SCRIP
DRUG MARKET DEVELOPMENTS
July | 2008 Vol. 19 | No. 7

Influenza: the avoidable killer

Influenza is a disease of global health significance against which the fight is far from over. The current environment surrounding influenza is therefore one of considerable investment, regulatory and policy change, and global co-operation efforts in an attempt to minimize the burden of seasonal influenza and maximize preparedness for a pandemic.

By Claude Allary and Dr Meredith Edwards

Despite the long-standing availability of vaccines, seasonal influenza still accounts for 300,000-500,000 deaths annually worldwide,[1] and creates considerable economic strain and burden on healthcare providers, during the intense four- to five-month influenza season each year. Not only do challenges remain in the reduction of morbidity and mortality caused by seasonal influenza, a real threat of pandemic influenza is today a genuine and increasing concern. The current environment surrounding influenza is therefore one of significant investment, regulatory and policy change, and global co-operation efforts in an attempt to minimize the burden of seasonal influenza and maximize preparedness for a pandemic.

Alongside the fiscal, economic, and medical challenges, is that of social awareness of the disease. According to Mr Peter Cook, CEO of Biota, an Australian biotech company active in developing drugs for influenza, "attitudes have to change; influenza is a big killer and nobody needs to die from this virus. Short-term challenges will be in overcoming apathy towards influenza, maintaining focus and continuation in fighting this disease, and getting products into use. In the long-term, there is no silver bullet argument for the influenza virus, a multifaceted approach is required."

Dr Michael Watson, executive vice-president, research and development of Acambis in the UK, also predicts future hurdles. "As with all vaccines, as coverage increases and disease disappears, people consider the need for vaccination less important. There is a huge educational challenge to help people to understand that the disease is only invisible because of the vaccine and that to keep it invisible vaccination coverage must stay high."

Influenza, commonly called the flu, is an acute respiratory illness that affects the upper and/or lower respiratory tract and is caused by viruses. Influenza virus strains are classified by their core proteins (A, B or C), species of origin (eg, avian, swine, human), geographic site of isolation, serial number, and for influenza A, by subtypes on the basis of the surface glycoproteins: hemagglutinin (HA) and neuraminidase (NA).[2, 3] Influenza A viruses are responsible for seasonal winter outbreaks of varying intensity, and on occasion, global pandemics of disease. Influenza B can also cause seasonal epidemics but usually only every two to four years, and is not thought to initiate pandemics, and influenza C viruses usually cause sporadic cases of mild cold-like illness only.

While pandemic flu outbreaks are not predictable, seasonal flu outbreaks usually occur between November and April in the Northern hemisphere. Person-to-person spread is by inhalation of infectious respiratory secretions usually through coughing and sneezing, and features of uncomplicated disease include sudden onset, fever, congestion, headache, sore throat, dry cough, aches and pains, and fatigue. An affected individual typically experiences five to six days of restricted activities, of which three or four are spent in bed. Serious complications can include secondary bacterial pneumonia and primary viral pneumonia, with a high mortality rate associated with the latter due to the inefficacy of antibiotics.

A significant economic burden

Influenza affects people of all ages, and places significant economic drain on individuals, healthcare services, and society. Recent estimates report there are 24.7 million cases of flu in the US annually with around 334,000 hospitalizations, 41,000 deaths and a total annual economic burden across all age groups of $87.1 billion.[4] Direct costs of medical treatment for influenza were calculated at $10.4 billion (12%), and indirect costs at approximately $76.7 billion (88%).[5] Days of productivity lost due to illness have been estimated at 44 million and lost earnings due to lost productivity from illness and loss of life have been calculated at $16.3 billion annually, about 20% of the total burden of influenza.[5]

Market size

The vaccine market can be divided into three groups: seasonal vaccines, pandemic vaccines (pre-purchase and on-demand agreements), and prepandemic and interpandemic vaccines (stockpiling). In 2006, the worldwide influenza vaccine market was estimated to be worth between $1-1.3 billion, and the majority of this market was from seasonal vaccines with approximately 350 million seasonal flu vaccine doses administered in western markets during the 2005-06 season. This market value figure also includes some vaccine stockpiling. Stockpiling with prepandemic vaccines, which would be used to boost the immune system in preparation for a pandemic, is an area of increasing activity.

It is challenging to predict the potential value of the vaccine market in the event of a pandemic, as there are two assumptions that have to be made. Firstly, the financing structure to be adopted under pre-purchase agreements (PPAs), which commit suppliers to provide certain quantities of the pandemic vaccine on the emergence of a pandemic. Secondly, it is difficult to put a dollar value on the on-demand segment which is dependent on a pandemic occurring.

Demand for pandemic vaccines under a two-dose scenario has been reported as approximately 13 billion doses (with the current world capacity under antigen-sparing scenarios being at best 2.4 billion doses). In addition, the global stockpiling market for influenza antiviral treatments is currently estimated to be worth $5.6 billion.

Prevention and treatment

The approach to influenza management is prevention, with vaccines and/or antiviral drugs, and treatment, in the form of supportive treatment and antiviral drugs.

The high rate of mutation and viral evolution of influenza prevents the immune system protecting against the new variants,[6] thus forcing the production of new vaccines each year, based on the latest virus strain. Importantly, the protective efficacy of these vaccines is highly dependent on the closeness of the strains in the vaccine to the viruses that are circulating during the outbreak. If there is a good match, vaccines can offer 50-80% protection against clinical influenza.[6]

Currently available vaccine preparations are the trivalent inactivated influenza vaccine (TIV, intramuscular, such as Sanofi Pasteur's Fluzone, Novartis's Fluvirin, CSL Biotherapeutics' Afluria etc) and a trivalent live-attenuated, cold-adapted influenza vaccine (LAIV, intranasal, Medimmune's (AstraZeneca) FluMist), which are both based on induction of virus-neutralizing antibodies primarily against the viral HA.

In terms of antiviral drugs, there are currently two classes used in the prevention and treatment of influenza: M2 inhibitors (amantadine and rimantadine), and neuraminidase inhibitors. The NA inhibitors, zanamivir (Biota/GSK's Relenza) and oseltamivir (Gilead Sciences/Roche's Tamiflu), are active against both influenza A and B, with zanamivir receiving approval for influenza prevention, in addition to treatment, in 2006. Antivirals play an important part in the armory against influenza, as explained by Mr Cook, "people need to see the approach to influenza as a multifaceted solution of which neuraminidase inhibitors play a useful and indispensable part."

Strategies for protecting against influenza

Strategies for reducing morbidity and mortality of influenza on a seasonal basis include annual vaccination programs, prophylaxis with antivirals, and secondary preventive measures (isolation, hand washing, personal hygiene etc).

Public policy regarding flu vaccination guidelines varies by country, but in many countries an 'at-risk' group is defined for which vaccination is recommended or reimbursed. This 'at-risk' group can include adults over 65 years, people (including children over six months) with certain chronic diseases, children taking aspirin, pregnant women, and healthcare/emergency service providers. However, despite widespread policy recommending annual vaccination, there have been claims that evidence supporting flu vaccination is weak[7, 8] particularly in reducing mortality in the elderly. Indeed, despite widespread public health measures to immunize over the past 20 years, no major reduction in influenza-related mortality has been seen.[8] In addition, it seems vaccination in the elderly does not necessarily translate into a reduction of illness burden during winter, as reported by Britain's Health Protection Agency (HPA) in 2007. Some researchers argue that many vaccine studies contain potential bias with study populations including only healthy seniors aged under 70, and endpoints based on overall mortality or illness rather than specific influenza mortality rates.[7]

However, this age group does seem a logical target given that 90% of deaths from seasonal influenza relate to people aged 65 or above.[7] There is therefore a strong theoretical justification for vaccination in the elderly, but if other population groups are neglected, especially children who are known to carry and spread the disease, the general consensus is that this alone will not be enough.

Vaccination of all healthy children or healthy adults, those considered at less risk of dying, is also a matter of debate. Dr Watson stated, "Ultimately we may see everyone in the population being offered vaccination against flu." In Ontario, Canada, free influenza vaccination is offered to all citizens, but the US is yet to follow suit. The US Centers for Disease Control and Prevention (CDC) held a workshop in late 2005 addressing this question and concluded that whilst vaccination of all children was an important goal and that vaccination should be made available to adults who want to protect themselves, vaccination of all adults was not to be made a recommendation.

Threat of pandemic

Three influenza pandemics occurred during the 20th century, and it is widely agreed that currently, the question is not "if" another pandemic will occur, but rather "when" –and of what severity. The imminent threat of a pandemic so early into this new century has been fuelled by the appearance of a highly pathogenic H5N1 avian influenza with pandemic potential in poultry, which has been sporadically transmitted to humans. H5N1 human infections in April 2008 totalled 381 cases according to the WHO, with fatalities of 241 (fatality rate >60%).[9] The H5N1 virus is not the only possible source of a pandemic, and other novel strains such as avian H9N2 and H7N3 influenza strains are also potential concerns –which highlights the biggest problem in preparing for, or trying to avoid, a pandemic: no one can predict what the virus strain will be.

Ideally, once the pandemic strain is known, the availability of a safe and effective pandemic vaccine, used preventively to vaccinate the global population, would seem the most efficient and cost-effective way to combat such a disaster.[10] However, the clause in this statement –'once the strain is known' – presents a major hurdle. The only true pandemic vaccine is a matched isolate vaccine against the strain of virus circulating in a pandemic. Other difficulties in the development of such a vaccine are current limitations in global production capacity (although efforts are being made to address this, as discussed later), and the time needed to manufacture it.

Given that by definition the pandemic strain will not be known until a pandemic is triggered, pre-pandemic vaccines are therefore being prepared from influenza viruses that have pandemic potential. The first pre-pandemic vaccine of this nature to be approved by the European Commission was announced in May this year. The vaccine, GlaxoSmithKline's Prepandrix, is indicated for active immunisation against the H5N1 subtype of the influenza A virus in people aged 18 to 60. GSK has already agreed contracts with Finland, Switzerland and the US as well as several other countries, and says that the vaccine could be stockpiled by governments. Whilst a justifiable and positive approach, the fact still remains that this strategy is based on hedging bets on likely pandemic strain candidates when the reality could be a completely unexpected mutation.

The time needed to produce a vaccine with traditional egg-based inoculation methods can be between six and nine months. Cell-culture production techniques cut this time to four months. However, WHO simulations of pandemic spread show that vaccination within the first three months of an outbreak would increase the probability of containing a pandemic. The US Department of Health awarded contracts worth together over $1 billion to develop cell-based vaccines in May 2006. The contracts went to GSK, Medimmune, Novartis, DynPort Vaccine and Solvay Pharmaceuticals. Novartis subsequently announced the UK launch of the first cell-based flu vaccine, Optaflu, in December last year for use in the 2008-9 influenza season. However, it seems that enthusiasm of some companies for this technique has dampened due to technical problems and also the cost of this method, which has not yet been proven to cost less than egg-based vaccine production.

The issue of time also presents a problem from a clinical development perspective, a point raised by Dr Stuart Robinson, head of business development at UK-based biotech PepTcell, "A new pandemic is expected in a few months or years and a big problem is that the research just cannot be done fast enough. A Phase III study in influenza requires a full flu season and thousands of patients." Therefore, another time saving strategy has been regulatory reform to allow for a mock-up system whereby the European Medicines Agency (EMEA) can review the safety, efficacy and quality of vaccines in advance of a pandemic being declared. Once the specific pandemic virus strain is known, a variation to the core dossier can then be approved in a matter of days. The first mock-up vaccine to receive a positive opinion by the EMEA was GSK's Daronix in December 2006. This was followed by Novartis's Focetria in February 2007 and then GSK's Pandemrix in February 2008. Therefore, whilst there have been regulatory adaptations to try and ensure that the time to availability of vaccines in the event of a pandemic is as fast as possible, the equilibrium between saving time and maintaining safety is a careful balance, according to Dr Robinson. "There is an imbalance between the expected timeline of a pandemic and the time needed to develop a new product. Accelerated development is needed but this can be a risky strategy so it is necessary to find the balance."

Who is best prepared?

Additional causes for concern in preparing for a pandemic have been related to product capacity limitations, or put more simply, demand outstripping supply. The WHO has stated that it is probable that insufficient production capacity will restrict global access to the pandemic vaccine, at least during the first phase of the pandemic. The WHO Global Vaccine Action Plan recommends that countries help manage this problem by developing seasonal influenza vaccination programs if they can afford to, and increasing influenza vaccine coverage in existing programs, thus providing industry with a clear forecast of demand and ensuring an incremental increase in seasonal vaccine production capacity.

Significant investment has therefore been stimulated in seasonal manufacturing facilities driven by the threat of pandemic. Roche announced in April 2007 that by using its own factories, third party manufacturers and licensing agreements in India, China and Africa, it was able to produce more than 400 million Tamiflu treatments annually such that supply orders from more than 80 countries (totaling approximately 215 million treatments) could be fulfilled. GSK announced in September 2006 plans to invest 500 million euros in a vaccine production site in northern France and Sanofi-Aventis confirmed late last year that it had invested 64 million euros to build a vaccine plant in China for the domestic market. The latter deal represented the biggest foreign investment to date in the biopharmaceutical field in China. Dr Watson explains, "We are entering a very important phase, with increasing vaccine supplies giving us the opportunity to expand flu protection to the whole population, such as the younger adults and children who can benefit greatly from vaccination."

The consequences of poor preparedness for an influenza pandemic could be catastrophic. French researchers[11] predicted in late 2005 that in the absence of control measures, half the world's population could be affected by a pandemic within 60 days and almost all cities within five months, with 500 million cases and four million deaths. This would appear

a conservative estimate when compared with the extremely severe and extensive pandemic of 1918, which resulted in more than 50 million deaths worldwide. This very real threat, in terms of mortality, morbidity and socioeconomic and financial cost (estimated at $2 trillion globally), has triggered countries worldwide to initiate and implement pandemic preparedness plans with varying degrees of political reform and increased investment. The WHO has taken the lead in coordinating, guiding, and stimulating these efforts, however it has been up to individual governments to decide on the best approach for their country.

Levels of pandemic preparedness and investment vary by country. Strategies fall into pharmaceutical (antiviral stockpiling, purchase of pre-pandemic vaccines, and signing pre-purchase agreements (PPAs)) and non-pharmaceutical (publishing pandemic preparedness plans, infection control etc) categories.

The US has been leading the way in terms of investment. President George Bush asked congress in late 2005 for $7.1 billion in emergency funding to prepare for a possible avian influenza pandemic. This included $1.2 billion to make 20 million doses of a vaccine against the current H5N1 strain, $2.8 billion to accelerate new flu-vaccine technology and $1 billion to stockpile more antiviral drugs in addition to the 2.3 million treatment courses already stockpiled at that time. Bush also asked for legislation to be passed that would reduce liability for influenza vaccine manufacturers. In November 2006, GlaxoSmithKline, Novartis and Sanofi-Aventis all announced US government contracts to supply H5N1 vaccine for stockpiling. The deals were all with the US Department of Health and Human Services (HHS) and were worth $40 million to GSK, $40.95 million to Novartis and up to $117.9 million to Sanofi-Aventis. Given the limited production capacity in the US, the 27.5 million doses ordered from GSK were to be manufactured in Canada, and Novartis announced it would produce the pre-pandemic egg-based vaccine at its facility in England, as the only plant licensed to manufacture flu vaccines internally was that of Sanofi Pasteur in Pennsylvania.

The US is acutely aware that its market is underserved and there has consequently been considerable public and private pressure to increase local production. Investment from funding in 2005 to remedy this deficit is now coming to fruition with the largest planned manufacturing facility for Novartis in North Carolina expected to be operational by 2013. On the other hand, Canada has emerged as a pioneer in pandemic preparation, establishing a domestic production capacity to meet the requirements of its entire population and already achieving nearly all of its targets for preparedness.

Europe is considered vulnerable to a pandemic due to its geography, population density and an already existing presence of the H5N1 strain in poultry. Despite this, overall preparedness is considered suboptimal with the WHO releasing a report in October 2007 stating that inadequate advance planning, including inadequate border control and poor on-the-ground administration and delivery of antivirals and vaccines, could threaten EU security. An EU-wide strategy for preparedness was attempted but proved unsuccessful with the European Commission Health Ministers failing to come to an agreement to proceed with a creation of a European strategic stockpile of antivirals in 2006. The responsibility was consequently handed to each national authority to ensure sufficient resources in the event of a pandemic. However, the Commission did announce 27 million euros in funding in September 2007 for 11 new research projects on pandemic influenza and avian flu.

To date, most EU countries have focused on antiviral stockpiling and matched isolate PPAs, with only limited vaccine stockpile purchases. The UK is regarded as the leading country in Europe in terms of pandemic preparedness. The British Department of Health has awarded advanced supply contracts worth £155.4 million over the next four years to GSK and Baxter Healthcare. It is also planning to double its stockpile following claims that the current supply of 14-16 million courses of Roche's Tamiflu (covering 25% of the population) must be tripled if a flu pandemic is to be effectively controlled. France is one of the next best prepared European countries, with initiatives in antiviral stockpiling planned to cover 50% of the population, PPAs to cover 100% of the population and significant hygiene promotion. Germany has stockpiled 7.7 million antiviral treatments in addition to vaccine PPAs. Italy's preparedness is considered good with coverage of 8.5% of the population with antiviral stockpiles and PPAs for 36 million doses of vaccine, however some believe there is weakness in the operational details, such as logistics and procedures to be followed in the event of a pandemic. Likewise, Spain is moderately prepared but doubts remain about its operational effectiveness.

Whilst Europe is vulnerable, and the US remains very concerned, Asia is considered to be the epicentre in terms of vulnerability. A pandemic, if it occurs, will likely start in this region. China is recognized as the most vulnerable country in terms of preparedness with no clear evidence of vaccine stockpiling or PPAs, however there is strong international pressure to reinforce influenza control. Hong Kong and Singapore, both affected by the SARS crisis of 2003, appear to be the best prepared in this region for a potential pandemic. Taiwan also seems well prepared with strong influenza surveillance programs and advanced pandemic planning and preparedness.

Future innovation

There are a variety of promising novel approaches being explored or developed against the influenza virus. Dr Watson believes most of the truly innovative new approaches will come from small biotech companies and academia, which has been the case for the vast majority of new vaccines developed over the past 10-15 years. "Vaccines are so complex now, with the choices of antigen, production platform, delivery platform, and adjuvants so broad that it is just impossible for any one company to be able to keep up with all these elements on their own. Vaccine companies need to embrace specialisation and partnerships," he commented.

M2e vaccines

Much research is ongoing into the possibility of developing a 'universal' flu vaccine which would cover for annual variations and allow for better protection against a pandemic. A much talked about approach to this goal are the M2e-based vaccines. These vaccines are proposed to generate a robust antibody response against the virus ion channel protein M2 which is highly conserved during virus antigenic change. Acambis is one company developing such a vaccine. Its recombinant vaccine, ACAM-FLU-A, which uses hepatitis

B core protein to deliver M2e, has completed a Phase I trial that demonstrated good tolerability and immunogenicity in man. It has also demonstrated protection of ferrets against avian flu. Dr Watson said that ACAM-FLU-A, which is being developed in conjunction with Professor Fiers and his team at the University of Ghent in Belgium, is "the most advanced of the M2e vaccines with proof of principle preclinical data and clinical data in man".

T cell epitopes vaccines

Another exciting approach to a universal vaccine is being developed by PepTcell. Its new candidate synthetic influenza vaccine (FLU-v) contains multiple T cell epitopes that are present within all influenza viruses. These viral epitopes stimulate cell mediated immunity rather than humoral immunity and could possibly confer long term immunity. The company's Dr Robinson said: "analysis of influenza strains going back 60 years showed that the peptides present in FLU-v have not changed during this time, are not affected by antigenic drift or major mutation, and are present in existing strains of both human and avian influenza strains". Results of preclinical studies of FLU-v in transgenic mice were published in the European Journal of Immunology[12] in 2007 that showed protection in 60% of mice from a lethal challenge of influenza. This vaccine is currently undergoing toxicology studies with plans for a Phase I study in early 2009.

Antivirals

In the field of influenza antivirals, there are next-generation flu drugs with improved product profiles that could compete with Roche's Tamiflu. One such product is CS8958, a long-acting neuraminidase inhibitor (LANI) which is being developed by Biota and its collaborator the Japanese firm Daiichi Sankyo, which combined their LANI research programs in 2003. Biota's Mr Cook said that CS8958 has completed Phase II trials in Japan, and is also undergoing parallel Phase I studies in a different population in the UK. He stated that the results of these studies are expected to be in the public domain by the end of 2008. One of the key potential advantages of Biota and Daiichi-Sankyo's antivirals is the dosing frequency, being a once only dose for treatment and once weekly dose for prophylaxis, compared with twice daily for five days for treatment with Tamiflu.

Other innovative approaches in development include alternative administration methods such as US based Iomai's flu vaccine patch, which uses split-virus antigen. Whilst a Phase I study showed that injected vaccine prompts a greater immune response compared with the patch vaccine, the needle-free approach offering the possibility of self-administration could have several potential benefits. Iomai was acquired by Intercell in May for $189 million. Novel approaches to flu diagnosis are also under development. Franco Italian company STMicroelectronics, in partnership with Veredus Laboratories (Singapore), launched the first molecular test for flu, VereFlu in March this year. This product is reportedly able to accurately identify the strain of flu in two hours.

References

1. Kamps BS, Hoffmann C and Preiser W (2006) Influenza report. Flying Publisher.
2. Rennels MB, Meissner HC, and the Committee on Infectious Diseases (2002 Technical Report: Reduction of the Influenza Burden in Children. 110(6):e80.
3. Stephenson I (2008) Epidemiology, pathogenesis, clinical manifestations, and diagnosis or avian influenza. UpToDate.
4. Williams JP and Lednar W (2002) New developments in influenza vaccine technology: A potential new prevention strategy for employers and managed care organizations. Am J Manag Care. 8:S143-S154.
5.. Molinari N-A, Ortega-Sanchez IR, Messonier ML et al. (2007) The annual impact of seasonal influenza in the US: Measuring disease burden and costs. Vaccine. 25(27):5086-96.
6. Hibberd PL (2008) Influenza vaccination in adults. UpToDate.
7. Jefferson T (2006) Influenza vaccination: policy versus evidence. BMJ 333(7574):912-5
8. Simonsen L et al. (2007) Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. Lancet Infect Dis 7(10): 658-66.
9. WHO. Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO. 30 April 2008
10. Osterhaus A (2007) Editorial. Pre- or post-pandemic influenza vaccine? Vaccine. 25:4983-4984.
11. Flahault A, Coudeville L, Vergu E and Grais R. Impact of Control Measures for Limiting the Geographic Spread of a Pandemic Influenza. Presentation 45th Annual ICAAC, Washington December 16-19 2005.
12. Stoloff GA and Caparros-Wanderley (2007) Synthetic multi-epitope peptides identified in silico induce protective immunity against multiple influenza serotypes. Eur. J. Immunol. 37: 2441-2449.

Claude Allary is managing partner and Dr Meredith Edwards is a consultant at Bionest Partners – a management consulting and corporate finance firm focused on the life sciences sector based in Paris and New York.