Pandemic provides backdrop for fourth ESWI conference

The 2009 H1N1 pandemic makes this ESWI conference more relevant than ever and is driving EU efforts to improve pandemic preparedness. Science has a major role to play in addressing unanswered questions.

“It’s quite timely that we’re having this meeting now, just after the first pandemic of the 21st century,” said Dr. A.D.M.E. Osterhaus, ESWI Chair, as he opened the Fourth ESWI Influenza Conference in Malta. Osterhaus was referring, of course, to the swine flu outbreak of 2009. He noted that the pandemic provided the opportunity to explore lessons learned and prepare for the next one. According to Osterhaus, this conference is also special because young scientists will present new data and all the scientific sessions will be co-chaired by a young scientist. “We’re cultivating the next generation of scientists,” said Osterhaus.

EU prepares to update pandemic preparedness across Europe

Osterhaus’ opening remarks were followed by a video message from John Dalli, European Commissioner for Health and Consumer Policy. Dalli recalled that back in December 2009, EU Member States agreed that by 2014, 75% of healthcare workers and people at risk would be vaccinated against influenza. He said that the EU is encouraging Member States to meet their commitments and suggested that “the time has come to update guidance on influenza pandemic preparedness across Europe.” Dalli described EU efforts to ensure equitable access to vaccines for all Member States by developing a mechanism for joint procurement.

Dalli concluded his message by underlining the important role of science. “It is only by combining the latest scientific knowledge with effective policy planning, that we will succeed in addressing influenza,” he said.

Nobel Laureate says “there’s still a lot to be solved”

Dr. Peter C. Doherty of St. Jude Children’s Hospital in Memphis, Tennessee and the University of Melbourne in Australia delivered the keynote address. Doherty gave a wide-ranging talk that presented influenza research performed over the past several decades. He summarized research findings, added his own conclusions and raised questions requiring further scientific investigation.

According to Doherty, the real problem with the influenza virus is that it’s highly contagious but the infected don’t necessarily feel sick while they’re infectious. On the plus side, unlike HIV, influenza infections are “self-limiting,” provided one can limit the damage. “We just need to get people through the acute phase,” said Doherty. For this purpose, Doherty ended his keynote with a challenge: “Can we make a universal vaccine?”
Scientists provide strong evidence for pandemic threat

Scientists have shown that H1N1 is geographically mobile and can reassort, and they have identified influenza virus strains that could mutate into the next pandemic virus. Experimental research has shown that with few mutations H5N1 can become airborne.

"Pigs DO fly." That was the message from Dr. Malik Peiris of the University of Hong Kong. Peiris was one of two keynote speakers during the plenary session on Monday. His talk, "When pigs fly." Insights on pandemic emergence", examined potential pandemic threats, focusing on the 2009 H1N1 pandemic strain.

Dr. Peiris was well-positioned to study the issue as about half the global population of pigs is to be found in China and 4,000-5,000 pigs are slaughtered everyday in Hong Kong alone. He and his team have been conducting a 14 year surveillance study of swine influenza in China.

Flying pigs?
Dr. Peiris' aim was to trace the origins and genomic evolution of the 2009 H1N1 pandemic virus. He found that after the triple reassortant genomic evolution of the 2009 H1N1 pandemic virus. Peiris said that the reassortment events in China gave clues how the pandemic virus emerged, even though the pandemic virus did not originate there.

Viral determinants of human transmission
Peiris next set out to identify viral factors that contribute to transmission risk for humans. He and his researchers studied tropism in the human upper respiratory tract in ex vivo cultures, transmission in ferrets and serological herd immunity. They identified one reassortant strain that severely infected both the nasopharynx and the bronchial tract. In the ferret study, this strain was also the only one which displayed any hint of aerosol transmission, according to Peiris.

On the hunt for a killer
Given that this reassortant virus shares 7 gene segments of common origin with the pandemic virus (but does not pre-date it), Peiris and his colleagues decided it warranted further study. They added to the reassortant virus the neuraminidase enzyme it was missing as well as 3 polymerase genes that had shown high levels of activity in tests. The new strain was not more infectious (only one out of three ferrets got infected) but the severity of the disease was enhanced.

"Despite these results, 915 – the reassortant virus – is the only virus of swine origin that does infect human tissue ex vivo and aerosol in humans," said Peiris. He found that sero conversion is broadening human immunity to swine viruses but not to avian viruses. Thus, according to Peiris the biggest danger would be reassortment of an H1N1 virus with an avian virus such as H5N1.

Peiris concluded his presentation with a strong message: "There's a need for a step change in surveillance of swine viruses and animal viruses in general."

H5N1: a persistent danger
Dr. Ron Fouchier of the Erasmus Medical Centre in the Netherlands delivered a similarly strong message during his presentation that H5N1 continues to be a pandemic threat.

Fouchier has studied H5N1 in Indonesia, one of countries hardest hit by avian influenza. The island nation of 240 million people has had 178 confirmed cases of avian influenza of which 146 have been fatal.

Vaccine failure
Intrigued by evidence that classical vaccines were failing, Fouchier and his colleagues used a Hemagglutination inhibition assay to study the antigenic drift of the new virus strains. "We discovered that only 1-3 substitutions are sufficient to cause large changes in antigenic drift," said Fouchier. Moreover, large antigenic differences between and within H5N1 clades could affect vaccine efficiency and even result in vaccine failure, warned Fouchier. Indonesia decided to switch to a different vaccine strain.

A "stupid" experiment leads to a valuable result
Fouchier and his team's biggest discovery, however, was based on what he termed a "stupid" experiment. He and his team introduced mutations, under strict laboratory safety procedures, by reverse genetics into laboratory ferrets. They then collected a nasal wash from each infected ferret and inoculated another ferret after a few days. They repeated this process ten times. The result? H5N1 had been transmitted to three out of four ferrets. "This virus is airborne and as efficiently transmitted as the seasonal virus," said Fouchier. His research team found that only 5 mutations, 3 by reverse genetics and 2 by repeated transmission, were enough to produce this result. "This is very bad news, indeed," said Fouchier.
Clinical approaches to pandemic preparedness

Early diagnosis and treatment is the key to stamping out a pandemic before it peaks and overwhelms the healthcare system. With this in mind, participants in the session “Clinical impact and diagnostic approaches” offered their views on ways to improve.

Dr Peter Openshaw of Imperial College in London provided a fascinating inside view of the UK’s efforts to combat the H1N1 pandemic, focusing on its clinical impact.

“The UK had one of the most highly developed pandemic preparedness plans in the world,” according to Openshaw, “and the risk of pandemic human disease was considered highest among threats as far as impact and likelihood, even higher than terrorism.”

The UK’s plan was centered on blunting the peak of any pandemic outbreak. “You can tolerate a slow-burning outbreak, but it’s the peak that causes a breakdown in health services,” said Openshaw.

The pandemic hit the UK’s shores in two waves: the first wave in the summer of 2009 and the second wave in the winter of 2009/10. During the first wave, flu-associated bed-days went from 4,163 in 2008 to 33,376 in 2009, a 7-fold rise, and, most alarmingly, the 17-39 year age group was particularly hard-hit, with bed-days increasing from 169 to 6,253 from October to December, a 37-fold increase.

Openshaw based his research on two studies: Flu-CIN, a study funded by the Department of Health that aimed to collect clinical information fast; and MOSAIC, a Wellcome/MRC funded study that focused more on the discovery of pathogenesis. The Flu-CIN study found that mild asthma increased patient risk, but that it was a risk factor for admission only, not for severe outcome.

The studies’ findings resulted in several changes including a revision of UK clinical guidance and a change to the UK’s antiviral, antibiotic and vaccination policy, away from prophylactic use in the case of antivirals.

To Openshaw perhaps the most important lesson is that “You need to be prepared in peacetime. You have to move very fast during a pandemic.”

Real-time PCR for mapping a whole entire genome sequences

Dr Martin Hibbard of the Genome Institute of Singapore described recent advances in Real-time Polymerase Chain Reaction (RT-PCR) technology. He noted that if a physician’s test for H5N1 is negative, RT-PCR could present an alternative to that process. “Genome sequences can be rapidly analyzed and sequenced, so the technique can help with the rapid identification of outbreaks,” said Hibbard.

The process works by extracting a total nucleic acid from a clinical sample. This is then amplified and hybridized onto a micro-array chip. The result is detection signals for an entire genome sequence which can then be analyzed using automated bioinformatics.

The technology has already proven itself useful. Singapore’s Ministry of Health used it to track which viruses were mutating most rapidly during the H1N1 flu pandemic, and in at least one instance even used it for person to person recognition.

In vivo imaging: a superior approach?

Koet Stittelaar of Viroclinics Biosciences in the Netherlands presented a very different diagnostic approach. Using CT imaging on ferrets, he and his group overcame the limitations of current analytical approaches. Current preclinical animal models examine the severity of disease (necropsy) at a single fixed point in time. But antiviral efficacy, for example, depends greatly on when treatment was begun. Moreover, with in vivo imaging, Stit-

“YOU NEED TO BE PREPARED IN PEACETIME. YOU HAVE TO MOVE VERY FAST DURING A PANDEMIC.”

DR. PETER OPENSHAW, IMPERIAL COLLEGE, LONDON, UK
Vaccination: history proves it works, whatever the disease!

Does the world’s long history of vaccination justify – despite the associated risks – its use in reducing the burden of disease? For all panel members of ESWI’s final workshop on Day 1, the answer was a resounding “yes”.

From Chinese variolation techniques against smallpox in the 1600s to today’s efforts to eradicate polio, “the history of vaccines in the fight against infectious diseases has been a success story,” Dr. Ab Osterhaus, ESWI chairman told the group, pointing to today’s near-eradication of diseases that were once the scourge of humanity such as measles. “We have the tools to fight these diseases with vaccines.”

Yet public fear and mistrust about the safety of vaccines often stand in the way of high vaccination rates. These obstacles can only be overcome by delivering the right information at the right time to those who communicate directly with the public: the media and other stakeholders.

“You have an opportunity every year to educate your media about the benefits of influenza vaccination: in the autumn when seasonal flu preparations begin,” Dr. Marc Van Ranst, researcher at Belgium’s University of Leuven, told his audience. “The knowledge you can impart to the media and thus to the public can influence them and prepare them for a pandemic whenever it hits.”

Public misperceptions about vaccination are rampant and can work heavily against the best efforts of science, however.

“Conspiracies of all kinds have always been there—even in Jenner’s time,” said Osterhaus, referring to the 18th English scientist who developed the first smallpox vaccine. “Today I’m most concerned with pseudo-scientists who say it is good to be exposed to disease in childhood to strengthen the immunological system! This has got to be fought. However, we as scientists have got to package our message in a different way if we want more effective communication with the public.”

Japanese health officials know that by direct experience, as panelist Dr. Masato Tashiro, told the group. Noting that Tokyo shifted away many years ago from mandatory flu vaccination for young children partly due to a hostile press that called the policy a violation of children’s rights, the government has since embraced voluntary vaccination and seen uptake rise – and mortality fall – among children since 2002.

The reason? “The government simply did a much better job of promoting the positive effects [of vaccination] for children,” said Tashiro.