no way to predict which strain might become capable of moving from person to person, the government is planning to stockpile vaccine for each of the main H5N1 strains going around the world.

In fact keeping the frequent genetic changes of the virus in mind, the US Department of Health and Human Services (HHS) has already authorized the development of a second vaccine formulation using one of the new strains of H5N1 that has emerged as it spreads from birds to people. As on date, companies are already developing and testing vaccines based on the strain that infected people in Vietnam in 2004, but at least two substrains have since emerged. The US researchers are now creating a new vaccine targeted at the second variety called A/ Indonesia/5/2005. The second vaccine may give drug makers a headstart if a version of the virus similar to the Indonesia strain begins spreading in people. It is estimated that it will take at least six months to produce a bird flu vaccine once a pandemic breaks out.

Meanwhile, HHS is also looking for proposals from companies to make vaccines using new technologies that do not rely on

eggs, as current influenza vaccines do, and perhaps using boosters known as adjuvants to stretch the vaccine supply.

NIAID initiates clinical trials on flu vaccine

As part of the Federal government's efforts to prepare for a possible pandemic involving avian influenza, the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, has been supporting the development and testing of candidate avian influenza vaccines. The Institute has begun a series of clinical trials to evaluate certain vaccine candidates.

In 2004, NIAID awarded two contracts for production and clinical testing of investigational vaccines against H5N1 to Sanofi Pasteur (Swiftwater, PA) and Chiron (Emeryville, CA). Both the companies are producing vaccines made from inactivated H5N1 viruses for NIAID to test in clinical trials. Under these contracts, Sanofi Pasteur has already delivered more than 8,000 doses to NIAID; Chiron will produce 10,000 doses, which shall be delivered to NIAID within the next few months.

The first clinical trial began in April 2005. It is testing the H5N1 vaccine produced by Sanofi Pasteur in 451 healthy adults aged between 18 and 64. This trial which is closed to enrollment, is investigating the safety of the vaccine and its ability to generate an immune response. A similar trial of the Sanofi Pasteur H5N1 vaccine in persons aged 65 and above, which began in October 2005, has completed recruitment. Another similar trial in children aged 2 to 9 years old opened in January 2006 and has also completed recruitment.

Currently, NIAID is testing a range of concentrations known as dosage levels of the Sanofi Pasteur H5N1 vaccine to evaluate safety and immunogenicity.

The preliminary data from the Sanofi Pasteur H5N1 vaccine shows that two 90-µg doses of the H5N1 candidate vaccine generated the highest immune response among those doses tested. NIAID is also discussing with manufacturers the production of an H5N1 vaccine with adjuvants-alum and MF59.

Avian flu diagnostic kit

HHS' Food and Drug Administration (FDA) has recently approved of a new laboratory test to diagnose H5 strains of influenza in patients suspected to be infected with the virus. The test was developed by another HHS agency, the Centers for Disease Control and Prevention (CDC).

The approved product is called the Influenza A/H5 (Asian lineage) Virus Real-time RT-PCR Primer and Probe Set. The test provides preliminary results on suspected H5 influenza samples within four hours once a sample arrives at the lab and testing begins, whereas previous testing technology would require at least two to three days to render results. If the presence of the H5 strain is identified, then further testing is conducted to identify the specific H5 subtype (e.g., H5N1). Information obtained from this test will be used to track cases of illness with this strain of virus.

US companies foray in bird flu drugs

Many of the US companies are currently conducting research either alone or in collaboration to develop a vaccine for the lethal flu. For example, Novavax Inc. is using the Virus Like Particle (VLP) approach to develop a vaccine, which uses recombinant DNA technology to produce antigenic structures that mimic a virus to produce a protective immune response without the risk of infection or disease. This is the first time that VLP technology has been applied to create an influenza virus vaccine. The technology is a particularly good fit for addressing pandemic influenza because it obviates the reliance on the supply of embryonated eggs for the production of the vaccine. Novavax has recently adopted a manufacturing process that reduces contamination risk and produces high, cost-effective yields of the influenza VLP vaccine.

Novavax has tied up with Bharat Biotech International based in Hyderabad, India to pursue the rapid development of pandemic influenza vaccine for India and certain other south Asian markets. Bharat Biotech will fund 100 percent of the pre-clinical and clinical studies for these markets and assist in developing an efficient manufacturing process for the VLP-based influenza vaccine.

Antigen Express, Inc., the wholly owned immunotherapeutics subsidiary of the US-based Generex Biotechnology Corporation has presented its Antigen Express H5N1 avian influenza vaccine program at the Third Annual DNA Vaccines Forum held in London, the UK. The strategy employed by Antigen Express focusing on the development of its novel H5N1 avian influenza vaccine utilizes small portions of the H5 protein that are modified to enhance antigen-specific stimulation of T-helper cells. Upon infection, such T-helper cell responses enhance the speed and strength of neutralizing antibody production. It is anticipated that the vaccine being developed will both impart some level of protection on its own and enhance the activity of other types of avian influenza vaccines, including DNA vaccines.

Another company, DelSite Biotechnologies has partnered with Invitrogen for process development of Avian H5 influenza nasal vaccine. DelSite is developing a nasal powder vaccine for pandemic avian influenza that combines its proprietary GelVac vaccine delivery system with an avian H5 influenza whole virion antigen. Preclinical studies were initiated in December 2004 and the formulation development has been going on using antigen produced at laboratory scale. The agreement with Invitrogen will allow DelSite to transition from the current lab scale procedures to a scalable manufacturing process in advance of initiating cGMP production for clinical trials.

And Baxter International is working with the US National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), to develop a cell culture-based H5N1 candidate pandemic influenza vaccine. The company will be providing the candidate vaccine to NIAID for clinical testing. Baxter's vero-cell system is capable of producing high yields of influenza virus without the addition of any animal-derived serum.

The European subsidiary of Baxter has received a contract from the National Health Service (NHS) in the UK to produce a stockpile of two million doses of candidate H5N1 influenza vaccine based on an avian strain. Under the agreement, Baxter will complete delivery of the stockpile to the NHS in 2006.

Regulatory approvals

To facilitate the vaccine manufacturer efforts, the US FDA has recently given them a blueprint for gaining approval for pandemic vaccines. It has laid down lucid guidelines for flu vaccine clearance to hasten their development and availability. The guidance also spell out steps needed for development and evaluation of vaccines using new technologies such as cell culture and recombinant manufacturing and potential approaches to stretching limited pandemic vaccine supplies such as adjuvant and different vaccine delivery methods.

Further as a pandemic vaccine needs to be a close match to the actual pandemic virus, commercial production cannot begin prior to emergence and characterization of the pandemic virus. WHO has, however, encouraged industry and regulatory authorities to develop fast-track procedures for licensing and marketing authorization of a pandemic vaccine, and this has been done.

Hungarian vaccine

Meanwhile, Hungarian researchers have devised a vaccine for humans against the current form of the H5N1 bird flu virus. This vaccine was developed by the Hungarian company Omnivest and has been approved by the country's pharmaceutical authorities. It is a product manufactured from an aluminium and phosphate viral gel which can be used to protect people working in close proximity to diseased birds.

Researchers believe that even if the virus mutates they would not have to experiment with new technology but would be able to manufacture a real vaccine within about eight weeks. Hungarian researchers have been working for six month to manufacture a vaccine against the current form of H5N1.

This is the first time the world health authorities are trying to stop a global influenza pandemic before it begins. The last influenza pandemic swept the globe in 1968. Many public health officials believe the world is overdue for another one.

Rolly Dureha