



EDITORIAL

Animals are the source of nearly all newly emerging infections. This has been demonstrated by the emergence of the West Nile virus, found in wild birds and mosquitoes, the SARS virus, found in pteropid bats, and of course the influenza A virus, found and spread primarily by free-living ducks. Indeed, all influenza A subtypes, divided on the basis of HA (to date 1–16) and NA (to date 1–9) antigens, have been found in migratory birds.

Due to rapidly changing human behaviour and animal ecology, infections are spreading faster and farther. Currently, an H5N1 avian influenza pandemic is looming over Europe and although human-to-human transmission has not yet been reported, the disease's burden on public and animal health is already enormous. Not only does the H5N1 AI virus have a death rate of over 50% in humans, millions of poultry, livestock and migratory birds are likely to die or be culled. In addition, poor coordination between different disciplines in response to influenza outbreaks is limiting our ability to deal adequately with the threat they pose to human and animal health.

To limit the effects of influenza on public health and livestock production, integrated and effective action from all the disciplines involved is urgently required. At ESWI's Second European Influenza Conference, 11–14 September 2005, Malta, the entire influenza stakeholder community was represented and were given ample opportunity to exchange information. The main outcome was indeed the acute need for a European Influenza Task Force: a well-structured collaboration among health experts, specialists in the fields of virology, epidemiology, pathology, ecology and agriculture, as well as policy makers, the European authorities and communication experts.

The duties of the task force would be to:

- Gain insight into the European picture of influenza, taking into account temporal

and geographical variation of influenza viruses in Europe and in those areas that may pose a direct threat to Europe. Besides human influenza viruses, those of several animal species like wild birds, poultry, pigs, horses and cats should be taken into account

- Prioritise research and integrate knowledge of different disciplines on human and animal influenza
- Advance early warning systems and intervention strategies for influenza outbreaks in humans and animals. Participation of industrial partners in this area is crucial
- Translate knowledge into policy advice, emphasising the integration of human and animal health strategies
- Increase the annual influenza vaccination rate to one-third of the human population in all European Union (EU) member states
- Create public–private partnerships between European authorities and vaccine manufacturers for research and development of pandemic influenza vaccine candidates and antivirals
- Establish adequate stockpiles of antiviral compounds for pandemic influenza preparedness in all EU member states.

The task force must be able to respond rapidly and effectively, therefore emergent data must be exchanged and integrated quickly. When the need occurs, outbreak management teams can be formed, consisting of task force representatives as well as local experts and policy makers from the affected countries. They would focus on geographical distribution and the species involved, and gain detailed knowledge of the different aspects of

the viruses and their interactions with hosts, assessing the risk of spread, and advising on the best options for intervention. During the SARS outbreak, the viability of this approach was shown by the World Health Organization teams formed to deal with this threat.

In line with its policy plan, ESWI intends to meet the stakeholders' needs. Currently, we are facilitating the formation of a European Influenza Task Force by helping to identify the respective participants and representatives, stimulating communication among them, and helping to create the political will and the required funding possibilities for this initiative. The following weeks will be crucial to the success of ESWI's initiative.

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INFLUENZA H5N1, UPDATE

Introduction

During outbreaks of highly pathogenic avian influenza (HPAI) in China and Hong Kong in 1997, human cases of infection with avian influenza A viruses of the H5N1 subtype were reported for the first time. Out of 18 confirmed cases, six were fatal. The culling of infected animals at live bird markets in December 1997 stopped the occurrence of new transmissions from birds to humans. However, during new outbreaks of HPAI in February 2003, two more fatal cases in a Hong Kong family with a travel history to China were reported.

Since December 2003, influenza A viruses of the H5N1 subtype again have caused massive outbreaks of HPAI in numerous Asian countries and again transmissions from infected birds to humans were reported. In China, Vietnam, Thailand, Cambodia, Indonesia and Turkey, and more recently in Iraq, a total of 170 confirmed human cases of H5N1 infections have been reported, of which 92 were fatal [1].

These events and the recent further spread of highly pathogenic influenza A viruses is of great concern considering the threat of new outbreaks of HPAI in poultry and the risk of the emergence of viruses with pandemic potential.

Host range

In addition to the transmission of avian influenza viruses from infected poultry to humans, the infection of various field species such as tigers and leopards, has been reported. In most of these cases the animals were fed carcasses of H5N1 virus-infected chickens. Horizontal transmission of the virus was also observed; in a tiger-breeding unit in Thailand, 147 out of 441 tigers died or had to be euthanised as a result of the consumption of infected chicken carcasses.

In order to better understand the pathogenesis of the virus and confirm its horizontal transmission, we have infected cats experimentally with a highly pathogenic H5N1 influenza virus [2]. As expected, the cats were very sensitive to infection with influenza virus A/Vietnam/1194/04 (H5N1).

In addition, two sentinel cats that were placed together with cats that were infected by the intratracheal route 2 days earlier also became infected. All cats developed clinical signs such as fever, and the disease was characterised as necrotising interstitial pneumonia by histopathology. In addition, with virus isolation and immunohistochemistry, virus replication was detected in various organs including liver, kidney, heart, brain and the submucosal and myenteric plexi of the intestines. Presence of the virus in nervous tissue of the gastrointestinal tract was only observed in cats that had been fed infected chickens. This raises the possibility that, via the lumen of the intestine, the virus can find a new portal of entry and disseminate to other organs. In all cases the presence of infected cells was associated with local inflammation and necrotic lesions.

The virus was not only excreted from the respiratory tract, but also found in the faeces of infected cats. This has also been the case in humans, which suggests that the virus can be transmitted via the faeco-oral route.

The observation that influenza A/H5N1 viruses currently circulating in Asia can infect cats, has a number of important implications:

- Cats are at risk during outbreaks of H5N1 for disease and mortality
- Cats not only could play a role in the spread of the virus within or between farms, but also in the transmission from birds to humans
- The infection of cats could provide the virus with the opportunity to adapt to efficient replication and transmission in a mammalian host, which could increase the risk of the emergence of a pandemic virus.

Clinical presentation

Most human cases of H5N1 infection concern individuals that have had close contact with infected poultry. Probable human-to-human transmission has been reported in isolated family clusters [3]. After an incubation time that can vary from 2 to 8 days, most patients develop high fever and an influenza-like illness with lower respiratory tract symptoms.

In a number of cases, diarrhoea was also observed and patients have been described with diarrhoea and encephalopathies without respiratory tract symptoms [3]. These findings correlate with the pathological changes we have observed in H5N1 virus-infected cats. It therefore cannot be excluded that in humans, viral replication in the central nervous system and the intestines is the cause of these symptoms. In any case, this atypical clinical presentation should be taken into account. Ultimately, viral pneumonia can lead to acute respiratory distress syndrome (ARDS) and multi-organ failure involving the heart and kidneys, resulting in death. As indicated above, the case-fatality rate is high (about 50%), however, the incidence of cases with milder illness is not known.

Geographic spread

Initially the spread of highly pathogenic influenza A/H5N1 viruses was restricted to countries in South-East Asia. From April 2005, wild birds, including geese at Qinghai Lake in central China, were infected with a virus variant that caused the death of thousands of birds. In July and August 2005, the virus spread further westwards causing outbreaks in poultry or wild birds in Western Siberia, Kazakhstan and Mongolia.

In October 2005, influenza A/H5N1 outbreaks were reported in poultry in Romania and Turkey, and in wild swans in Croatia. In December 2005, the Ukraine reported the first influenza A/H5N1 outbreak.

By February 2006, a rapid geographical spread of influenza A/H5N1 viruses had been observed. The virus was detected in poultry in Iraq, Egypt, India and Nigeria. In nine other countries – Azerbaijan, Bulgaria, Greece, Italy, Slovenia, Iran, Austria, Germany and France – the virus was detected in wild birds, especially swans [4].

The virus could have been spread by the transport of infected poultry or poultry products. It is also possible that wild birds were responsible for the further spread of H5N1 viruses into the European continent, although this has yet to be confirmed. Chances are that influenza H5N1 outbreaks will further

increase in those affected areas. During the winter months, wild birds with different

migratory routes can come into contact with each other in African countries or the Middle

East, where transmission of the virus between infected flocks and uninfected flocks can take place. There is a chance therefore, that during spring migration birds flying northwards into Europe have come into contact with infected birds. Alternative modes of virus spread include legal and illegal import of birds or bird products from endemic areas, as was reported in Belgium, the UK and Taiwan.

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EVOLUTION OF H3N2 INFLUENZA A VIRUSES IN HUMANS AND THE EFFECT ON SIALIC ACID BINDING

Winters in Europe are associated with the spread of influenza. In recent years, however, data from UK surveillance schemes such as the Royal College of General Practitioners Weekly Returns Service, suggest a decline in the severity of seasonal influenza indicated by fewer reports of influenza-like illness (ILI) [1]. Over the past 5 years, winters with less influenza disease have become the norm in England.

The human respiratory tract presents a formidable challenge to the influenza virus. Cilia lining the airway epithelium sweep foreign particles back up the mucociliary escalator and the glycocalyx – a complex web of glycosylated proteins and lipids – forms a barrier protecting the respiratory epithelium. Mucus is laden with decoy receptors in the form of sialyloligosaccharide-containing mucins, and innate defence molecules such as the collectins mannose-binding lectin (MBL) and surfactant protein-D (SP-D) bind to foreign glycoproteins as part of the antiviral host defence. In addition to immune surveillance, interactions between the virus and glycosylated receptors in the respiratory tract may drive evolution of the virus as it adapts to humans. Despite these factors, the influenza A H3N2 subtype has circulated continuously in the human population for almost 40 years, demonstrating the capacity of the virus for evolutionary adaptation.

In the mid-to-late 1990s, many influenza reference laboratories found that clinical influenza isolates could no longer agglutinate chicken erythrocytes routinely used in haemagglutination inhibition (HI) tests. As haemagglutinin relies on the interaction between viral haemagglutinin (HA) and sialic acid displayed on the surface of erythrocytes, this phenomenon suggested the receptor-binding characteristics of the circulating haemagglutinin must have changed in some way. To investigate this, we assembled a panel of viruses from the archives at the Health Protection Agency Centre for Infections, London, UK. This panel, which formed the basis for much subsequent work, comprised H3N2 isolates ranging from the pandemic-era of 1968–1969 through to modern times, and included representatives from many of the antigenic subtypes that circulated during this time. Isolates were carefully selected to avoid the influence of egg-adapted mutations in HA and therefore, only cell-grown material was included to preserve the receptor-binding properties of the original clinical isolate.

Haemagglutinin assays with the viruses revealed a clear decline in ability to agglutinate chicken erythrocytes over time, possibly due to loss of affinity for α -2,3-linked sialic acid found on these cells [2]. The exact nature of the observed receptor-binding

changes was investigated using glycopolymers displaying α -2,3 (3'SL) and α -2,6-linked (6'SL; 6'SLN) sialic acid synthesised in the University of Reading Chemistry Department, Reading, UK. Specifically, HA-binding affinity for 3'SL declined over time. Affinity for 6'SLN was more variable but recent viruses also had a low affinity for this receptor analogue. When these data were related to the molecular changes that occurred during evolution of the virus, it was clear to see that reduced binding to 3'SL and 6'SLN was accompanied by an increase in the number of potential glycosylation sites on HA from seven to 11 or 12. During antigenic drift, HA has become increasingly glycosylated to shield antigenic sites from the immune system. However, these bulky sugar chains added in the vicinity of the receptor-binding pocket might interfere with the HA–sialic acid interaction. Interestingly, using reverse genetics we found that deletion of a potential glycosylation site on HA changed the pattern of erythrocyte binding such that the virus regained the ability to agglutinate chicken erythrocytes.

The development of primary cell cultures of human airway epithelium (HAE) is an exciting innovation that has recently been used to study virus pathogenesis and cellular interactions of diverse respiratory viral pathogens including influenza virus, RSV, PIV3 and

SARS [3]. HAE accurately recapitulate human airway cellular morphology and the highly complex glycocalyx layer consisting of tethered and soluble mucins, many terminating in sialic acid. HAE developed at the UNC Cystic Fibrosis Center at the University of North Carolina, USA, were used to investigate the biological consequences of the receptor-binding changes that we had observed. Sialic acid receptors for human influenza (α -2,6-linked sialic acid) are widespread on the tracheobronchial epithelium and found on both ciliated and non-ciliated cells in HAE [3]. Accordingly, human strains of influenza A could efficiently infect HAE and cause widespread destruction of the ciliated epithelium.

Surprisingly, the avian virus receptor (α -2,3-linked sialic acid) was found on ciliated cells in HAE, and these cells were infectable with avian strains of influenza, although the infection was limited compared with human viruses. Moreover, the most recently isolated human viruses infected a greater proportion of non-ciliated cells compared with those isolated in 1969 shortly after the introduction of H3 surface antigen from an avian source. This perhaps reflects the decreased receptor-binding capacity of recent viruses for α -2,3-linked sialic acid found on ciliated cells, as demonstrated in haemagglutinin and synthetic sialic acid binding studies. The consequences for the virus of losing affinity for sialic acid and infecting a minor population of airway cells could be decreased virulence due to less efficient replication or reduced transmission.

Whether these properties of modern viruses translate to decreased virulence and less severe disease in humans is an interesting question. Highly glycosylated viruses are indeed less virulent in a mouse model compared to earlier less glycosylated viruses [4]. Furthermore, these highly glycosylated viruses showed increased susceptibility to neutralisation by the lung collectins MBL and SP-D, suggesting that reduced virulence may be due to enhanced recognition and clearance by sugar recognition molecules of the innate immune system.

Recent surveillance in the UK indicates a decline in reported ILI in the community [1], and it is interesting to speculate whether this is due to reduced transmissibility or

diminished virulence – the consequences of decreased receptor-binding affinity and increased HA glycosylation. Of course these epidemiological findings could also be driven by widespread immunity to H3 and greater impact of vaccination programmes. However, after such a prolonged circulation, the question is whether there is further capacity for H3 evolution? Furthermore, it remains to be seen whether the apparent decline of H3N2 leaves the door open for a new pandemic virus to emerge [5].

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A NEW AVIAN INFLUENZA VIRUS REASSORTANT H5N7 SHARES GENES WITH HIGHLY PATHOGENIC STRAINS

In September 2003, H5 influenza A infection was detected for the first time in Denmark in an outdoor-bred commercial flock of 12,000 mallards that had shown increased mortality for some time. Reverse transcription-polymerase chain reaction (RT-PCR) with sequencing identified the strain as a previously undescribed subtype combination, H5N7. The strain was isolated from pools of respiratory tissues, brain and internal organs.

Full genome characterisation of H5N7 revealed a possible reassorted strain of both low pathogenic and highly pathogenic avian influenza virus.

Identification of H5N7

Characterisation of the haemagglutinin (HA) gene revealed a 95.6% nucleotide sequence identity with a highly pathogenic (HP) H5N2

strain from Italy (A/Chicken/Italy/312/97) and the neuraminidase (NA) gene showed 96.8% nucleotide sequence identity with a HP H7N7 strain from The Netherlands (A/Chicken/Netherlands/01/03). The H5N7 HA sequence showed highest sequence identity to HP H5; however, the HA1/HA2 cleavage site sequence K-E-T-R, was without the multi-basic residues typical for HP strains [1]. The H5N7 strain showed a 98.1% HA nucleotide

sequence identity with two low pathogenic (LP) isolates of H5N2 avian influenza virus (AIV) (A/Duck/Denmark/65047-P8 and -p13/04) found in faecal samples from wild ducks in Denmark in 2004. Based on the finding of AIV H5, all 12,000 ducks were culled in order to eliminate the possibility of virus spread to commercial poultry with the additional risk of drifting into a HP type. No evidence of human AIV infection was demonstrated among the people handling the ducks.

The H5N7 subtype combination had not previously been reported and the possibility of reassortment in the internal proteins with HP AIV strains had to be addressed. The H5N7 strain possessed sequence characteristics of a LP virus strain and the chicken intravenous pathogenicity index value was 0.00; however, the H5N7 virus was isolated from multiple organ tissue cultures, a characteristic for HP AIV. Moreover, the combination of HA and the internal proteins might have unpredictable influence on the virulence and pathogenicity of a virus [2]. Therefore, it was necessary to characterise the full genome of the new H5N7 strain.

H5N7 possesses internal proteins of highly pathogenic origin

It is believed that all 16 subtypes of HA and nine of NA are perpetuated in the wild waterfowl population and reassort at high frequency. We full-length sequenced the genome of the H5N7 strain and made comparisons with HA and NA sequence homologues closest to H5N7, the LP A/Duck/Denmark/65047/04 (H5N2) and the HP A/Chicken/Netherlands/1/2003/(H7N7), respectively, and in relation to representatives of known genetic lineages of influenza A in the GenBank.

Although it is difficult to assign subtype origin of AIV internal genes, we found that the H5N7 strain most probably was a reassortant between a H5N2, H7N7 and possibly a H6 subtype virus (Figure). The basic polymerase gene 2 (PB2) of H5N7 was common to both H5N2 and H7N7 strains with a nucleotide identity of 97.2%. The nucleotide sequence of the PB1 gene was about 95% identical to both of its closest relatives H5N2 and H7N7. The acidic polymerase protein (PA) gene showed 98% identity to the PA gene of H5N2. The nucleoprotein (NP) gene showed highest

identity to a H6 subtype (A/Duck/Hong Kong/3096/99 [H6N2]) (96.9%), and grouped phylogenetically with the NP genes of A/Teal/Hong Kong/W31/97 (H6N1) and A/Quail/Hong Kong/G1/97 (H9N2), believed to have contributed to the internal genes of the 1997 HP H5N1 strains from Hong Kong (not shown). The matix gene (M) had 98.1% identity to H5N2 but the closest isolate in GenBank was that of a H6 subtype (98.6%) (A/WDK/ST/1737/2000 [H6N8]). The non-structural gene (NS) had greatest nucleotide sequence identity to the human fatal case isolate A/Netherlands/219/03 (H7N7) (98.4%). The NS gene of the H5N7 isolate belongs to the NS phylogenetic subgroup A as does the H7N7 strain, while the NS gene of the H5N2 strain belongs in subgroup B (not shown). The NS gene was the only one closely related to genes of the current HP H5N1 Z genotype.

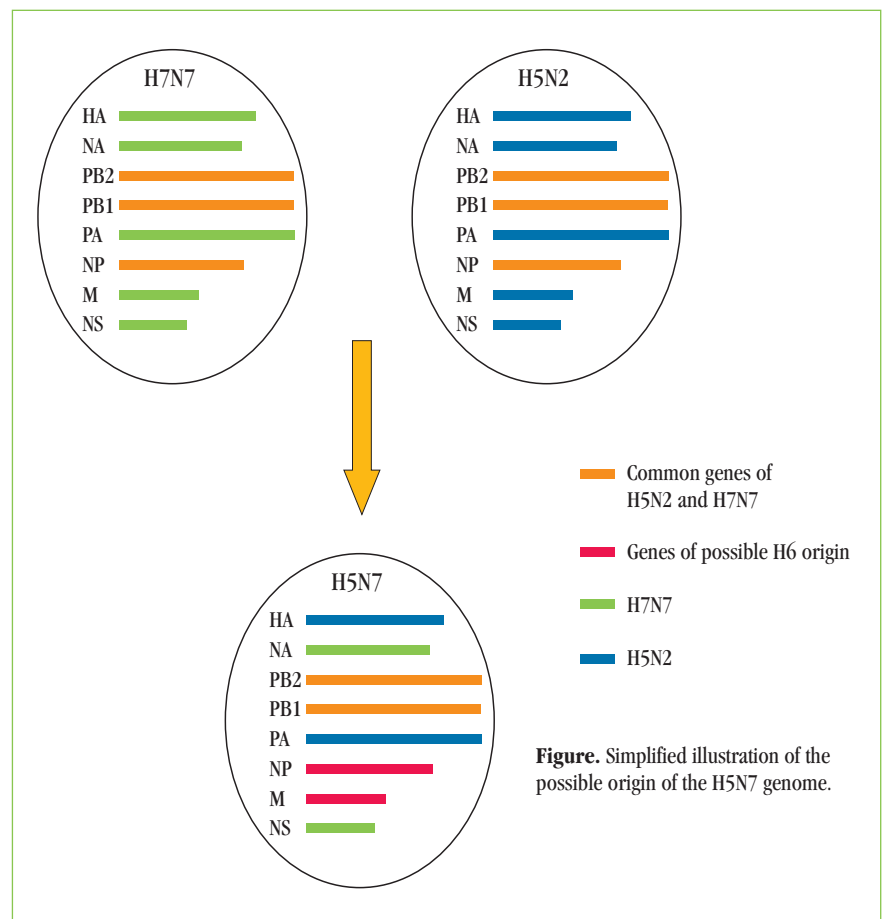
Determination of pathogenicity and inhibitory drug resistance

The A/Netherlands/219/032 (H7N7) isolated from the human fatal case in The Netherlands in 2003 differed by 14 substitutions in the HA,

NA, PB2, PA and NS proteins from other human and avian infectious H7N7 virus at that time [3]. Some of these substitutions were also found in segments of the new H5N7 genome, namely PB2 V297I, PA F666L, NA P458S and NS V137I. It is not known if any of these substitutions influence host infection, virulence or the multi-organ tissue tropism observed for the H5N7 strain. No sequence indications of HP were found in the internal proteins, e.g. substitution PB2 E627K or NS1 D92E. Host-specific amino acid residues in the H5N7 genome were all of avian origin and the HA protein possessed the amino acid HA Q226 and G228 indicating preferential binding to the avian-like NeuAca2,3-Gal receptor.

Our results suggest that the H5N7 strain is LP and is not adapted to a mammalian host. The H5N7 strain did not have any sequence indicators of resistance to matrix or neuraminidase inhibitory drugs. The presence of the virus in the brain and internal organ pool may be explained by weakness due to systemic bacterial infection in the sick mallards.

LP H5 AIV might be precursors for HP strains. Therefore, if a newly reassorted AIV virus,



like the new H5N7 with segments of HP avian origin, is allowed to circulate in the poultry or wild bird breeding colonies, it has the potential to develop into a HP strain. The experience with the 1918 Spanish flu virus has shown that pathogenicity to humans is not solely dependent on a multibasic cleavage site or multi-organ tropism, but likely the combination of genes, especially the HA and polymerase genes, is essential for high virulence [2]. Our results emphasise the need for full genome surveillance for LP AIV strains in order to be prepared for drifted or reassorted strains.

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INTERNATIONAL MEETINGS ON PANDEMIC PREPAREDNESS AND CONTROL

Due to the continuing spread of the highly pathogenic H5N1 influenza virus, a universal sense of urgency developed in 2005 to increase pandemic preparedness planning. Demonstrating this sense of urgency, a unique meeting was organised in November 2005 at the World Health Organization's (WHO) headquarters in Geneva [1]. This meeting was co-sponsored by four international agencies: WHO, the World Food and Agriculture Organization (FAO), the World Organization for Animal Health (OIE), and the World Bank. The meeting was attended by more than 600 experts from over 100 countries. The aim of the meeting was to establish precise needs and priorities, and the best ways in which to meet these. There was clear consensus that as no virus of the H5 subtype had ever circulated widely among humans, vulnerability to a pandemic caused by such a virus would be universal. Many participants agreed that pandemic influenza is a threat to the scientific, technical, political, social, economic, agricultural and health sectors of society, and also has implications for both national and global security. Indeed, the SARS epidemic some years ago provided an indication of how a future outbreak of pandemic influenza might have major social, political and economic consequences, as well as a

heavy toll on human health in a closely interconnected and interdependent world. It was estimated that based on the scenario of a mild pandemic, mortality could range from 2 million to 7.4 million deaths worldwide and global economic losses of around US\$800 billion within 1 year.

So far, the virus has established its strongest foothold in small backyard flocks in rural and peri-urban areas, where control is most difficult and opportunities for human exposure the greatest.

Apart from the health issues and strategies to pre-empt and/or control the consequences of a future pandemic, the meeting clearly recognised the need for pandemic preparedness plans to also include strategies for ensuring business and societal continuity.

To date, in many affected countries, management has been driven by the crisis at hand rather than by results-based planning. Public information, particularly that concerning risk communication, has not succeeded in achieving an adequate public understanding of the issues in line with the level of risk. This has either resulted in panicked over-reaction or the perpetuation of high-risk behaviours. The particular vulnerability of parts of Africa to

avian influenza emerged as a matter of great concern during the meeting. This continent has an estimated 1.1 billion chickens, mostly produced in backyard farming systems; mass culling would be extremely difficult to accomplish and the resources to compensate farmers or pay for animal vaccines are not available. Traditional practices and rural poverty favours the home slaughter and consumption of birds when signs of illness appear in a flock, as has been demonstrated in a recent outbreak in Nigeria. The incidence of human cases is sometimes linked to behaviour that can be avoided.

Overall, the WHO has identified five priority actions for the international community:

- Reduce human exposure to the H5N1 virus
- Strengthen early warning systems
- Intensify rapid containment operations
- Provide real-time information about the evolution of a pandemic to ensure that resources, which will be strained everywhere, will be invested in measures having the greatest likelihood of success
- Coordinate global research, including the accelerated development of pandemic vaccines and expanded production capacity.

In January 2006, a follow-up meeting to the November meeting was held in Beijing, China. During this pledging conference, an amount of US\$1.9 billion was raised by donor countries to support the priority activities for global, regional and national pandemic preparedness [2].

Apart from general measures, the availability of adequate volumes of antiviral agents and pandemic vaccines will be of key importance to contain the impact of a future pandemic. During a meeting held in Geneva, Switzerland on 7–9 November 2005, the WHO's Director General Dr Lee Jong-Wook summarised the central points raised about vaccines: "A universal non-specific pandemic vaccine may be the ultimate protective solution for human influenza. 'Smart' solutions are being investigated. Issues of technology transfer, resolution of licensing and regulatory obstacles, sustained use of GMP and prequalification are under discussion. Predictable, increased orders for seasonal flu vaccine will support greater manufacturing capacity, including in developing countries." He recommended the following action: "Map out a global strategy and work plan for coordinating antiviral and influenza vaccine research and development, and for increasing production capacity and equitable access."

Vaccine production capacity and equitable distribution are clearly very inter-related. Global pandemic vaccine production capacity clearly also depends on the unit dose and dose regimen needed for protection. Preceding the above meeting, the WHO had organised a meeting on development and evaluation of influenza pandemic vaccines on

2–3 November 2005. During this, vaccine manufacturers presented their progress with their respective developments of candidate pandemic vaccine formulations [3]. The meeting revealed that significant progress for the development of candidate pandemic vaccines has been made. Eight influenza vaccine manufacturers are already involved or are about to start clinical trials in 2006. One mock-up dossier has been filed according to the European Medicine Evaluation Agency (EMA) [4] in 2005 and four more such dossiers are expected to be filed in 2006.

Recent clinical studies with nonadjuvanted candidate pandemic vaccines have shown that unrealistically high doses are required to confer protection based on serological findings. Today, various prototype vaccine formulations with different strains and adjuvants are being investigated. Because of the vast clinical experience with aluminium compounds as adjuvants in vaccines, 'alum' is currently the most used adjuvant for pandemic vaccine formulations. MF59 – another common adjuvant – has also been safety tested and is used in an existing influenza vaccine formulation in many European countries.

Overall, current evidence from clinical trials with recent candidate pandemic vaccines indicate that the total antigen content required for a vaccine to be effective may be a limiting factor for the production of adequate volumes of vaccines when they are needed. Reasonable progress has been made towards the development and potential registration of candidate pandemic vaccines in 2005. However, research efforts should be

increased with a high priority to further reduce the necessary antigenic content of pandemic vaccines so that available and new production facilities can produce the maximum number of effective vaccine doses. This is of key importance to achieve the ultimate goal of equitable accessibility of pandemic vaccines for the world population.

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ESWI calls for the creation of a

EUROPEAN INFLUENZA TASK FORCE

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CALENDAR OF EVENTS

Date/Venue	Title	Organiser/Secretariat
3–5 May 2006 Basel, Switzerland	24th Annual Meeting of the European Society for Paediatric Infectious Diseases	Kenes International/ESPID 2006 17 Rue du Cendrier, PO Box 1726 CH-1211 Geneva 1 Switzerland Tel: +41 22 908 0488 Fax: +41 22 732 2850 E-mail: espid@kenes.com
7–11 May 2006 San Juan, Puerto Rico	19th International Conference on Antiviral Research	Courtesy Associates Tel: +1 800 202-973-8790/ +1 800-453-1357 E-mail: ISAR@courtesyassoc.com
8–10 May 2006 Baltimore, Maryland, USA	Ninth Annual Conference on Vaccine Research	National Foundation for Infectious Diseases 4733 Bethesda Avenue, Suite 750 Bethesda, Maryland 20814-5278 USA Tel: +1 301 656 0003 x19 Fax: +1 301 907 0878 E-mail: info@nfid.org
3–5 July 2006 Stellenbosch South Africa	7th Congress of the International Federation of Infection Control	Nelda Rousseau Unistel Consultus (Pty) Ltd PO Box 19063, Tygerberg, 7505, South Africa
27–30 August 2006 Florence, Italy	12th Conference of the European Society of General Practice/Family Medicine	Viale Matteotti, 7 50121 Firenze, Italy Tel: +39 055 50351 Fax: +39 055 5001912
3–6 September 2006 Birmingham, UK	9th Annual Meeting of the European Society for Clinical Virology	E-mail: paul.klapper@escv2006.co.uk sue.skidmore@escv2006.co.uk
18–20 October 2006 Vienna, Austria	The Second International Conference on Influenza Vaccines for the World	IVW 2006 Secretariat Meetings Management The Barn, Rake Meadow Station Lane, Milford Surrey, GU8 5AD UK Tel: +44 (0) 1483 427770 Fax: +44 (0) 1483 428516

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