

The European Scientific Working group on Influenza

December 2009, No. 26

EDITORIAL

As this is the first issue of ESWI's *Influenza* bulletin since the World Health Organization declared phase 6 over the current H1N1 'Mexican flu' pandemic, many of the articles in this magazine focus on issues related to the influenza pandemic: risk groups, virus evolution, lessons learnt from the emergence of H1N1 in the southern hemisphere and the availability of pandemic vaccines. Scientific focus on the new H1N1 flu virus is of utmost importance at a time when the public at large and, unfortunately, some policy makers are tending to minimise the threat of the pandemic due to the fact that the virulence of the new virus is at the low end of what was expected. The infection rates, however, are considerably higher than during a seasonal flu epidemic, and if the virus were to gain the ability to spread even more efficiently, the picture of virulence and mortality rates could still change dramatically.

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To do so, they translate their scientific expertise into clear messages and activities aimed at public health experts and healthcare workers. The organisation of pandemic preparedness workshops for public health officials is an excellent example of such an ESWI activity. The second edition of these workshops was held on 25 September in Brussels, Belgium and brought together health experts from 15 different European countries. In a highly interactive meeting, speakers and attendees focused on the threat

of the current Mexican flu pandemic and the different approaches in the various European countries. The outcome of the meeting was of particular interest as the attendees called for strong European Union (EU) leadership and support when it comes to pandemic preparedness. However, from the workshop debates it also became clear that the EU member states strongly defend their public health systems. Rationalisation of vaccination policy is a sensitive matter, underscoring how much confusion there is among ministries of health. This is also shown by the mixed, if not confusing, array of policy responses from one country or region to the next. Although vaccination is the cornerstone of prevention, vaccination policy is very inconsistent, even in Europe. Eighty per cent of French, Dutch and Belgian risk groups are being vaccinated, while only five per cent are vaccinated in other, mainly Eastern European, countries.

Close collaboration between influenza stakeholders like public health officials and healthcare providers is the aim of yet another major ESWI project: the establishment of Country Influenza Stakeholders Networks in individual European countries. The Finnish network is exemplary to the way national influenza stakeholders can join forces to improve seasonal and epidemic influenza response. Similar networks are being set up in the Czech Republic, Portugal and Hungary. Through these networks, ESWI aims to realise its objective of reducing the number of influenza victims in Europe.

I am convinced that ESWI's actions and activities will contribute to developing a European prevention strategy for seasonal influenza as well as a pandemic preparedness and response strategy.

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Chair, ESWI



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PANDEMIC H1N1/09: THE UK SITUATION, ANTIVIRALS AND VACCINES

Pandemic influenza in the UK

The current influenza pandemic began in Mexico in March [1]; by July, 135 countries were affected with nearly 100,000 laboratory-confirmed cases and more than 400 deaths [2]. In the UK, infection rates were approximately 60 cases per 100,000 by 20 July, but after a lull coinciding with the school summer holidays, a second wave is now appearing. The size of this wave remains difficult to predict, and many people now seem to be immune because of asymptomatic infections during the first wave.

UK antiviral drug policy

The UK government purchased a stockpile of approximately 40 million doses of oseltamivir, with the intention of providing prophylaxis to household and school contacts of index cases. Mathematical modelling indicated that prophylactic use could slow the initial stages of an outbreak and therefore reduce the peak number of cases. This would reduce the impact on essential services and medical care.

Although sensible and well reasoned, there was uncertainty about the impact of this policy and concern over the use of antivirals in uninfected contacts. Clearly, many would take antiviral drugs without benefiting. Minor but troublesome gastrointestinal and central nervous system toxicity was reported in 10–20% of individuals, which had implications for the ongoing policy. There was also concern that prophylactic use could increase the risk of oseltamivir resistance, although there has been little evidence of transmission of resistant strains.

Once it was no longer possible to fully contain UK spread, the emphasis moved to treatment of infected people. Studies show that delayed treatment is less effective, and that by 48 hours after symptom onset the benefits become hard to demonstrate. Treatment within the first few hours of illness is ideal but practically difficult, particularly when there are very large numbers of cases.

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The UK established a telephone helpline staffed by non-medical personnel who asked questions designed to identify patients with pandemic influenza. If certain criteria were met, a unique

identifying number was issued and the caller was instructed to despatch a non-infected individual (a flu friend) to a collection point to collect oseltamivir. The National Pandemic Flu Service lessened demand on family doctors and in only the first month of operation issued 450,000 courses of antiviral treatment. It is not known how many of these courses were actually used, but it is certain that many courses were given to those with illness fitting the criteria but not caused by influenza. The diagnosis of influenza infection by clinical criteria is imperfect. In a recent report of children with confirmed infection in Birmingham, 29/71 (40%) did not fit the Health Protection Agency's definition and 12/64 did not have fever $\geq 38^{\circ}\text{C}$ [3].

Monovalent H1N1/09 vaccines

An important part of the UK preparations for pandemic influenza was the pre-purchasing of 'sleeping' contracts for pandemic vaccine. It is now planned that 9.5 million people at greatest risk will be the first to be vaccinated, using family doctors and district nurses to target households, schools and workplaces.

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The at-risk groups include those aged 6 months to 65 years with clinical risk of serious disease, pregnant women, household contacts of susceptible individuals and those >65 years recommended to have the seasonal vaccine. All front-line health staff and carers (2.1 million people) have also been recommended for vaccination, both for self protection and to prevent spread to susceptible people. Unlike the USA, the UK has opted not to recommend general vaccination of school-age children. Although such children are the major disease vector, they do not usually develop severe illness.

The two vaccines that will be used initially in the UK are made by GlaxoSmithKline (GSK) and Baxter. The GSK vaccine, Pandemrix[®] (a split virion inactivated adjuvanted vaccine containing 3.75 μg of antigen from A/California/07/2009 H1N1v-like strain x 179A, propagated in fertilised hens' eggs), contains the adjuvant AS03 and thiomersal as a

preservative. The Baxter vaccine (Celvapan[®]) is a whole virion inactivated Vero-cell produced product containing 7.5 μg of antigen. This is produced from wild type A/California/07/2009 H1N1 virus inactivated by formaldehyde and UV radiation. It does not contain an adjuvant or thiomersal.

Pandemrix is provided as a box of 50 multi-dosed viral vials of 2.5mL suspension, and two boxes containing 25 x 2.5mL vials of adjuvant. Each 5mL of reconstituted vaccine is designed to provide 10 0.5mL doses, and each pack is therefore sufficient to vaccinate 500 individuals. Pandemrix seems effective in single dose in those aged 10–65 years, for children <9 years, a half dose is recommended.

It is not yet clear how the public will respond to the offer of vaccination. In a recent survey of 1,458 women by mumsnet.com, 50% of pregnant women said that they would 'probably or definitely' refuse and about 25% would 'definitely or probably' not wish their children to be vaccinated (*The Guardian*, Wednesday 2 September 2009). If the vaccine appears to be safe during its early use and there is a high level of public concern about pandemic influenza, the vaccination campaign may reach a large proportion of the population. Persuading healthcare staff to accept vaccination and provide leadership is a major challenge in some settings.

Conclusions

The UK's aggressive policy towards planning, antiviral use and vaccination is hoped to have led to considerable mitigation of the influenza pandemic. Continuation of this policy, modified in the light of experience, will (it is hoped) also have a favourable impact on the anticipated second wave. However, the effect of the UK's policies is difficult to judge at this stage and the approaches taken by different nations need to be carefully assessed to improve planning for future outbreaks.

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RISK GROUPS FOR PANDEMIC INFLUENZA

Given the current production capability for pandemic influenza vaccines, it is clear that there will be a shortage for some time before enough vaccine can be produced to vaccinate large segments of the population, especially in countries with full population coverage. Instead, a stepwise approach to vaccination based on precisely defined risk groups will be required, and this will be even more accentuated in countries with limited vaccine stockpiles.

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At-risk groups should be customised to country epidemiology. Priorities are shown in the following groups.

Pregnant women

Seasonal influenza is associated with cardiopulmonary hospitalisations. The risk is greatest in the third trimester, 3–5 times higher than for non-pregnant women and even higher with comorbidities present. Of the 45 deaths from pandemic H1N1 virus infection reported to the CDC from 15 April to 16 June 2009, six (13%) were in pregnant women, including one death from the original series of 34 pregnant cases. Of the pregnant women who died, one was in the first trimester, one in the second trimester, and four were in the third trimester. All the women were fairly healthy before their influenza illness [1].

Those with chronic medical conditions

Chronic pulmonary disease, including asthma (particularly if systemic glucocorticoids have been required during the past year); cardiovascular disease, except isolated hypertension; active malignancy; chronic renal insufficiency; diabetes mellitus; immunosuppression; neurological and neuromuscular disorders. Cases of severe pandemic H1N1 influenza A, including pneumonia and acute respiratory distress syndrome, have

been reported in obese individuals without known underlying conditions, particularly in those with severe obesity. The majority of deaths were caused by severe viral pneumonia and acute respiratory distress syndrome. Bacterial co-infection was also present in a minority. Fifty to eighty per cent of severe cases have underlying conditions [2].

All patients in risk groups should be treated with either oseltamivir or zanamivir, even if disease is mild. The World Health Organization particularly recommends prompt antiviral treatment for children with severe or deteriorating illness. Antivirals may also be beneficial in pregnant women.

Healthy young adults aged 15–49 years

Age distribution of severe and fatal cases shifts to an older age group than that of all confirmed cases. The median age of laboratory confirmed cases is 12–17 years based on data from the UK, USA, Japan, Chile and Canada. The median of hospitalised cases in the USA is 26 years. The median age of fatal cases is 37 years in the USA and 20–49 years in Mexico.

Healthy children

Children under 5 years old are at an increased risk of contracting the H1N1 virus. Similar to the regular strain of flu, the CDC notes that children under the age of 2 years are at a higher risk of hospitalisation from pandemic H1N1 flu. Therefore, they recommend pandemic H1N1 flu vaccination for children under the age of 5 years via either nasal or injection form. Vaccination is currently not recommended for children below 6 months of age, however relatives in close contact with the infected should be immunised.

Healthy adults aged 49–65 years

Risk in this age cohort is moderate, however still higher than in healthy adults >65 years.

Healthy adults >65 years

A hospitalisation rate of 11% observed from reports in the USA is overestimated due to the mild nature of most cases. The overall



hospitalisation rate for Europe at present is around 5–6%. Data for the UK up to early July 2009 indicated a hospitalisation rate of 1–2%.

Professional risk groups

People with higher professional exposure and those maintaining necessary functions of state should be immunised. According to national pandemic plans, stress is placed on immunisation of healthcare workers (HCWs) and critical infrastructure workers. Immunisation of HCWs is the priority. The estimated need ranges from 1% to 2% of the total population [3].

People with higher professional exposure and those maintaining necessary functions of state should be immunised.

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ANTIVIRAL RESISTANCE

Osetamivir-resistant strains of human seasonal H1N1 emerged in late 2007 and had spread globally by mid 2008. This event, when anti-influenza drug use was low, undoubtedly caused fears and uncertainties over the extensive drug use in the current pandemic situation. This leads to the question: is influenza resistance to antivirals inevitable?

Mechanism of antiviral resistance

Several mechanisms by which influenza viruses can become resistant to neuraminidase inhibitors (NIs; oseltamivir and zanamivir) and M2 blockers (adamantanes) have been extensively described. Adamantane resistance, caused by a mutation in the M2 ion channel protein, was dominant globally in H3N2 viruses from 2005 onwards, and later in specific clades of seasonal H1N1 viruses, precluding the use of these drugs [1]. Resistance to NIs is more difficult to monitor. There are several common mutations and, while they are almost exclusively in the neuraminidase (NA) protein, many are NA subtype specific, and have different cross resistance patterns within the drug class. It is simple, quick and relatively cheap to genotypically screen for these common and best understood mutations in surveillance programmes to rule out resistance. However, the recent description of a novel mutation causing phenotypic resistance to zanamivir [2] (albeit unclear if this was present in clinical material) deftly shows that we cannot be complacent in our current understanding of influenza viruses and mechanisms by which they can evade antiviral treatment.

Potential of widespread NI resistance in pandemic H1N1 2009 influenza

Surveillance programmes running for the last 10 years have found sporadic NI-resistant influenza viruses. Experimentally, such viruses were widely thought to be less fit than sensitive strains, and with lower transmissibility. This dogma was shattered by the H275Y-containing human H1N1 strain, which was sufficiently fit to transmit not only well, but better than its sensitive counterpart. The pandemic H1N1 2009 strain has a different constellation of genes, from multiple sources. The mechanism that made oseltamivir-resistant seasonal H1N1 transmissible should not be assumed to be the same for oseltamivir-resistant pandemic H1N1 2009 viruses.

To date, 28 cases of oseltamivir-resistant pandemic H1N1 2009 virus carrying the H275Y mutation have been detected worldwide, out of more than 10,000 viruses tested [3]. This proportion (0.3%) is similar to the level of resistant influenza viruses detected sporadically in untreated populations through various surveillance programmes over the last 10 years, and significantly lower than some studies in treated populations, where an incidence of up to 18% resistance was found. Transmission of resistant pandemic H1N1 2009 virus has not been proven to date.

Impact of emergence of NI-resistant pandemic H1N1 2009 influenza

The majority of influenza infections, both seasonal and pandemic H1N1 2009, are mild and self limiting. The benefits afforded by NI treatment are a shorter symptomatic period, and a reduced level and duration of viral shedding. The impact of resistance will therefore be higher infectivity; however, now that the new pandemic H1N1 strain is circulating widely, mitigation of spread by limiting viral shedding is no longer a priority. In the vast majority of individuals there would be no long-term consequences. In those with a high risk of complications, for whom treatment is recommended, the clinical impact of resistance may be higher. But even in those individuals at high risk of severe disease, the majority still have an uncomplicated course of infection.

Countermeasures for NI-resistant influenza

So, can we guard against resistance to NIs? The answer unfortunately is probably no. Influenza is a highly adaptive organism which always finds a way to surprise us. Perhaps the best way to approach resistance is to hope for the best but expect the worst. We can use the drugs we have wisely. The highest risk factors for generation of NI resistance seem to be treatment of severely immunocompromised individuals and use of post-exposure prophylaxis (PEP). The World Health

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Organization no longer recommends PEP, stating instead that close monitoring and early treatment if symptoms develop is preferable. Zanamivir treatment or dual therapy is a wise consideration for immunocompromised individuals, where clinical condition allows. There is a continued need for community surveillance but also a spotlight on close monitoring of high-risk individuals and an active response to patients refractory to treatment. With early detection of resistance we can mitigate the impact by preventing transmission, through combination or switching therapies. Lastly, we can improve our arsenal against influenza with new drugs against novel targets or alternate administration routes to maximise effectiveness.

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With a vaccine for pandemic H1N1 2009 virus on the horizon, there can be a shift away from a reliance on antiviral therapies for protection, but complacency is not an option.

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AVAILABILITY OF PANDEMIC H1N1 VACCINES

The threat of an emerging pandemic caused by the highly pathogenic avian H5N1 virus in 1997 motivated the global community to work at full speed to prevent or contain such a potential disaster. It was clear from the onset that safe and effective vaccines against H5N1 would provide the best possible strategy to manage and control a future pandemic. As soon as the first H5N1 strain for vaccine production was made available by the World Health Organization (WHO), vaccine lots were made for clinical testing. These early vaccines were poorly immunogenic, requiring high doses as well as a booster dose. It was therefore quickly realised that the available vaccine production capacity would be woefully inadequate to supply the global population with a pandemic H5N1 vaccine. The vaccine industry responded responsibly and invested in the expansion of global production capacity, adapted its existing production facilities to higher safety containment levels, developed adjuvants to lower the antigenic content required for an adequate immune response and initiated or accelerated alternative production technologies, such as cell culture.

Registration authorities faced their own challenges. If non-classical pandemic vaccine formulations were to be developed and used in a pandemic situation, safety and efficacy had to be ascertained before these products could be allowed on the market. Although there were guidelines in place for the registration of new influenza vaccines, the investments as well as the time required to fulfil these criteria would be a barrier to quick access in the event of a public health crisis. Therefore, registration authorities developed guidelines, which sought a careful balance between registration requirements and timely accessibility. In Europe, the 'mock-up dossier' procedure was introduced. Safety and serological data from a number of clinical studies with mock-up pandemic strains should be conducted and reported in a mock-up dossier for which approval could be obtained. If the real pandemic strain then emerged, a registration could be given for the real pandemic vaccine based on the approved mock-up dossier with limited additional clinical data. Based on this principle and studies with H5N1 vaccine formulations, a number of new, adjuvanted and cell-cultured H1N1 pandemic vaccines obtained approval from the European Agency for the Evaluation of Medicinal Products (EMA). As part of the registration requirements, further post-licensure studies and an intense pharmacovigilance programme to monitor safety and efficacy will be carried out with each of the pandemic vaccine formulations.

The first clinical studies with H1N1 pandemic vaccines show a very different picture from those with H5N1. In contrast to H5N1 vaccine, it seems that immunisation with one single standard antigenic dose already provides an adequate seroresponse. This is good news for the total global vaccine production capacity, but still there will not be enough pandemic vaccine for the whole world population.

How many H1N1 vaccine doses will be available? This question cannot be answered at the moment, because it depends on the choices countries make for the vaccines they intend to use. Non-adjuvanted vaccines or adjuvanted vaccines? Will the Scientific Advisory Group on Emergencies recommend one dose or two doses for an immunisation schedule based on existing and forthcoming clinical data?

Although the ethical principle of 'equitable distribution' of pandemic vaccine was mentioned by various international health authorities at the pandemic preparedness phase, no concrete measures were taken to implement such a strategy. Some vaccine companies have made commitments to donate pandemic vaccines to the WHO (150 million doses to date) for use in developing countries. To date, nine countries have agreed to donate 10% of their ordered vaccine doses for a similar purpose.

Although the ethical principle of 'equitable distribution' of pandemic vaccine was mentioned by various international health authorities at the pandemic preparedness phase, no concrete measures were taken to implement such a strategy.

Ensuring maximal vaccination coverage of prioritised groups is key to mitigating the impact of an influenza pandemic. The benefits of the timely availability of a pandemic vaccine are neutralised if prioritised groups do not receive it. Vaccine uptake among healthcare providers (top on the SAGE list of recommended groups! July 2009) is traditionally low.

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INFLUENZA LABORATORY TRAINING REPORT

During the first week of June, I won a scholarship to attend the ESWI's Influenza Laboratory Training Course at the Erasmus Medical Centre in Rotterdam, The Netherlands.

Together with 17 other participants, I entered the practicum room on the 17th floor of the Erasmus Medical Faculty on Monday morning. The participants were a mixture of molecular biologists, microbiologists and laboratory technicians from laboratories all over Europe, mainly working on influenza diagnosis. It was very interesting talking and sharing experiences with them and understanding that most of us face the same problems during our work. I think that I have made some good friends there and I hope that we will collaborate with each other again.

The course provided an overview of commonly used techniques for the detection, identification (typing and subtyping) and serology of influenza viruses, and was designed in a special way to accommodate all the backgrounds present. In my case, as I work in the National Influenza Centre near the Institute of Public Health, Albania, it was a great pleasure to sit and wear the Erasmus lab coat, even for a short period of time, and be a student again.

The course was organised with both practice and theory in topics such as propagation of virus in cell culture (e.g. Madin-Darby Canine Kidney), monitoring of the cytopathic effect of the cell line, performing a commercial rapid test for influenza type A and B detection, direct fluorescence assay, ribonucleic acid isolation, preparing the mixes for polymerase chain reaction (PCR) using the TAQMAN assay, and sequencing. The latter was very interesting because, beyond the basic techniques on influenza detection, I was interested in learning about the molecular techniques and the haemagglutinin inhibition (HI) test.

We also had the possibility of watching a video presentation about the techniques of virus neutralisation and inoculation in embryonated chicken eggs. This made it very easy for us to reproduce the technique ourselves, supported all the time by a group of experts who were on hand and always ready to help us or answer our questions.

Due to the large number of participants, we worked in a large practicum room which had all the necessary equipment to perform our experimental work, using vaccine strains only for safety reasons.

Each day we were also able to see very interesting presentations from different experts on influenza research. Some of the useful issues addressed in these presentations included collection and transport of specimens, laboratory diagnosis of influenza, quantitative real-time PCR using TAQMAN assay, and the threat from



and preparedness for the new pandemic strain of influenza A/H1N1. Meanwhile, Professor Osterhaus announced the 'welcoming' of phase 6 of the pandemic by a World Health Organization announcement late in the afternoon of 11 June.

We also heard about phylogenetic analysis techniques and tools, as well as the surveillance of avian influenza in wild birds and antigenic cartography based on the HI assay, which I found very useful.

Finally, I would like to express a special thanks to the entire Erasmus group of experts who helped us a lot. Many thanks to Theo, Ruud, Monique, Nella, Gerrie and Pascal.

To close, I would like to say congratulations and thank Guus Rimmelzwaan and Ab Osterhaus and, of course, to ESWI for the excellent work in designing this course, which was helpful for all of us.

This was a great opportunity for me and if I had the chance, I would be very happy to do it again. I recommend everybody to try this experience.

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PANDEMIC A (H1N1) VIRUS EVOLUTION

The first 71 isolates of pandemic A (H1N1) virus were antigenically and genetically homogeneous – more homogeneous than a typical A (H3N2) dominant season [1]. The A/California/07/2009 strain was representative of those early viruses and was chosen as the initial vaccine candidate. Those first 71 isolates were from a limited region – the then current geographic extent of the pandemic – and were isolated almost entirely from Mexico and the USA. It was not known at the time whether this antigenic homogeneity would continue in the ensuing months. Nor was it known what the characteristics of the virus had been in the estimated several months [2] prior to the detection of the outbreak in humans. The antigenic characteristics of the virus before the early samples remain unknown, but the antigenic characteristics now, 6 months (at the time of writing) after the A(H1N1) pandemic strains were first isolated in humans, are known.

By October 2009, approximately 2,500 A(H1N1) pandemic viruses from around the world have been characterised antigenically by the World Health Organization (WHO)

Collaborating Centres, and approximately 1,500 A(H1N1) pandemic viruses have been sequenced in at least the HA1 domain of the haemagglutinin. These viruses remain antigenically and genetically homogeneous, still showing less heterogeneity than that seen in a typical A (H3N2) season. Antigenically, the A/California/07/2009 strain is still representative of A (H1N1) pandemic viruses, and was the strain recommended by the WHO consultation on vaccine composition for the southern hemisphere for 2010 [3].

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PANDEMIC H1N1 2009: 10 OBSERVATIONS FROM THE AUSTRALIAN EXPERIENCE

1. Pandemics vary in intensity. The 2009 H1N1 pandemic in Australia has been mild overall but indigenous Australians and pregnant women have been at higher risk of hospitalisation and death. Indigenous Australians accounted for 20% of hospital admissions but represent only 2.6% of the Australian population, while pregnant women accounted for 11% of hospital admissions and represent about 1.1% of the population [1]. The risk for morbidly obese people may also have been increased.
2. Children and young adults have been the groups most affected. The median age of infection has been reported as 21 years. Although accurate clinical attack rates have yet to be determined, an estimate from New Zealand suggested a clinical pandemic attack rate of 7.5% [2] and the best fit to the Meltzer models for hospitalisations in Victoria was consistent with a clinical attack rate of 5% [3]. The elderly appear to have some degree of protective immunity.
3. The rates of influenza-like illness (ILI) were above normal seasonal influenza activity and similar to previous moderate influenza seasons in 2003 and 2007. However, ILI rates may have been inflated in 2009 by increased presentations to general practitioners following widespread publicity about the pandemic.
4. The number of laboratory-confirmed influenza notifications was high due to the increased demand for testing and indicated a much more severe influenza season than was actually experienced.
5. The 2009 H1N1 pandemic appears to have a low value for R, the effective reproductive number. Unpublished estimates of R from a number of Australian states range between 1.2–1.4. A low value of R is consistent with the observed relatively short duration of the pandemic.
6. The median age of almost 5,000 hospitalised cases was 32 years with equal proportions of males and females [1]. As with seasonal influenza, young children were most frequently admitted to hospital with pandemic influenza but people aged 65 years and above were admitted less frequently.
7. A pandemic paradox, yet to be fully explained, is why such a high proportion (13% nationally and up to 20% in Victoria) of hospitalised patients (median age 43 years) needed transfer to intensive care units (ICU). Although 20% of hospitalised indigenous patients and 7% of hospitalised pregnant women needed ICU admission, more than one-third of ICU patients with H1N1 infection had no comorbidities. In Queensland the median length of intensive care stay was 9 days (range 1–66 days) [1].
8. More than 180 deaths from H1N1 in Australia have been reported, very much less than the 3,000 deaths modelled to occur from seasonal influenza. Deaths from pandemic H1N1 occurred at a median age of 54 years compared to the median age of death from seasonal influenza of 83 years (data from 2001 to 2006) [1].
9. Preventative measures such as school closures in Victoria appear to have had little impact on containing the pandemic, probably due to the continued mixing of these age groups outside of the school environment. Border screening, using thermal imaging cameras and health declaration cards, was ineffective in delaying the pandemic H1N1 virus entering Australia.
10. Pandemic plans are inevitably incomplete and need to remain flexible. Plans would benefit from having a 'severity index' included in their detailed responses.

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THE FOURTH ESWI INFLUENZA CONFERENCE

11-14 SEPTEMBER 2011 | MALTA

CALENDAR OF EVENTS

| Date/Venue | Title | Organiser/Secretariat |
|--|---|--|
| 29–30 January 2010 Nice, France | 8th Annual Infectious Diseases Conference | Continuing Medical Education Office 3560 Business Drive Suite 130 Sacramento, CA 95820 USA Tel: +41 916 734 5390 E-mail: cmereg@ucdavis.edu |
| 3–5 February 2010 Amelia Island Florida, USA | ISIRV The International Symposium on Neglected Influenza Viruses | Contact via web: https://www.isirv.org/about/contactus.cfm |
| 11–14 March 2010 Chinese Taipei | XII International Symposium on Respiratory Viral Infections | The Macrae Group LLC 230 East 79th Street New York, NY 10075 USA Tel: +1 212 988 7732 Fax: +1 212 717 1222 E-mail: info@themacraegroup.com |
| 25–28 April 2010 San Francisco, USA | International Conference on Antiviral Research (ICAR) | Courtesy Associates 2025 M Street, NW Suite 800 Washington, DC 20036 USA Tel: +1 202 973 8690 Fax: +1 202 331 0111 E-mail: ISAR@courtestassoc.com |
| 4–8 May 2010 Nice, France | 28th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID) | 1–3 Rue de Chantepoulet PO Box 1726 CH-1211 Geneva 1 Switzerland Tel: + 41 22 908 0488 Fax: + 41 22 906 9140 E-mail: espid@kenes.com |
| 10–13 May 2010 Vienna, Austria | 20th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) | 20th ECCMID 2010 c/o Congrex Switzerland Ltd. Association House Freie Strasse 90 4002 Basel Switzerland Tel: +41 61 686 77 11 Fax: +41 61 686 77 88 E-mail: basel@congrex.com |
| 2–7 September 2010 Hong Kong SAR, China | Options for the Control of Influenza VII | c/o Integress Meetings and Events Hong Kong SAR China 2 Ravinia Drive Suite 605 Atlanta, GA 30346 USA Tel: +1 404 591 3284 Fax: + 1 404 233 2827 E-mail: lynne.pryor@meetintegress.com |
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