Variability is its specialty

Influenza vaccine shortages and the spectre of an avian influenza epidemic

In early October 2004, the US Food and Drug Administration (FDA; Rockville, MD, USA) announced that influenza vaccine supplies for the coming winter season would be dangerously low. The vaccine produced by Chiron (Emeryville, CA, USA) in the UK was contaminated with bacteria and was therefore unusable, which effectively cut the total US supply in half. The news unleashed a veritable frenzy in the USA, where citizens are unaccustomed to healthcare rationing. 'Medical tourism' has been one creative response to the vaccine shortage: Americans are paying US\$105 to take the high-speed ferry from Seattle, Washington, to Victoria, British Columbia, or are crossing other borders into Canada to get influenza vaccines. Earlier this autumn, pictures of the elderly waiting in line for hours for an influenza shot, and the death of one woman who was queuing in the hot sun in the southeastern USA, dominated the news coverage.

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To deal with the clamour for the vaccine, the US Centers for Disease Control and Prevention (CDC; Atlanta, GA, USA) convened an ethics committee to draft principles for the future use of influenza vaccines and to determine who has the highest priority—the elderly, infants, children or the chronically ill. Meanwhile, federal and local authorities made deals with foreign governments to buy additional doses of vaccine. The shortage even became a campaign issue before the presidential election,

Fig 1 | A colorized transmission electron micrograph of avian influenza A H5N1 viruses (in brown) growing in MDCK cells (in green). Image reproduced courtesy of C. Goldsmith, J. Katz and S. Zaki © (1997) Centers for Disease Control and Prevention, Atlanta, GA, USA.

with Democratic candidate John Kerry asserting that the lack of government subsidies for vaccine production was to blame for the fact that only two companies still produced influenza vaccine for the USA. President George W. Bush promised that he would try to obtain additional doses from overseas—a week after he said that it was unsafe to import cheaper drugs from Canada.

Because new virus strains emerge every year, the composition of a vaccine must be tailor-made. Depending on the virulence of the virus, supply sometimes outstrips demand, whereas at other times there can be a glut of the vaccine. Consequently, profits vary and companies are reluctant to deal with such uncertainty. In addition, the production of the vaccine in chicken eggs is slow and inflexible, and a last-minute shortfall can take on crisis proportions. However, the true extent of the problems with the system of producing

influenza vaccines became clear in November 2004, during a US Congressional investigation, when the FDA revealed that it had discovered substantial contamination problems at the Chiron facility in Liverpool, UK, more than a year ago. Instead of taking action against the company, they requested voluntary compliance. British authorities inspected the plant in September 2004 and found continuing problems, but were prohibited by law from sharing their findings and never passed their observations on to the FDA.

In an effort to shave a few months off the vaccine-production cycle to respond to an emerging pandemic, some companies are exploring cell-culture methods to replace the use of embryonated eggs

On the bright side, not everybody needs the vaccine. According to John Treanor of the University of Rochester's Medical Center (Rochester, NY, USA), influenza vaccination "is designed primarily to reduce morbidity and mortality, and probably has little effect on the transmission of influenza or the overall number of cases" (Treanor, 2004). A recent study estimated that only 43 million doses would be required to immunize high-priority groups, so the shortfall might not be of great importance. Maria Zambon, Director of the influenza laboratory of the UK Health Protection Agency in London, UK, agreed: "Just because you are vaccinated doesn't mean you won't get infected, it only means you won't get severely infected." How problematic a vaccine shortage will be depends on the severity of this year's subtype, she added.

INFLUENZA CHRONOLOGY

1918	The Spanish influenza pandemic kills more than 40 million people worldwide.
1936	The first influenza virus is grown in fertilized chicken eggs, which allows companies to produce large amounts of influenza vaccine.
1944	Americans are the first to be immunized against influenza.
1947	The newly formed World Health Organization (WHO) establishes its worldwide surveillance system to produce early warnings of epidemics.
1957–1958	The H2N2 Asian influenza pandemic kills 1 million people.
1968–1969	An H3N2 reassortment of a Eurasian wild waterfowl influenza virus with a human strain leads to a pandemic that claims 1 million lives.
1983–1984	An outbreak of an avian H5N2 epidemic occurs in the USA. The virus has a low mortality rate among humans, but 17 million birds are slaughtered to prevent its spread.
1997	The first case of a human infected with an avian H5N1 strain without intermediary mammalian infection is reported in Hong Kong, China. A total of 18 humans become infected and six subsequently die. The Hong Kong Government orders the destruction of the entire poultry population of the city.
1999–2001	An avian H7N1 epidemic in Italy mutates within 9 months into a highly pathogenic form. About 13 million birds are slaughtered.
1999	Hong Kong reports several mild cases of avian H9N2 in children.
2001	The WHO initiates its Global Agenda for Influenza Surveillance and Control.
February 2003	The avian H5N1 strain infects three humans from Hong Kong who visited mainland China, one of whom dies.
Feb/March 2003	Avian H7N7 appears in the Netherlands and starts spreading from birds to humans. More than 1,000 people become infected, 83 individuals fall ill and one person dies.
December 2003	Avian H5N1 breaks out in Korea, Thailand and Vietnam.
January 2004	The health authorities in Thailand and Vietnam report human infections with avian H5N1, which are linked to the Korean cases. Subsequently, another seven Asian nations report a total of 43 cases of humans who are infected with H5N1 from poultry.
October 2004	Thailand reports 12 deaths from H5N1 and another 17 infections. Vietnam reports 20 cases of human H5N1 infection.

However, the problem might be complicated by the resurgence of the highly pathogenic H5N1 avian influenza virus in domestic poultry in Asia during the past few months (Fig 1; see sidebar). “The current outbreak of H5N1 avian flu in Asia represents the most serious pandemic threat since 1968,” said Klaus Stöhr, the leading influenza expert at the World Health Organization (WHO). “[It] is a stark warning that conditions are highly favourable for the emergence of a pandemic virus.” This virulent strain was first found to infect humans in 1997 in Hong Kong, China. Although its spread was arrested by the prompt culling of the entire poultry population of the city, it re-emerged during late 2003 and early 2004. Earlier in 2003, another virulent strain of avian influenza, H7N7, surfaced in the Netherlands, causing one human death (Enserink, 2004). Albert Osterhaus, a virus expert at Erasmus University (Rotterdam, The Netherlands) described that outbreak in press reports as “a dress rehearsal for a real pandemic.”

According to the WHO, an influenza virus must fulfil three conditions to activate a pandemic: a new virus must emerge against which the population has little or no immunity, it must be able to replicate in humans and cause disease, and it must be transmissible among humans. The Asian avian influenza strain has already met the first two conditions. “What steps must occur for the virus to become easily transmitted to humans, we don’t know,” commented Richard Webby of St Jude’s Children’s Medical Center (Memphis, TN, USA). “But while we do know that there is a huge array of avian viruses in the aquatic reservoir, we have no way of assessing risk.” Zambon agreed: “We have no way of knowing whether a pandemic will occur, and when.” The WHO estimates that a new pandemic could cause between 20 and 50 million human deaths worldwide, compared with the Spanish influenza pandemic of 1918, during which at least 40 million people died.

Osterhaus has warned that the European Union must develop an avian influenza vaccine immediately; but according to Zambon, there are no such plans at present. Although Chiron and Aventis-Pasteur (Strasbourg, France) are working to develop a vaccine for the USA, testing did not begin until winter 2004 and it will not be available before the summer of 2005. The WHO convened a meeting in November 2004 with vaccine manufacturers and government

Fig 2 | A 1976 New Jersey Influenza Immunization Campaign. © (1976) Centers for Disease Control and Prevention, Atlanta, GA, USA.

representatives to set priorities that include collecting good scientific data on pandemic vaccine formulation, securing funding for clinical trials and exploring 'antigen-sparing' approaches to stretch limited supplies. Indeed, recent studies indicate that giving healthy adults 20–40% of the regular dose of influenza vaccine intradermally could be as effective as giving the full dose intramuscularly (Belshe *et al*, 2004; Kenney *et al*, 2004). In addition, two antiviral drugs—adamantanes and neuraminidase inhibitors—are available, although the supplies are limited. In an effort to shave a few months off the vaccine-production cycle to respond to an emerging pandemic, some companies are exploring cell-culture methods to replace the use of embryonated eggs. Aventis-Pasteur is collaborating with Crucell NV (Leiden, The Netherlands) to use a human retinal cell line to produce an H5N1 vaccine that cannot be grown in eggs because the virus is toxic to chicken embryos. Baxter International (Deerfield, IL, USA) is using a green monkey-derived cell line, Chiron is exploring the use of canine kidney cells for regular influenza vaccines, and Treanor is developing a baculovirus cell line in conjunction with Protein Sciences Corp. (Meriden, CT, USA).

The present vaccine shortage might not substantially increase the risk that avian influenza could recombine with human strains outside Asia to become transmissible among humans—but no one knows for sure. "In order for a reassortment of a human and avian flu virus to occur, you would need to have the rare conjunction of two rare events in a single individual," said Zambon. "Unfortunately, there is no evidence either way on whether these viruses are adapting to humans or not. Until we work out the 'rules' governing this adaptation, we will not be able to assess adequately the risk of a given virus," said Jeffrey Taubenberger, Chair of the Department of Molecular Pathology at the US Armed Forces Institute of Pathology (Rockville, MD, USA). "While there is no historical precedent for a highly pathological avian influenza poultry-based pandemic, unfortunately with influenza, variability is its specialty."

...the last two pandemics during the twentieth century were caused by a reassortment of a human strain with an avian influenza virus

Fig 3 | Stored boxes of swine influenza vaccine. © Centers for Disease Control and Prevention, Atlanta, GA, USA.

All influenza viruses are adapted to elude host defences by shifting genes to produce new antigenic variants while they replicate in humans and animals—a process known as antigenic 'drift'. A further characteristic of type-A influenza, which is not shared by type-B influenza, is its ability to swap or reassort genetic material—a process known as antigenic 'shift'. Conditions that favour antigenic shift include humans living in close proximity to poultry and pigs, which is one reason why influenza epidemics often originate in Asia. Pigs are susceptible to both avian and mammalian viruses, and can therefore serve as 'mixing vessels' in which new subtypes are created. Also of concern is the fact that H5N1 is able to infect domestic cats, which commonly live in close proximity to humans (Kuiken *et al*, 2004). According to the WHO web site, there is also evidence that, at least for some of the 15 avian influenza virus subtypes, humans themselves can serve as the mixing vessels. Because there is no immunity to a new subtype, and because no extant vaccines can confer protection against shifts, such recombination events have resulted in highly lethal pandemics—the last two pandemics during the twentieth century were caused by a reassortment of a human strain with an avian influenza virus.

Containing an H5N1 outbreak therefore requires further measures beyond monitoring infections and developing a vaccine at

top speed. "Measures to contain H5N1 in Asia include depopulation of affected birds, improving hygiene at sites of large commercial flocks, and improving communication—making workers aware of the risks," said Zambon. "The WHO is coordinating these efforts in Southeast Asia, but success is variable according to [the] country and willingness to accept that there is a problem," she added. Developing nations with lower gross domestic products are less likely to view the situation as problematic, and it is more difficult to control backyard poultry farms than commercial enterprises, Zambon said.

However, scientists are making progress in understanding some of the molecular mechanisms that underlie the destructiveness of influenza strains, such as H7 and H5. "Virulence data are accumulating, especially that the [haemagglutinin gene of influenza A] plays a role," said Taubenberger. "Our group has also generated data to show that the 1918 NS1 was an effective type I interferon blocker in human cells. The role of the immune response to the 1918 virus constructs as compared to other viruses in mice and tissue culture is being actively investigated, and it is very likely that the host response contributes to the pathophysiology of viral infections." In the tissues of victims of the 1918 influenza pandemic, scientists found severe lung pathology, massive pulmonary oedema and inflammatory responses, including interleukin-2R and interferon- γ ,

apoptosis, oxidative damage, and upregulation of T cells and macrophages (Tumpey *et al.*, 2004). The intrinsic properties of the 1918 strain's haemagglutinin and neuraminidase proteins obviously caused a more severe immune response, culminating in a far more destructive infection, according to the authors.

Another study of the 1997 H5N1 Hong Kong strain showed that it potently induces tumour-necrosis factor- α (TNF- α), which can cause serious complications through an exaggerated inflammatory host response (Seo *et al.*, 2004). Robert Webster from St Jude's Children's Research Hospital showed that, unlike other influenza viruses, the H5N1 subtype is resistant to the anti-viral effects of interferons and TNF- α , which he believes could also explain the extreme host response to the 1918 strain. He found that the pathogenicity of this virus is also related to the immune status of the host and the dose to which they are exposed—what proves fatal to one patient might be less serious for another. "But the ability to escape the first line of host immune defence may be an important determinant of pathogenicity of the influenza virus in humans, in whom interferon and TNF- α play an important role in reducing viral burden," Webster commented.

The current US flu vaccine shortage holds important lessons to be learned—and fast—if we are to face a potential pandemic, said Webby. Faster vaccine production, new vaccines, and improved and coordinated international efforts to report and contain outbreaks are imperative. At one extreme lies the threat of the 1918 pandemic. At the other extreme lies the situation that occurred in 1976, when US President Gerald Ford pressured Congress to allocate funds to vaccinate hundreds of millions of Americans against swine influenza (Figs 2,3). The epidemic never materialized—only liability cases from individuals who developed Guillaine-Barré syndrome after being vaccinated. "The bottom line is that, unless the government authorities of every country implement mechanisms that equitably limit vaccine liability, no prospective vaccine for H5N1, H7N7 or any other threatening influenza virus is likely to be produced for universal human use," according to Webby & Webster (2003). For a virus that specializes in variability, scientists and policy-makers must walk a narrow line between over-reaction to vaccine shortages and under-reaction in light of a possible avian influenza pandemic.

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A focus on the individual

Germany has begun to reform its university system to make it more attractive to both foreign and German scientists and students

In January 2003, *Time* magazine published a feature article on the 'brain drain' of the brightest researchers in Europe to the USA (Chu, 2004) and cited two German scientists who, on returning from the USA, were so upset about the situation that they planned to cross the Atlantic again as soon as possible. *The Scientist* was another journal that ran several articles about this problem (Stafford, 2004). The foreign press are not alone in highlighting the problem—these criticisms are also shared by German scientists. Thomas Tuschl, an assistant professor at Rockefeller University (New York, NY, USA), explained why he left a group leader position at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany, to work in the USA. "I had to get really good postdocs in order to withstand the competition," he said, and he found it easier to attract them to his laboratory at Rockefeller University than if he had stayed in Germany. Gunter Meister, one of Tuschl's postdocs who actually plans to return to Germany, was even more blunt. "[Science in] Germany is not attractive, not even for Germans," he said, referring to the arcane and unpredictable career paths for young scientists. Many science policy-makers and administrators in Germany share his view. "It is safe to say that the new academic generation was not sufficiently supported over the last few years," commented Hans-Jürgen Prömel, Vice President for Research at Humboldt University in Berlin, Germany.

Rather than nurturing the best and brightest, the post-war educational system in Germany focused on equality and equity, which ensured free and broad access to education but created mediocrity in many areas, including research

The good news is that the problem has dawned on both university presidents and the federal government in Berlin. Since she took office in 1998, Edelgard Bulmahn, the German Minister for Education and Research, has initiated various schemes to make Germany more attractive to both German and foreign students and scientists alike. The main initiatives are the creation of junior professor positions to give young scientists more independence earlier in their career, along with financial support for selected universities. In addition, the German government has increased its budget for education and research, despite strained finances: in late November 2004, the Ministry of Education and Research announced that the 2005 budget will see another increase of 4%. Although these developments are welcomed by many scientists and science administrators, for Germany to be able to compete effectively with the USA and other nations, these must be the beginning, not the end, of much needed reforms.