

The European Scientific Working group on

INFLUENZA

INFLUENZA A(H1N1) PANDEMIC: THE RIGHT STEPS WERE TAKEN.

Science-based arguments
to support this statement.

Prof. Ab Osterhaus, *Erasmus MC Rotterdam*
Prof. Peter Openshaw, *Imperial College London*
Prof. Arnold Monto, *University of Michigan*

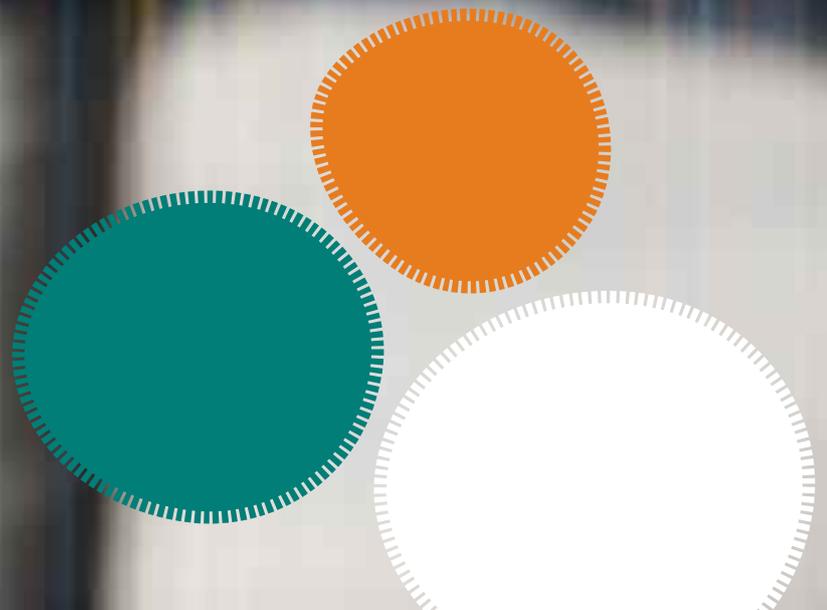


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Prof. Ab Osterhaus

Dr. Osterhaus currently holds the positions of Professor of Virology, Medical Faculty, Erasmus Medical Center, Rotterdam (since 1993); Professor of Environmental Virology, Veterinary Faculty, State University Utrecht (since 1990); Director of the National Influenza Center (NIC), Rotterdam (since 1993); Director of the WHO Collaborating Centre for Arboviruses and Haemorrhagic Fever Reference and Research, Rotterdam (since 1995); Member of the Dutch Health Council (since 1995); Chairman of the European Scientific Working Group on Influenza (ESWI) (since 2000); CSO of ViroClinics BV and of ViroNative BV (both spin-offs of the Erasmus MC holding).

Dr. Osterhaus studied at the University of Utrecht, where he also completed his doctorate in 1978.

From 1978 to 1994 he held various positions at the National Institute of Public Health and the Environment (RIVM) in Bilthoven, the Netherlands.

Dr. Osterhaus is also a member of numerous professional societies including: American Society for Microbiology, Society for General Microbiology, European Scientific Working Group on Influenza, European Society for Veterinary Virology, European Society for Clinical Virology, European Association for Aquatic Mammals, Dutch Society for Microbiology, Dutch Society for Laboratory Animal Science, Dutch Society for Immunology, International Society for Vaccines, American Society for Virology, and European Society of Tropical Medicine and Hygiene. He is a member of the Royal Dutch Academy of Sciences and was recently awarded the Royal decoration of Commander in the order of the Dutch Lion.

Furthermore he holds many editorial positions for scientific publications, is the winner of several scientific awards, holds several patents, has been the supervisor and mentor of more than 40 PhD students. Over the last 20 years, Dr. Osterhaus has identified more than a dozen "new" viral pathogens and he is author of more than 800 scientific publications.

Prof. Peter Openshaw

FRCP PhD FMedSci
Professor of Experimental Medicine

Dr. Openshaw became the founding Director of the Centre for Respiratory Infection in 2008, bringing together many of Imperial College's established leaders and groups with expertise in molecular, cellular, animal and human studies of respiratory infections.

He is a member of the Clinical Information Network (FLU-CIN), a national Department of Health funded study of over 1000 patients admitted to UK hospitals with swine flu. He also leads a UK-wide consortium of 45 co-investigators in 8 cities working to understand variations in disease severity in hospitalised patients with influenza, under the banner of MOSAIC (mechanisms of severe acute influenza consortium). He currently holds grants totalling over £10m.

He has advised the Department of Health as a member of the Scientific Pandemic Influenza panel and is a member of the Clinical Countermeasures Subgroup. He serves on the Joint Committee on Vaccination and Immunisation (JCVI) subgroup on influenza and RSV prophylaxis (2009) and is a member of the Scientific Advisory Group in Emergencies (SAGE), chaired by the Chief Government Scientist, which advised the UK government on pandemic H1N1 influenza. He was a member of the Academy of Medical Sciences Vaccines Working Group.

Prof. Arnold Monto

Arnold S. Monto is Professor of Epidemiology at the University of Michigan School of Public Health in Ann Arbor and is Founding Director of the Bioterrorism Preparedness Initiative. The major focus of his work has been the epidemiology, prevention and treatment of acute infections in the individual and the community. These activities have included work on the occurrence and characteristics of the infections as well as potential for vaccine prevention and antiviral treatment. Respiratory infections, in particular influenza, have been a major interest, with special reference to the evaluation of vaccines in various populations and the assessment of the value of antiviral such as amantadine, rimantadine and the neuraminidase inhibitors. He has worked on these issues in tropical as well as temperate regions. He led the studies of respiratory infection in Tecumseh, MI, a landmark study of infection in the community. Dr. Monto was closely involved in the US HCFA-sponsored studies, which made influenza vaccine a covered benefit for older individuals. He has also studied other approaches to influenza vaccine use, particularly to control transmission of the virus in the community and in nursing homes. He is currently involved in assessing the efficacy of various types of influenza vaccine, the neuraminidase inhibitors in prophylaxis and therapy of influenza, as well as non-pharmaceutical interventions in interrupting transmission. His recent activities have also included evaluation of face masks and hand hygiene in the control of influenza transmission. He works extensively with national and international organizations on issues related to pandemic preparedness and was a member of the WHO Influenza Pandemic Task Force. During his tenure at the University of Michigan, Dr. Monto has also served for periods of time in the Acute Respiratory Infection program at the World Health Organization, Geneva, and as Scholar in Residence at the United States Institute of Medicine/National Research Council. He has been a member of the Pulmonary Diseases Advisory Committee and the National Heart, Lung and Blood Institute and of the National Allergy and Infectious Disease Advisory Council. He has also served on various United States and international advisory bodies addressing the overall response to the problem of emerging and reemerging infections, control of influenza in the seasonal and pandemic situation, and bioterrorism preparedness. He is the past president of the American Epidemiological Society.

FOREWORD

The outbreak of the Mexican influenza A (H1N1) virus was declared a pandemic by the World Health Organization (WHO) on 11 June 2009. Now, more than half a year later, the impact of the pandemic is at the low end of what was prepared for. As a consequence, some critics argue that the pandemic preparedness measures taken by EU member states were out of proportion. Some even suggested that people's fear of the pandemic has been orchestrated by the pharmaceutical industry.

However, misconstruing the role of science in the regulation of health technologies, which have brought so many benefits to society, holds severe dangers to public health protection against future threats. Correct and science-based information is indispensable in this discussion.

To provide such information, the European Scientific Working group on Influenza (ESWI) organized the third edition of its Pandemic Preparedness Workshop for Public Health Officials on 22 January in Brussels. More than 30 public health officials from 19 different countries attended the meeting, demonstrating their need for state-of-the-art and unbiased data about the H1N1 pandemic.

This magazine provides a report of the lectures and the discussions held at the workshop. The text can be copied freely. Additional questions to the workshop's faculty can be asked via ESWI's management (contact details see back of this magazine).

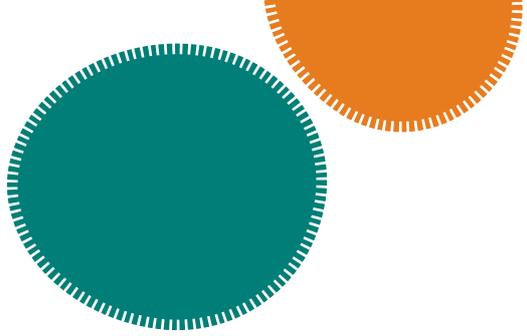
The workshop's faculty

Prof. Ab Osterhaus
Erasmus MC Rotterdam

Prof. Peter Openshaw
Imperial College London

Prof. Arnold Monto
University of Michigan

ESWI is a partnership organisation with a clear mission: reducing the number of influenza victims in Europe. ESWI shares this aim with WHO. Like WHO, ESWI aims to raise awareness about the dangers of influenza and the beneficial effects of influenza vaccination and treatment.



INFLUENZA VIRUSES: SEASONAL VS. PANDEMIC

The genetic and symptomatic differences between seasonal versus pandemic influenza viruses are a roll of Nature's dice. No one can predict with certainty which virus will be the more virulent, which the least troublesome. While pandemic flu viruses have usually proven the more deadly, the reverse can also occur, with seasonal viruses matching or even exceeding the virulence of a pandemic flu. Whatever its genetic basis, the intensity of a virus's threat flows as much from its rate of transmissibility between humans as from its inherent virulence.

In Spring 2009 a new influenza, H1N1, began circulating among humans in Mexico. Thousands were infected before it spread across North America in April and then, mainly due to air traffic, to more than 80 countries by mid-year.

US researchers identified the new virus as likely originating from pig influenza viruses via genetic re-assortment. Clinical manifestations of the new "Mexican flu" or "swine flu" were relatively mild by the end of May 2009, and reminiscent of what is normally seen in seasonal influenza although there were more gastro-intestinal symptoms observed.

Though the new flu's case fatality rate proved to be relatively low, the initial figures from Mexico were hard to interpret. It became clear, however, that the burden of disease and mortality was high among the aged, as usual, but also among relatively young people (see figure page 5).

Moreover, health officials also were informed that the new virus' transmissibility proved at least comparable with that of seasonal influenza viruses. By late April the World Health Organisation (WHO) declared its pre-pandemic Phase 5 alert, signalling that widespread human-to-human transmission of the virus was underway.

Clear messages about the importance, the safety and the efficacy of the pandemic vaccines are key to convince prioritized groups to take the vaccine. Here is an overview of the most commonly asked questions about the virus, the disease and the intervention strategies practiced.

The burden of disease and mortality was high among the aged, as usual, but also among relatively young people.

The new H1N1 virus is milder than originally feared, but it can still mutate into something worse.



How does the new Mexican flu H1N1 virus differ from seasonal flu? Is its 'burden' on humanity higher, lower or the same?

The latest H1N1 virus is milder than originally feared, but it can still debilitate and kill – or mutate into something worse. “It is also important to note that H5N1 has not gone away,” warns Prof. Ab Osterhaus, a virologist at Rotterdam’s Erasmus Medical Centre. “It is still prevalent in Asia and the Middle East.”

How is the new variant of H1N1 virus distinct from seasonal flu?

- aside from the very old, it targets adolescents and young adults in the 15-44 age range
- H1N1 causes gastro-intestinal problems in 20 percent of cases – far higher than seasonal flu victims
- its transmissibility is high

Finally it is important to note that it has not genetically re-assorted with seasonal viruses such as H3N2 or with avian H5N1 viruses.

DIFFERENT AGE OF THOSE DYING OF SEASONAL AND H1N1/09 FLU

CMO's briefing update on fatal cases

	Age (years)		
94%		64+	19%
5%		45-64	21%
<1%		15-44	39%
<1%		0-14	21%

Seasonal flu

Swine flu

Journal of Infection

CMO's enquiry

H1N1 is milder than feared but, unlike seasonal flu, it singles out the young as the above statistics from the UK's Chief Medical Office demonstrate. "There was virtually no pre-existing immunity to this virus in young people," says Prof. Peter Openshaw of London's Imperial College.

SURVEILLANCE

Were surveillance activities in Europe effective in dealing with H1N1? Could the virus have been detected earlier?

How did an Asian swine-based flu get into Mexico when pigs are not transported across the Atlantic or Pacific? Probably the best guess is that there was a human link.

“One problem with the Mexican environment from which the virus apparently emerged: there is only limited influenza surveillance ongoing

in humans and animals”, says Osterhaus. “By the time authorities in Mexico understood the threat, the highly-transmissible virus had already spread to the USA and Canada – too late for containment.”

Even so, Europe was ready. “We had more surveillance information than at any time in the past,” says

Openshaw. “But it’s clear we need more international coordination and, in the UK, a regulatory and legal environment that does not prevent or delay research.”

H1N1 SURVEILLANCE IN THE USA

“None of us expected the virus would originate in our own backyard, along the Mexican border,” says Arnold Monto, professor at the University of Michigan and flu policy advisor to the US government. “However, surveillance in the US has been extensive.”

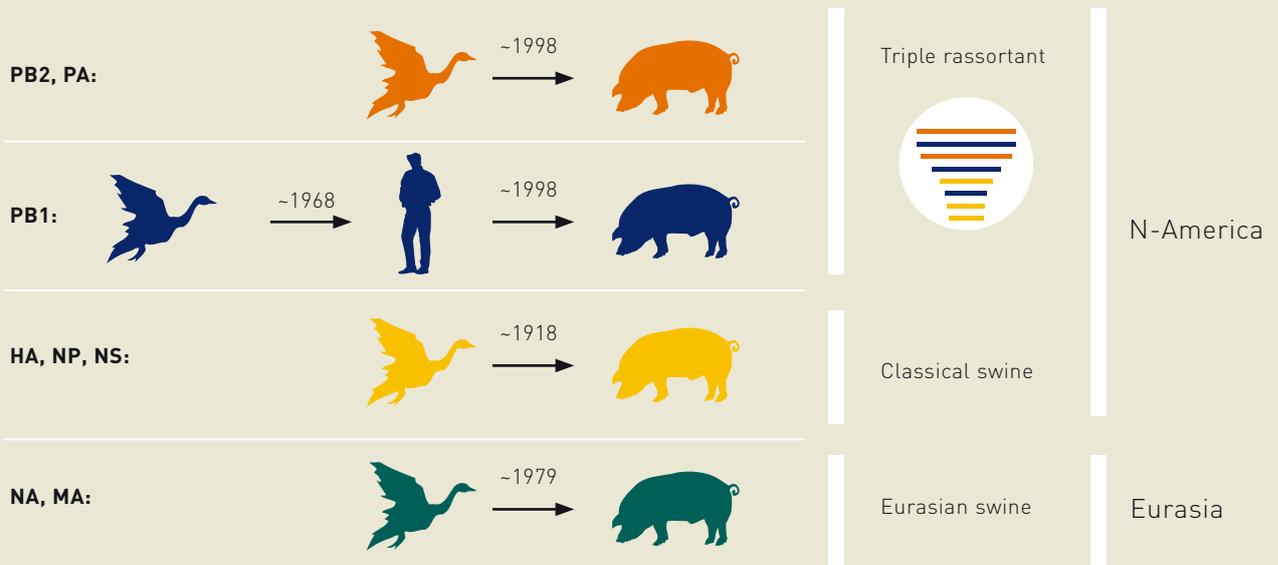
Initial reports from Mexico were confusing and “there was real concern we were dealing with a lethal kind of infection. Were victims there getting intensive care late, or were the rapid-developing symptoms due to the fact that availability of care across Mexico is uneven? We didn’t know, but it became evident we were dealing with the tip of an iceberg since the virus’ transmission rate was so high,” he said.

According to Monto, better surveillance in Mexico would have given the USA a few more critical weeks for early preparation. “It would have given us the ability to produce vaccines before the ‘autumn wave’ [of infection] instead of during it. This would have made an enormous difference and it’s one of the surveillance lessons learned.”

Another lesson is how to handle the surge. “If the pandemic wave had gone on another week, our country’s intensive care units could not have handled all the cases,” he observed.

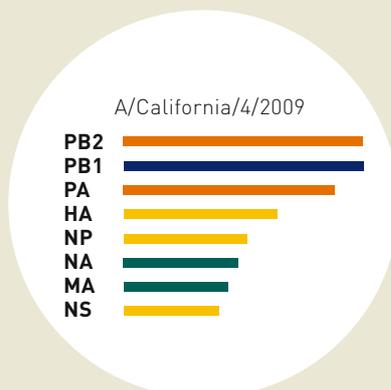
We need more international coordination and must remove any hurdles that prevent or delay research.

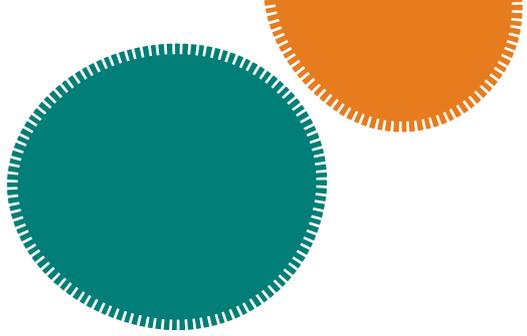
The origin of the 'Mexican flu virus' as deduced from sequence analysis of the respective genome segments of the virus. All the eight genome segments originate from avian influenza A viruses and were introduced into pigs directly from birds or through a human intermediate host. The colour codes correspond with those of the parent viruses. Where and in which species the final reassortment has taken place has not fully been elucidated and remains a matter to be confirmed.



THE MEXICAN FLU VIRUS

Courtesy: Ron Fouchier





PANDEMIC PREPAREDNESS: THE RIGHT STEPS TAKEN?

Was Europe and the rest of the world prepared for the H1N1 pandemic? Did planning fall short of the mark – or did public health authorities such as the WHO over-react, thus undermining their credibility? Were the excess supplies of pandemic vaccines and antivirals ordered by governments a waste of taxpayers' money? And finally, was the pandemic threat exaggerated by vaccine producers or health authorities? These are the questions for which the general public, policymakers and the media now want answers.

Some governments went for heavy supplies of H1N1 medicine such as the UK, which stockpiled 40 million doses of the Tamiflu antiviral. Did they and the WHO go overboard?

Seven months after declaring the H1N1 pandemic in June 2009, WHO is now accused of having moved too fast to declare its pandemic, while failing to grasp the virus' relatively mild nature.

Most health officials and researchers opt for prudence, and consider WHO made the right choice based on the information it had. "WHO's phases were properly applied since they only pertained to the spread of a novel virus causing community-level transmissions," says Monto, adding that when WHO's Phase 6, full-pandemic H1N1 alert was declared,

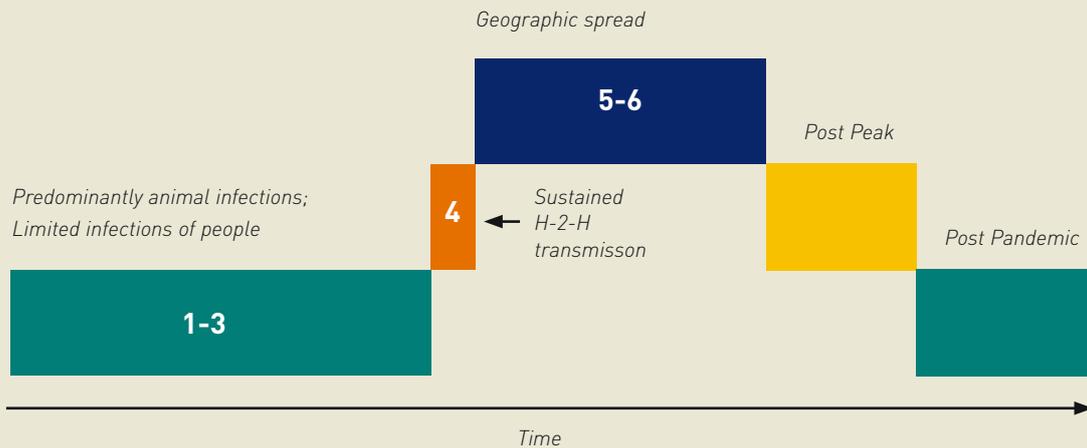
"it stressed that this was not expected to be severe and advised countries not to close borders." Osterhaus agreed: "If I was an adviser to governments or WHO, I would have done exactly the same. There was prove that we did have a real pandemic outbreak of influenza."

As for allegations that industry collaborated with authorities, Openshaw said: "This is one of the most irritating questions. Yes, these companies have watched the money roll in, but what has driven the situation is the history behind influenza and the havoc it can cause."

WHO's phases were properly applied since they are based on the virus' transmissibility and not its virulence.

What has driven the situation is the history behind influenza and the havoc it can cause.

WORLD HEALTH ORGANISATION'S REVISED PHASES (Applied in 2009)



Above: The World Health Organisation revised its three-year old pandemic alert stages in 2008 to establish a tighter link between surveillance of high human-to-human transmission rates and the subsequent geographic spread of infection. The system does not track a disease's severity – only its spread.

INFLUENZA PANDEMIC POLICY AND THE MEDIA: IF YOU DON'T EXPLAIN, DON'T COMPLAIN ABOUT THE PAIN YOU GAIN

Staying “on message” about the risks of influenza and the necessity of proper planning applies equally to two important target markets: policy-makers and the media. Says Monto: “One of our biggest worries is to convince the public and our government that a [high virulent] flu pandemic could happen again – in less than the 50 years since the last one occurred in 1968.”

Hiding behind bureaucracy is not an option, notes Openshaw. “The UK's chief medical officer went before the press every week to face the public. Most journalists want insight. The UK's Science Media Centre was very effective in getting the message across, and I strongly recommend that each country do something like that.”

Policy and planning were sensible, and proportionate to the perceived risk.

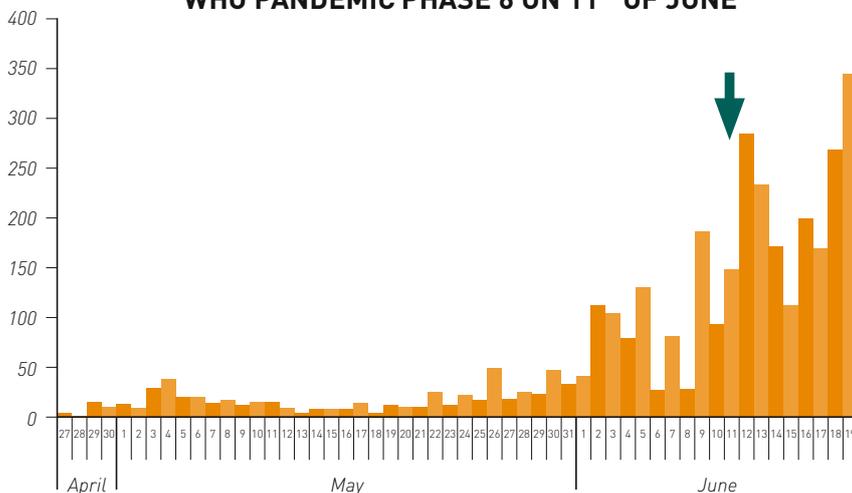
Some say WHO and the pharmaceutical industry engaged in fear-mongering by exaggerating the risk of H1N1. How plausible is this?

“WHO has been criticized for calling this a pandemic when the H1N1 disease turned out as relatively mild,” observes Erasmus Medical Centre’s Ab Osterhaus. “But that was justified because its alert phases are based on the virus’ transmissibility and not its virulence.”

Researcher Peter Openshaw of London’s Imperial College said there may be “some very powerful lobby groups who put pressure on policymakers” but this is more than balanced by politicians’ concern

about the public good and their own popularity with voters. As a health adviser to the UK government, Openshaw said “I have never been contacted or put under pressure by any interested party. Our conditions with industry were openly declared and we avoided all new, informal or unofficial contacts with industry during the outbreak.”

WHO PANDEMIC PHASE 6 ON 11th OF JUNE



European Centre for Disease Prevention and Control.

CASE STUDY: THE UK’S APPROACH TO PANDEMIC PREPARATION

Were the UK’s pandemic preparations excessive? Not in the view of Imperial College’s Peter Openshaw. “Policy and planning were sensible, and proportionate to the perceived risk,” he says. “The government sought and accepted the advice of the scientific community.”

Openshaw said H1N1’s international spread was a question of “when, not if.” Noting that scientific articles describing the outbreak began to appear as early as May 2009, he said researchers aimed to establish the basic disease parameters to put into their statistical models to predict how H1N1 might spread and impact on human populations around the world.

“In the early stage, we were reasonably afraid that our healthcare services would be completely overburdened. There were reports from Mexico City in April and May describing the effects of the outbreak on hospitals there, with up to a third of all patients suffering from flu. There were also reports of the hospital healthcare workers dying—quite scary,” he said. “So our reaction here in the UK was not exaggerated or excessive. At the height of the epidemic we met in Whitehall [the seat of British government] at least once a week being fed information from several different modelling teams, each working to develop the most reliable models as a guide for policymakers.”

VACCINES: THE HEART OF THE ISSUE

Have pandemic vaccines been proven to be effective against the current H1N1 pandemic virus? Were they sufficiently tested for safety in Europe and are there any safety issues after their administration? If not, then why were doctors and other health care workers (HCWs) in certain countries reluctant to receive or administer the pandemic vaccines? Were vaccine recipients unnecessarily medicated in view of H1N1's relative low virulence, and how to explain the lag between demand and production of vaccines?

Vaccine availability in times of crisis: public investment versus private production

The vast majority of the world's vaccine companies for seasonal flu are in Europe – about 70 percent. Despite this productive muscle and best efforts by industry, "it still takes about half a year to respond to a flu situation," Ab Osterhaus told the ESWI workshop. Currently, worldwide production capacity stands at 900 million doses of seasonal influenza vaccine. Though this is a significant improvement

compared to five years ago, Osterhaus said health officials in his own country are cautious about their vaccine expectations.

"We anticipated production problems and reflected that in the contracts with industry. One must realize that for seasonal flu there are often problems in having the right virus strain for production in time. In case of shortage you only receive a percentage of what you ordered," he said.

Can Europe improve its vaccine response time? "We have been sitting on our hands for the last decades. If we want to be prepared for the next pandemic, we had better start investing now," he said, adding that national vaccination policies need addressing, too. "There were more than 20 different vaccination protocols for risk groups across Europe: something needs to be done about this."

POTENTIAL INFLUENZA A(H1N1) VACCINE MANUFACTURERS



With the vast majority of world production of seasonal flu vaccine concentrated in Europe, other regions such as South America and Asia now realise they should not be dependent on foreign production or they will be at the end of the line for distribution.

Gap between potential demand and anticipated supply (94 million/week, low yield)

Vaccines: are they safe? Are they efficient? And who should use them?

All the pandemic vaccines used in EU members states had been approved by the regulatory authorities on the basis of safety and efficacy data, according to procedures that had been implemented before the pandemic started.

Are additives to vaccines such as merthiolate or adjuvants harmful? According to WHO and EMEA, they are not. Observes Osterhaus: "Merthiolate in vaccines has long been practiced

and its use in low concentrations as a conservant in 'multi-vials' is harmless. Furthermore the adjuvants used in these vaccines have also been tested extensively and satisfactory for safety and efficacy in animal and human trials.

One big question is whether the vaccines of winter 2009 will offer any protection in 2010. In his view, younger people who've been vaccinated "will be protected for a much longer period,

based on what we know about other adjuvanted vaccines. Currently, there is very little variation in the H1N1 virus, and even if we do see drift of the virus, there has probably been good priming in Europe with the vaccination. I think there will be some carry-over immunity to the next season, though risk-groups are another story: they should be vaccinated in the next seasonal influenza vaccination programme."

Public-private dialogue on vaccine development and stockpiling: a sensitive issue

Public health officials have mixed feelings about dialogue with industry regarding coordination of vaccine development and stockpiling – and yet it is an important dialogue.

"This should not be discouraged," says Osterhaus. "If you look at anti-cancer or anti-HIV treatments, for example, they have all come from industry and

save many lives. If you refuse to talk to the private sector, fine with me, but the consequences would be serious: The public sector no longer produces vaccines or other medicines."

The World Health Organisation does interact with industry, but in a very disciplined way, according to Osterhaus. "WHO's talks with health

authorities sometimes take place with industry in the room, but after this a session is held without them being present. As long as you are transparent about it, this can work. But to cut off all dialogue with industry would be bad for public health."

SEASONAL VS. PANDEMIC VACCINES: THE ESSENTIAL QUESTIONS

Millions of people in Europe were vaccinated against H1N1? Was this really necessary?

Yes. Although it is too early to determine the overall effect of measures, and the disease burden that has been prevented and the lives have been saved. The cost-effectiveness of measures still needs to be determined, but a policy of "better safe than sorry" is the responsible thing to do.

Why were so many doctors and health professionals reluctant to vaccinate or become vaccinated?

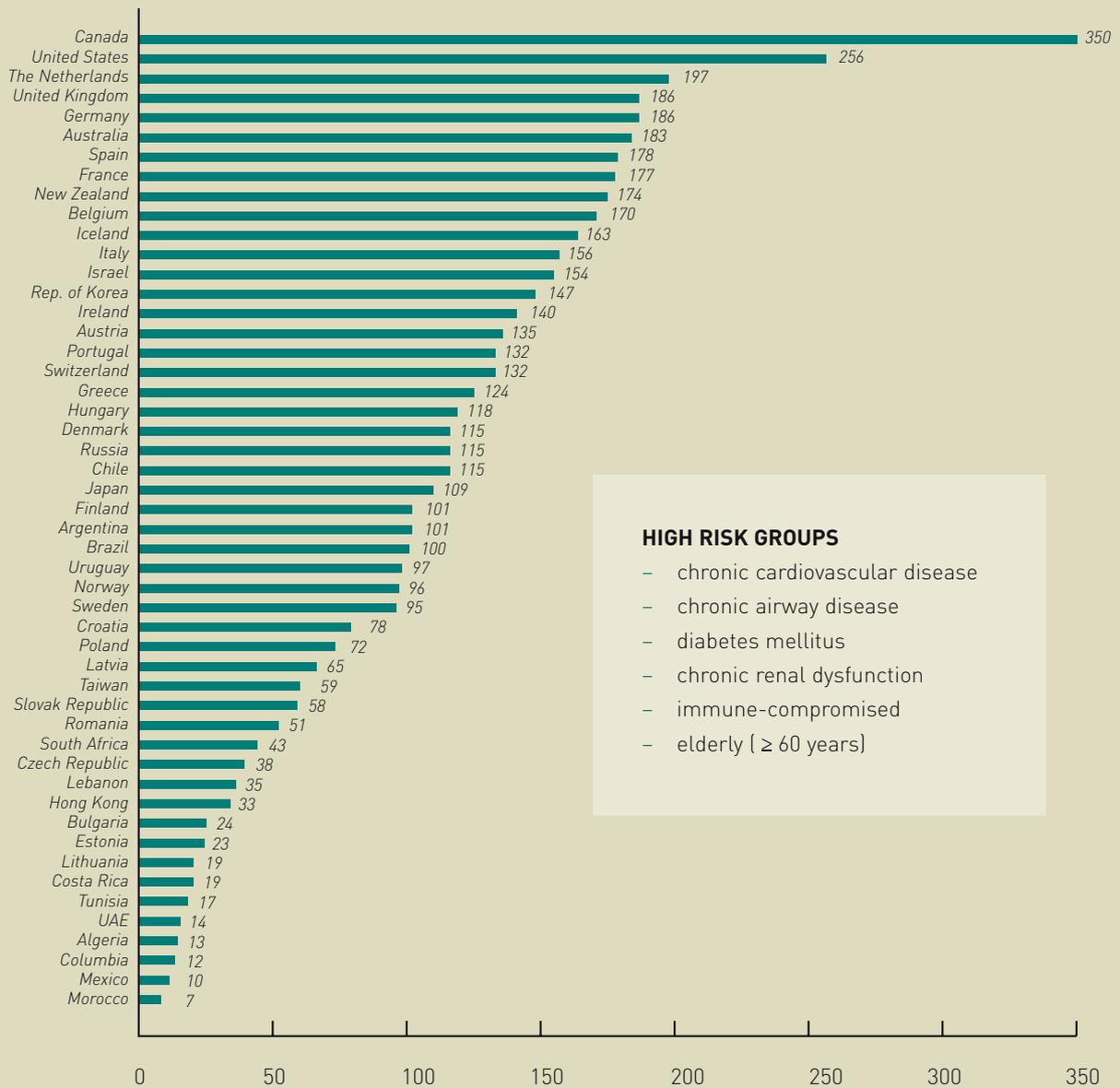
There are many differences of compliance between

EU countries, from high (>80%) to low (<20%). Lack of trust and coordinated information were the main negative drivers.

What about evidence that natural infection with swine flu induces some protection against more dangerous virus types? Isn't it better not to vaccinate?

No. While the pandemic H1N1 virus has caused relatively mild disease in the majority of infected people, its overall burden in those infected was too high to take the risk of not vaccinating. This pandemic virus cannot be considered a truly "attenuated vaccine" virus.

DOSES OF SEASONAL INFLUENZA VACCINE DISTRIBUTED PER 1,000 POPULATION



HIGH RISK GROUPS

- chronic cardiovascular disease
- chronic airway disease
- diabetes mellitus
- chronic renal dysfunction
- immune-compromised
- elderly (≥ 60 years)

MIV Study Group, 2005

Failing to use the seasonal influenza vaccination to the full extent, weakens a country's pandemic preparedness.

ANTIVIRALS : STOCKPILES, THERAPY AND VIRAL RESISTANCE

Policymakers between, and even within, different countries are split over the effectiveness of antivirals in combating influenza viruses. This diversity of opinion translates into equal amounts of confusion for the general public, which has watched some industrially advanced societies embrace the practice of administering antiviral doses while others reject them out of hand as ineffectual and a waste of resources. The definitive answer is still “out to jury” with the research community, however.

The efficacy of antivirals is not conclusive across the research community, but the evidence is encouraging

Monto:

Antivirals have been used in many ways across the globe. For example, in the UK, which had one of the largest antiviral stockpiles in 2009, a sizeable amount of antiviral drug was used in an effort to contain the outbreak, especially in schools.

“Containment was not possible at that point, but attack rates were reduced,” says Monto. “In the US antivirals have been used extensively for treating children, pregnant women and severe cases in other adults. Early evidence shows improved outcomes with early treatment.” He added that the US government has strived so that patients with the presumptive disease would be treated quickly – before laboratory tests were available.

As for virus’ resistance to antivirals, he said that “has not been an issue, and only expected side effects have been seen so far.” According to Osterhaus, there is some resistance to the antiviral known as Tamiflu. “We have encountered this in more than 150 sporadic cases. The particular

mutation involved is predominantly seen in immuno-compromised people. We’ve also seen it before in seasonal flu, which popped up about three years ago. In that case the resistant virus became more fit than the sensitive virus and replaced it. Fortunately this has not happened with the Mexican flu virus.”

The UK chose the costly and politically risky path of making antivirals widely available to its public, knowing that many doses would go to people who would never get the flu. It only demonstrates that every public health stance on pandemics has its sharp advantages and disadvantages.

THE UK'S APPROACH TO ANTIVIRAL STOCKPILING CARRIED UNAVOIDABLE POLITICAL RISK, ALONG WITH A HEAVY INVESTMENT COST

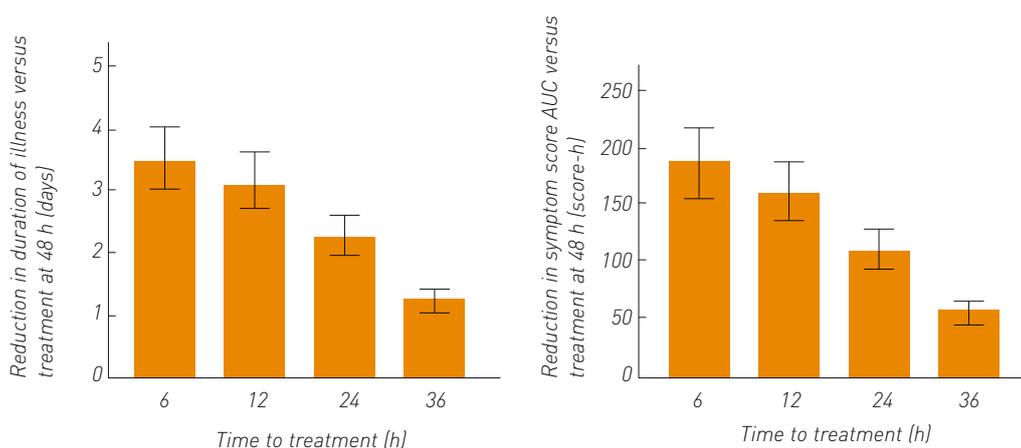
"What we did in the UK was sensible and necessary," observes Peter Openshaw, professor and influenza adviser to the government. "If we hadn't done it, we would have been heavily criticized."

London opted to build up a stockpile of 40 million courses of Tamiflu – with a limited shelf life. "That was a big investment, though we had some stocks of inhaled zanamivir as well," he said.

Openshaw said there was a lot of discussion about how to communicate the change from prevention of

infection to treatment to the public. "We had to make it clear that the decision to stop treating contacts wasn't a sudden u-turn in policy but an anticipated move, planned in advance," he said. "The government set up a national pandemic flu phone service where the public could call in and get the information they needed, including permission to pick up Tamiflu at their local pharmacy. This took a lot of pressure off family doctors, but clearly had risks."

EARLY ADMINISTRATION OF ORAL OSETAMIVIR IS IMPORTANT



Aoki, F.Y. et al. J. Antimicrob. Chemother. 2003 51:123-129; doi:10.1093/jac/dkg007

The UK's distribution of antivirals during the pandemic: how did it unfold?

According to Peter Openshaw, the UK's department of health found itself "handing out a lot of antivirals to folk we knew wouldn't actually have flu. Not surprisingly, there were reservations about this. However, I don't think we had much choice," he said.

"Do antivirals work, you ask? The use of antivirals has been questioned by sceptics, but we know from animal and clinical studies that, as a rule, you need to start treatment very early if it's going to make much difference.

What next: could a full-force pandemic still strike?

"In the US, we have already had two waves of the pandemic virus. The first wave occurred in large regions, but did not involve the whole country. The second autumn wave was more wide-spread," says Monto.

Though there is a debate in the United States about whether there will be a third mid-winter wave in the country, he warned that other countries that have not seen much infection will probably experience this winter wave.

"Many parts of the world are only now beginning to see the start of pandemic H1N1 activity. They are the countries where deaths will occur in cases that might otherwise survive with antiviral treatment and intensive care," he said. He also insists that the world should not forget that occasional transmission to humans of the far more virulent avian H5N1 virus strain "is still occurring."

Given early, they really seem to work," said Openshaw.

He added that one major imperative is to create a more positive legal and ethical environment in the UK that better accommodates research needs. "If we could get blood samples early on to see how many people were infected but showed no signs, it really would have helped. Anxiety, misinformation and legal obstacles often prevent getting quick results," he observed.

So, what may happen next with the pandemic H1N1 virus? Per Osterhaus, the following are factors to watch out for:

- co-circulation with human H1N1 and H3N2 or avian H5N1, which may lead to re-assortment with human seasonal or avian flu viruses
- change of virulence in a possible future wave through mutation
- acquired antiviral resistance through mutation
- introduction of a novel pandemic virus from the animal world, e.g. based on H5N1
- re-appearance of the Mexican flu virus annually as a seasonal flu virus

Anxiety, misinformation and legal obstacles often prevent getting quick results.



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