



Influenza

INFORMATION AND NEWS ON INFLUENZA

EDITORIAL

The recent severe acute respiratory syndrome (SARS) episode and the avian H5N1 and H7N7 influenza virus outbreaks in Hong Kong and The Netherlands have once again shown the crucial importance of ESWI's strategic objective: 'To reduce the impact of epidemic and pandemic influenza in Europe by optimising the ways to combat the disease'. Indeed, the world has been warned that an influenza pandemic may be imminent, making ESWI's policy plan all the more relevant.

By adopting this plan in 2002, ESWI made official its decision to use communication to realise its strategic objective. This objective was translated into three operational goals: a) to contribute to, and improve surveillance activities of the disease, the virus and the vaccine usage; b) to convince policy makers to implement the appropriate measures; and c) to increase the awareness of the disease's impact and control possibilities.

An action plan was drawn up with concrete actions for 2002–2003. It is now time to reflect on ESWI's achievements in the past couple of years and to look ahead to 2004–2005. A new action plan is to be approved by the Executive and Members Meetings at the end of 2003.

In 2002–2003, important steps were taken towards realising the ESWI objectives: the existing communication lines with influenza policy makers were deepened by the publication of our first newsletter. In 2003, ESWI initiated a special issue of the journal *Vaccine*,

dedicated to influenza. It marked the 56th World Health Assembly and all participants received a copy. Eight thousand copies were also distributed to all possible stakeholders in the field of influenza and very importantly, ESWI now has links with national policy makers and experts. Communication with professionals about influenza is a core activity, and through local networks ESWI collaborates with key players nationally in several European countries. By close collaboration with national health organisations and

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experts, ESWI aims to learn about countries' specific problems and needs, and to suggest solutions from our experience elsewhere. In 2003, ESWI began collaborating with Sweden, Germany and Poland. Action plans for these countries were discussed and refined at workshops. In 2004, networks will be established in two other countries.

ESWI intends to continue its current work and to take on new activities, which will be reported in the next issue of this bulletin. In the meanwhile, I call upon all readers to join forces in the fight against influenza. I am convinced that together we can reduce the disease's impact in Europe.

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ESWI COLLABORATES WITH NATIONAL INFLUENZA NETWORKS

The mission statement of ESWI is 'to reduce the impact of epidemic and pandemic influenza in Europe by optimising the ways to combat the disease'. This objective is very much in line with the recently adopted resolutions of the 56th World Health Assembly of the United Nations, which addressed the global issue of influenza control and containment.

In 2002, ESWI adopted a policy that focused on raising awareness of the disease's burden, the need for effective routine immunisation programmes and the appropriate use of antiviral agents to better control influenza.

The recent SARS episode, avian H5N1 influenza virus outbreaks in Hong Kong, and the avian H7N7 outbreak in chickens in The Netherlands, warned the world of yet another pandemic influenza outbreak. The

World Health Organization (WHO) produced a number of documents to facilitate National Pandemic Preparedness planning. The WHO recommended increased vaccine use during inter-pandemic periods.

In line with these global efforts, ESWI has decided to liaise with the major stakeholders for influenza control in Europe. The aim is to improve the control of influenza in each country.

During 2003, there have been workshops involving policy makers and influenza experts from Germany, Poland and Sweden. They thoroughly analysed the infrastructure for controlling influenza nationally by SWOT (strengths, weaknesses, opportunities, threats) analysis, and developed action plans. WHO representatives facilitated the discussions.

National representatives of ESWI and WHO considered the workshops useful, as everyone had the opportunity to exchange information on influenza and influenza control, and to evaluate influenza control programme-related problems in each country. ESWI expects the action plans to be politically endorsed so that they can be implemented, to increase the control of annually recurring influenza outbreaks.

If this approach is successful, ESWI is willing to liaise with stakeholders in other European countries that need to improve national influenza control.

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THE EFFECTIVENESS AND COST-EFFECTIVENESS OF VACCINATING LOW-RISK GROUPS AGAINST INFLUENZA TO REDUCE TRANSMISSION TO HIGH-RISK GROUPS

Influenza vaccination of elderly people and other high-risk groups such as those with chronic pulmonary and cardiovascular disorders is established policy in most European countries [1]. In a 2002 position paper, the World Health Organization recommended vaccinating healthcare workers and household contacts of those at high risk, and discussed the possibility of vaccinating children and healthy adults [2]. As yet there is no consensus in Europe on the public health benefits of immunising low-risk groups.

The West Midlands Health Technology Assessment Collaboration at the University of Birmingham, UK received funding from ESWI for systematic literature reviews of current evidence on the effectiveness and cost-effectiveness of vaccinating certain low-risk groups. These included healthcare workers, children and household contacts of those at high risk.

The first part of the review – on healthcare workers – identified two cluster randomised controlled trials. Both showed a modest reduction in all-cause mortality among hospital patients after a staff vaccination programme was introduced. Twenty-seven other studies, of various designs, relevant to the implementation of influenza vaccination programmes for healthcare workers were also identified. These were assessed for quality and information on adverse events, vaccine uptake rates, reasons for non-vaccination and absenteeism due to influenza. The incidence of influenza and influenza-like illness among healthcare workers was summarised.

In the second part of the review we assessed not only the clinical- and cost-effectiveness of vaccinating children to protect high-risk groups, but also the effectiveness and safety of child influenza vaccines in general. We could not find any systematic review of influenza vaccine in

children – yet it is important information when considering the ethical implications of vaccinating children to protect others.

We are currently developing a system dynamics model to look at cost-effectiveness. The model's parameters will come from information gathered through the systematic reviews. The study will be completed in February 2004.

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ACUTE RESPIRATORY INFECTIONS WITH UNUSUAL MORTALITY IN MADAGASCAR, 2002

Madagascar, the world's fourth-largest island, is in the Mozambique Channel in the southern hemisphere. In 2002, its population was estimated at 16,473,000. The island

has a narrow coastal plain, a high plateau and mountains at the centre. The climate is tropical along the coast, temperate inland and arid in the south. Data from the capital

area indicate that influenza viruses circulate from January to September with a peak of virus isolation in July. Acute respiratory infections (ARIs) increase in the cold season

and are highest in June and July in the highlands [1].

In 2002, influenza viruses, mainly type B, were detected in the capital, Antananarivo for many weeks without noticeable mortality. Then outbreaks of ARI in remote villages in the province of Fianarantsoa on the high plateau about 450km southeast of the capital were reported. In mid-July, a humanitarian organisation (Akamasoa) [2] gave the first alert of unusual mortality from ARI. The Malagasy Ministry of Health (MinSan) contacted the Institut Pasteur de Madagascar (IPM) to jointly investigate on site. The ARI outbreak had begun in Sahafata in the first week of June. The local register of Akamasoa showed that there were 1,458 new cases in the week 13–21 July, which meant 162 new cases per day. With 1,500 cases in Sahafata (2,160 inhabitants), the attack rate reached 70%. Those proportionally most affected were young children (aged 5 and under) and elderly people (60 and over). Twenty-seven deaths were recorded from the start of the outbreak to 6 August; the case fatality rate was 2%, which is high for inter-pandemic influenza.

The MinSan/IPM team collected samples from 39 cases. One influenza A (H3N2) virus was isolated and identified as antigenically related to the vaccine variant A/Panama/2007/99(H3N2) by the Laboratory of Virology of IPM (M. Andrianarivelo and D. Rousset). By the end of July, a second outbreak had hit Ikongo, another district of the same province. The MinSan/IPM team immediately went to this very remote area to investigate. By early August, the Soavinandirana military hospital alerted IPM to the suspicious deaths of four fragile patients in acute respiratory distress whose X-rays had signs of atypical pneumonia. In the absence of clinical samples for laboratory diagnosis, doctors concluded that death was caused by respiratory distress due to a viral infection.

Faced with this situation, MinSan asked the World Health Organization (WHO) for help. The WHO team was led by C. Paquet (Institut de Veille Sanitaire [InVS], France) with I. Bonmarin, InVS, France; T. Uyeki, Centers for Diseases Control and Prevention, USA; K. Ait Ithlef, WHO Headquarters, Geneva; B. Koumare, WHO sub-regional, Côte d'Ivoire and J-C. Manuguerra, Institut Pasteur, France. They arrived in Antananarivo on 14 August to conduct an epidemiological field

investigation in the province of Fianarantsoa, study the national system of disease surveillance and use laboratory backup at IPM. Their objectives were to confirm the aetiology of the outbreak and make recommendations.

The ARI data collected monthly between January 1999–April 2002 in Fianarantsoa province showed a seasonal pattern, which was more obvious in the highlands than in coastal districts. In the highlands, there is a winter peak between May and September [3]. In 2002, the winter increase in influenza and pneumonia cases was higher than in previous years. The morbidity peak in July 2002 was twice as high as those for each of the previous 3 years in the districts of Fianarantsoa 2 and Ikongo. During those years, the peak of ARI coincided with a peak in mortality (all causes and respiratory conditions) [4]. Although there were more deaths due to all causes in these districts in July and August 2002, the observed ratio of deaths to ARI cases was similar to those seen in the previous 3 years, indicating that the causative agent was of low virulence [4]. This suggested that the higher mortality figures in these districts simply reflected the larger number of infected people.

Up to 28 August, 156 respiratory samples had been collected. The MinSan/IPM team sampled two sets of these from mid-July to the first week of August 2002, one from Sahafata and one from Ikongo and surroundings. The WHO team collected more samples in Sahafata, Ikongo and Manandriana. By this date, a total of 27 influenza viruses were isolated, typed as A (H3N2) by RT-PCR and antigenically characterised by haemagglutinin inhibition tests as closely related to the vaccine variant A/Panama/2007(H3N2). This confirmed the identification of the first isolate [4]. A number of PCR products had been sequenced. Both the H3 and N2 deduced amino acid sequences were very close to those of the vaccine strain and particularly to other strains such as A/Paris/457/2002(H3N2), which were isolated in the 2001–2002 winter season in France. The phylogenetic trees based on nucleotide sequences showed that the Malagasy strains and the French isolates were related. Altogether, the sequence data correlated the antigenic characterisation, further confirming that the Malagasy isolates were antigenically and genetically 'common' [3].

MinSan reported a total of 30,304 cases of influenza in the outbreaks. There were

754 deaths, 95% of them outside the health-care system. Influenza outbreaks were reported in 13 districts out of 111 in four of the six provinces. Fianarantsoa was the most affected, with 85% of total cases [5].

In conclusion, epidemiological and virological data showed that the outbreaks of ARIs with high mortality were due to influenza A (H3N2) viruses. These were neither antigenically different nor more virulent than those isolated in the 2001–2002 season. The unusual mortality among young children and the elderly was probably due to higher attack rates. Increased transmission may have been due to poor living conditions and an unusually cold and wet winter. Malnutrition and limited healthcare may have been worsened by political unrest.

In Madagascar, as in most developing countries, few people are aware of influenza, and problems such as malnutrition, limited healthcare, shortage of drugs and lack of influenza vaccine make it difficult to control outbreaks. Generally, the impact of influenza in most developing countries, especially in Africa, is poorly understood.

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AVIAN INFLUENZA – RECENT DEVELOPMENTS

Influenza A viruses that infect poultry can be divided into two distinct groups based on their ability to cause disease. The very virulent viruses cause highly pathogenic avian influenza (HPAI), which may cause up to 100% mortality. These viruses have been restricted to subtypes H5 and H7, although not all of the subtypes cause HPAI. Other viruses are less virulent, mostly causing mild respiratory disease, depression and egg production problems in laying birds (low pathogenic avian influenza [LPAI]). Current evidence [1] supports the hypothesis that HPAI viruses are mutations of H5 or H7 LPAI viruses that have been introduced to poultry from wild birds [2,3].

Until recently, HPAI was considered a rare disease in domestic poultry. Only 17 episodes were reported worldwide from 1959–1998 [4]. From 1997 to date, 14 significant outbreaks due to H5 or H7 subtypes have been reported in poultry, three of them affecting human health. Recent outbreaks in poultry are:

Hong Kong 1997–2003 H5N1

HPAI due to H5N1 virus first occurred in poultry in Hong Kong on three chicken farms in March–May 1997 and then re-emerged in November [5,6]. This virus was isolated from a child who died in Hong Kong and by December 1997 the same virus was confirmed by isolation to have infected 18 people, six of whom died [7]. There was evidence of very limited human-to-human spread [8]. Surveillance of Hong Kong poultry markets in December 1997 [6] showed widespread H5N1 infections. Control was established by the slaughter of all poultry. HPAI H5N1 virus re-emerged in poultry in 2001 and 2002, but the virus was genetically

distinguishable from the 1997 virus [8]. Twenty-two farms were infected between January and March in the 2002 outbreak, and approximately a million birds were slaughtered [9]. In February 2003 at least one fatal human H5N1 infection occurred (M. Peiris, personal communication).

Italy 1999–2001 H7N1

In March 1999 the first LPAI virus of H7N1 subtype was isolated and in 9 months, 199 farms became infected. In December, the virus mutated and HPAI was confirmed, causing 413 outbreaks. Over 13 million birds died or were slaughtered [10]. No human cases were reported.

The Netherlands, Belgium and Germany 2003 H7N7

At the end of February 2003, HPAI was suspected in layer farms in The Netherlands. The outbreak was confirmed with the isolation of a HPAI virus of H7N7 subtype. The infection spread, causing 241 confirmed outbreaks and the death or culling of over 30 million birds. In the middle of April the infection spread to Belgium causing eight outbreaks and the death or culling of approximately 2.3 million birds. There was also a single outbreak in Germany, close to the border with The Netherlands, and 400,000 birds died or were culled.

During the outbreaks in The Netherlands, several hundred people involved in the culling presented with conjunctivitis and/or influenza-like illness. Eighty-six were confirmed as infected with H7N7 virus [Koopmans et al., submitted; Fouchier et al., submitted]. There were also three probable cases of human-to-human transmission. Following the initial detection of H7N7 in

such cases, all staff involved in the outbreaks were treated prophylactically with antiviral drugs and vaccinated against human influenza to reduce the chance of reassortment between human and avian viruses. It was decided to do this as H3N2 virus was circulating in the area at the same time.

A 57-year-old veterinarian, who had not received prophylactic antiviral drugs and had been in contact with infected birds, was admitted to hospital with severe headache and fever. Subsequently he developed a severe respiratory condition and died. H7N7 virus was recovered from a broncho-alveolar lavage 9 days after the onset of illness [Fouchier et al., submitted].

One of the most alarming aspects of the recent avian influenza (AI) infections is that these viruses have the potential to infect humans, with serious public health repercussions. Possibly the most important consideration for AI virus infections of humans is that while infections to date have been limited in their human-to-human spread, it is quite feasible that AI and human influenza viruses could simultaneously infect humans or pigs. This could result in reassortment between the two viruses, so that a virus would emerge with the internal genes from the human virus (allowing easy transmission between humans), but with the haemagglutinin/neuraminidase from the AI virus, which could lead to a new pandemic [11].

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EUROPEAN COMMUNITY SUPPORT FOR INFLUENZA PANDEMIC PLANNING

Influenza pandemics have a huge impact on human health, causing high morbidity and mortality. Recent cases of human infection by avian influenza viruses in 1997 (H5N1 in Hong Kong), 1999 (H9N2 in Hong Kong and China) and 2003 (H5N1 in Hong Kong and H7N7 in The Netherlands) show that animal influenza viruses continue to threaten human health. In 1997, the human H5N1 infections prompted worldwide attempts to develop a safe vaccine. With the resources and technology available at the time these were not very successful, mainly due to the antigenic novelty and the high degree of pathogenicity of the H5N1 virus.

The EU recognised that we are poorly equipped to diagnose the emergence of possible pandemic influenza viruses and to rapidly produce a safe, effective vaccine. Two influenza pandemic planning projects are addressing these concerns.

Novafllu2001

The European Commission awarded a grant for a proposal on 'Novel vaccination strategies and vaccine formulations for epidemic and pandemic influenza control' (Novafllu2001, grant number QLRT-2001-01034). This multicentre (six groups from four countries) project aims to improve the efficacy and production of epidemic and pandemic influenza vaccines through:

- Improving epidemic vaccine strain selection by retrospective and prospective analyses. Computer models will aid in the interpretation of haemagglutinin inhibition (HI) assays and nucleotide sequence analyses.
- Improving vaccine strain selection and reference reagents for pandemic influenza. A new pandemic is most likely to be caused by birds directly or indirectly introducing novel subtypes of haemagglutinin (HA) and neuraminidase (NA) into the human population. Influenza A virus surveillance in European

and Asian wild birds will give valuable insight into currently circulating avian influenza viruses. Molecular cloning of all the prototypic HA and NA gene segments will help to rapidly generate recombinant influenza vaccines by reverse genetics techniques. The availability of recent avian strains of all subtypes also allows us to update reference reagents for diagnostic purposes.

- Implementing reverse genetics techniques and cell culture production methods to increase flexibility and yield of influenza vaccines. Reverse technology currently relies on the use of expression vectors in human or murine cells, neither of which is approved for vaccine production. Reverse technology needs to be adapted for use in embryonated chicken eggs and cell culture, which have been approved. We are also studying in detail determinants that could improve production yields or adaptation to the cell substrate.
- Using novel antigen delivery systems to improve the immunogenicity of vaccines. Alternative antigen delivery systems such as replication defective pox virus vectors and defective influenza viral particles are being evaluated as vaccine candidates.
- Examining correlates of protection. We are studying the role of cytotoxic T cells as possible targets for vaccine-induced protective immunity.

The project is in full swing and is being carried out in true European collaborative spirit.

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Flupan

The project 'Preparing for an influenza pandemic' is supported by the European Commission (Flupan, grant number QLK2-CT-2001-01786). It is a multicentre (six groups from four countries) project to develop and rehearse procedures for

improved pandemic influenza responses. We will:

- Get more information about circulation of influenza viruses in birds and pigs in Europe. Influenza viruses will be fully characterised antigenically and genetically, paying particular attention to detection of H5 and H7 viruses.
- Develop better diagnostic tests to monitor zoonotic infections. Tests will be validated using human sera (sero-surveillance and case controlled studies) from places that have had poultry infections.
- Produce a safe vaccine virus in Vero cells from a highly pathogenic H7N1 avian virus, using reverse genetics technology. The vaccine virus will be a reassortant bearing N7, modified H7 NA (removal of multibasic amino acids at cleavage site) and the remaining six genes from the attenuated vaccine virus A/PR/8/34.
- Produce an inactivated vaccine in Vero cells from the reverse genetics derived H7N1 virus.
- Test the H7N1 vaccine virus for immunogenicity and efficacy in preclinical studies and for safety and immunogenicity in phase I clinical studies.
- Investigate other low technology methods for production of cell culture influenza vaccines.
- Develop libraries of reagents for vaccine production from different influenza virus subtypes.

There has been good progress, despite delays in obtaining approval for biosafety aspects of the work and the intervention of SARS and H5N1 influenza earlier this year.

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INFLUENZA VIRUSES PAVE THE WAY FOR BACTERIAL INFECTION

Since the 1918 pandemic we have known that secondary bacterial infections often complicate influenza. Most influenza-related deaths are due to pneumonia. Secondary bacterial infection was detected in three-quarters of fatal or life-threatening pneumonias during the pandemics of 1957 and 1968. Later epidemiologic studies show that interpandemic

influenza can also induce severe bacterial pneumonia. Common pathogens detected in secondary bacterial pneumonia are *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae*.

In children with influenza, otitis media is probably the most common reason for

giving antibiotics. Otitis media occurs in 24–35% of children with influenza. Some children diagnosed with otitis media may have viral infections only, but most are thought to be bacterial superinfections.

Intervention studies have also shown that influenza leads to bacterial infection.

Vaccination against influenza prevents otitis media in children and hospital admissions for pneumonia in elderly adults. Studies of neuraminidase (NA) inhibitors in influenza have shown decreases in bacterial complications and antibiotic use, even though the populations studied have not included those most vulnerable to secondary infections, due to underlying illnesses or extremities of age.

Influenza infection probably affects the host in such a way that bacteria commonly carried in the nasopharynx can invade and cause infection. Destruction or dysfunction of the ciliated respiratory epithelium may enhance bacterial invasion. The cytokine response to influenza may upregulate bacterial receptors in the lung, or prime the host for a dysfunctional cytokine response to bacterial infection. Influenza is known to induce neutropenia and depress chemotactic and phagocytic function of monocyte-macrophages. Together, these disparate effects make the host susceptible to bacterial infection.

In experiments, influenza viruses increase adherence and invasion of bacteria in respiratory epithelial cell lines. In a chinchilla model, influenza infection increased the

occurrence of pneumococcal otitis media. In our laboratory, a mouse model of lethal synergism between influenza and pneumococcus has been developed [1]. Influenza infection primes mice for lethal pneumonia after low-dose challenge with pneumococcus. Using this model, the role of viral NA in the synergism was studied. Oseltamivir improved survival of mice from secondary bacterial pneumonia, independent of its effects on viral replication and influenza morbidity. Oseltamivir also reversed the effect of influenza virus on adherence of pneumococcus in respiratory epithelial cell culture [2]. These studies suggest that viral NA activity promotes adherence and invasion of pneumococcus by cleaving sialic acid from host cells, exposing cryptic receptors for pneumococcus.

H3N2 influenza epidemics kill more humans than H1N1 or influenza B virus epidemics, and there are more secondary bacterial infections with H3N2 viruses than with other subtypes. The NA of N2 viruses generally has higher activity than that of N1 or B viruses. We are exploring the hypothesis that differences in viral NA activity affect the ability of influenza strains to induce secondary bacterial infections, explaining the differences in mortality during epidemics. To find out the

specific role of NA, we are using reverse genetics to produce influenza viruses that differ from each other only in the NA gene, and testing them in various infection models.

The interaction between influenza viruses and bacteria has a major role in influenza morbidity and mortality in humans. We need a better understanding of this interaction to develop intervention strategies. Experimental studies using cell culture and animal models can reveal the molecular mechanisms.

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RESOLUTION OF THE 56TH WORLD HEALTH ASSEMBLY – PREVENTION AND CONTROL OF INFLUENZA PANDEMICS AND ANNUAL EPIDEMICS

The 56th World Health Assembly adopted a far-reaching resolution in May 2003. World Health Organization (WHO) member states expressed concern about the general lack of national and global preparedness for a future influenza pandemic, particularly in view of the likely high mortality, social disruption and economic costs. They were also concerned that the impact of influenza in developing countries was poorly documented and recognised the need for improved vaccine formulations, increased manufacturing capacity, more equitable access to antiviral drugs, and better disease surveillance. Better use of vaccines for seasonal epidemics would help to ensure that manufacturers meet demand in future. Pandemic preparedness plans would allow a more rational and cost-effective response to seasonal epidemics.

The resolution urges WHO member states:

- where there is a national influenza vaccination policy, to increase vaccination

of all people at high risk, with a goal of having at least 50% of the elderly population vaccinated by 2006 and 75% by 2010

- where there is no national influenza vaccination policy, to implement one by assessing disease burden and economic impact of annual influenza epidemics
- to implement national plans for preparedness for influenza pandemics, particularly ensuring adequate supplies of vaccine, antiviral agents and other vital medicines
- to heighten preparedness for epidemics and pandemics through strengthening national surveillance and laboratory capacity
- to support research and development on improved influenza vaccines and effective antiviral preparations, particularly their suitability for use in developing countries.

The resolution requests the WHO to:

- continue to combat influenza through new partnerships

- continue to lead in coordinating the priority activities set out in the global agenda on influenza surveillance and control
- support developing countries in assessing the disease burden and economic impact of influenza and implementing national policies for influenza prevention
- continue to strengthen global influenza surveillance as a crucial component of preparedness for seasonal epidemics and pandemics of influenza
- provide technical support to member states in the preparation of national pandemic preparedness plans
- search with other partners for solutions to the present global shortage of, and unequal access to, influenza vaccines and antiviral drugs, and to make them more affordable.

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LESSONS FROM SARS FOR INFLUENZA PANDEMIC PREPAREDNESS

The need to plan for influenza pandemics was essentially raised when the World Health Organization (WHO) released guidance for countries on national contingency plans. The WHO states that actions taken should be determined by factors including route of transmission, contagiousness and severity of the virus, healthcare capacity, surveillance networks, additional manpower and resources and stockpiling capacities.

The events of September 11, 2001 also strengthened the need to prepare responses to intentional threats, and the fear of smallpox has prompted countries to develop action plans for fighting a re-emergence of the virus. Planning for influenza pandemics has been similarly strengthened with enhancement of surveillance networks and sharing of international data. If a small number of cases occur, ring vaccination can be

instigated, followed by further actions to reduce the impact if spread occurs, and alertness for successive waves.

The SARS outbreak exploded at the beginning of 2003. The WHO released an exceptional global alert because of ignorance of the causative pathogen, the high rates of nosocomial transmission and the number of fatalities recorded. There were two other reasons for this unprecedented alert: the first cases of SARS occurred in Southern China, where a novel influenza virus was thought more likely to emerge, and there were five human cases of H5N1 in February. The successful containment of the virus is certainly related to WHO's global approach and the rapid and aggressive response from affected countries. The Internet, which was used to detect the problem and rapidly share information, was certainly the main

aid to success. Existing influenza pandemic preparedness plans will be adapted following the success of actions implemented during the SARS episode. These included the extraordinarily rapid identification and sequencing of the virus, the detection by performant software (through the Internet) of the first cases in South Asia, the reduction of cases by border control measures, and the cohorting of patients in heavily affected countries. During the SARS outbreak, it was particularly difficult to control panic, rumours and stigmatisation. These factors cannot be underestimated when planning for the next influenza pandemic.

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PROGNOSIS OF THE SARS EPIDEMIC: THE SEASONAL FACTOR

SARS has currently disappeared. This may be due to the health authorities in the countries concerned taking hygiene measures and identifying and isolating cases and their contacts, all of which helped to contain the disease. However, we would like to propose another explanation: that the optimal season for SARS coronavirus has simply ended.

Human coronavirus infections, which are well-known causes of the common cold, have clear seasonal patterns of transmission. Virus isolation and rises in antibody titre for all types of coronaviruses are rare outside December to May [1]. In contrast, adenoviruses circulate throughout the year. Seasonal patterns of transmission could be due to more favourable environmental conditions for virus survival, such as the indoor relative humidity [2], or behavioural changes that increase transmission, such as indoor crowding.

Pandemic influenza viruses do not always follow the seasonal pattern of inter-pandemic influenza transmission. The second wave of the 1890 pandemic occurred in London in May and June [3], and the first wave of the Spanish influenza pandemic in 1918, with few deaths, was in spring and summer [4]. However, the first and third wave of the 1890 pandemic, the great second and third waves of the Spanish pandemic, and all waves of the influenza pandemics of 1957 and 1968 were in autumn and winter [3–6].

Cases of SARS are thought to have occurred in the Chinese province of Guangdong as early as 16 November 2002 [7]. In Hong Kong, the first cases were detected in February 2003. Unfortunately, we do not have data for the temporal occurrence in Southeast Asia of classic human coronavirus infections. In view of the epidemiological data, it may well be that the SARS coronavirus has disappeared like the classic human coronaviruses in the northern hemisphere, partly because of public health measures, but also because of changing environmental conditions for virus survival and spontaneous behavioural changes in people. We conclude that there is a distinct possibility that the virus will return next autumn, either from a continuing low-level circulation in humans or from animals. Because the virus could have spread ("seeded") unnoticed into new geographic areas during the summer and because of the lack of herd immunity, this second wave could be more extensive than the first one. Its relatively low contagiousness may prevent a major influenza-like pandemic if it is properly contained. However, given the possible seasonal predilections of the virus, it is too early to claim victory before the next winter season.

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