ESWI

... EUROPEAN SCIENTISTS FIGHTING INFLUENZA

The European Scientific Working group on

INFLUENZA

ANSWERING THE INFLUENZA THREAT: PANDEMIC VS SEASONAL INFLUENZA

Prof. Ab Osterhaus, *Erasmus MC Rotterdam*
Prof. Bruno Lina, *University of Lyon*
Prof. Kristin Nichol, *University of Minnesota*
Dr Ted van Essen, *Utrecht University Medical Centre*

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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. Bruno Lina

Dr.Lina currently holds the positions of Professor of Virology, Université de Lyon (since 2001); Head of the laboratoire de Virologie Est des Hospices Civils de Lyon (since 2006); Head of the UCBL-CNRS FRE3011 research Lab on Influenza virus (since 2007), Director of the National Influenza Center (NIC), Lyon (since 1999); Member of the French Pandemic planning committe and Comité de lutte contre le Grippe of the Ministry of Health (since 1997); Chair of the Groupe d'Experts et d'Information sur la grippe (since 2005); Chair of the WHO Advisory Group for the sharing of virus and benefits (since 2008); President of the European Society for Clinical Virology (since 2007). Dr.Lina studied medicine at the University of Lyon where he graduated as a MD in 1990 and completed his PhD in 1994.

Dr. Lina is also a member of several professional societies including: American Society for Microbiology, European Society for Clinical Virology, Société Francaise de Microbiologie.

He was awarded Chevalier de la Légion d'Honneur in 2010.

He has been the Co-PI of several national and international collaborative projects in the fields of virology in the past 8 years.

Furthermore he holds editorial positions for scientific publications for the Journal of Clinical Virology and the Influenza Research and Treatment Journal. He is the winner of the ASM Young Investigator award (1994), holds several patents, has been the supervisor and mentor of more than 15 PhD students. Over the last 16 years, Dr. Lina is author of more than 100 scientific papers, including reviews, book chapters. He has been the author of a Book on the A(H1N1) pandemic virus and asked for numerous junior scientific review of pandemic viruses in Junior scientific reviews in French.

Prof. Kristin Nichol

Dr. Nichol is Professor of Medicine at the University of Minnesota and Associate Chief of Staff for Research at the VA Medical Center in Minneapolis. Dr. Nichol's research has focused on issues relating to adults vaccines with a special emphasis on influenza and pneumococcal vaccination. She has pursued observational studies and clinical trials in such areas as successful delivery strategies, determinants of vaccination behavior, side effects associated with vaccination, and the clinical efficacy and cost effectiveness of vaccination. Dr. Nichol has authored more than 100 publications in these areas and has given presentations at numerous national and international meetings.

Dr. Nichol is Chairperson of the Minnesota Coalition for Adult Immunization – a position she has held for 20 years. This group provides leadership for enhancing adult vaccination for the entire state of Minnesota. She also served for 15 years as the Department of Veterans Affairs ex officio member of the US Advisory Committee on Immunization Practices (ACIP).

Dr. Nichol received her MD and MPH degrees from the University of Minnesota and her MBA from the University of St. Thomas. She pursued her internal medicine training at the University of California in San Francisco and the University of Minnesota. Dr. Nichol is boarded in Internal Medicine and Preventive Medicine.

Dr Ted van Essen

Dr. G.A. (Ted) van Essen has been a General Practitioner since 1976 and Vocational Trainer since 1981 in Amersfoort, the Netherlands. He is also Assistant Professor (since 1992) at the Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht. He was President of the Dutch College of General Practitioners from 2000-2004.

Dr. Van Essen was born in the Netherlands and educated at the University of Groningen (M.D. and G.P.) and at Utrecht University were he received his Ph.D. Dr. Van Essen was a member of the Dutch Influenza Foundation, the Dutch Pneumococcal Foundation and different local, regional and national GP organisations. He is a member of the Influenza Vaccination Committee of the Dutch Health Council.

Some of his recent publications (amongst others) include: Which determinants should be targeted to increase influenza vaccination uptake among health care workers in nursing homes?Vaccine. 2009 Jul 23;27(34):4724-30. Epub 2009 May 29.Influenza vaccination of healthcare workers, oseltamivir resistance and prepandemic vaccination. Expert Rev Resp Med 2008; 2: 703-5. Threat of an influenza pandemic: family physicians in the front line. BMC Fam Pract. 2009;10(1):11. Influenza immunization of Dutch general practitioners: Vaccination rate and attitudes towards vaccination. Vaccine. 2008;26(47):5918-21. Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data. Lancet. 2008 Mar 15;371(9616):908-14. Influenza vaccination coverage and reasons to refrain among high-risk persons in four European countries. 2006. Inhaled Zanamivir Versus Placebo for the Prevention of Influenza Outbreaks in an Unvaccinated Long-term Care Population. J Am Med Dir Assoc. 2005 Macroepidemiology of Influenza (MIV) Study Group. The macroepidemiology of influenza vaccination in 56 countries, 1997-2003. A report from the Macroepidemiology of Influenza Vaccination (MIV) Study Group. 2005 Clinical effectiveness of influenza vaccination in persons younger than 65 years with high-risk medical conditions: The PRISMA Study. Arch Intern Med. 2005

FOREWORD

On 10 August 2010, Margaret Chan, head of the World Health Organization (WHO), formally declared that the H1N1 swine flu pandemic has entered the post-pandemic period. ESWI regarded this declaration a hinge moment for public health, since it offers a perfect opportunity to look back and assess the efficacy and effectiveness of the H1N1 pandemic approach in Europe. At the same time, it is the right moment to look ahead and to emphasize the importance of continued vigilance, since, in the words of Margaret Chan: "Pandemics are unpredictable and prone to deliver surprises".

ESWI organized its Fourth Influenza Workshop for Public Health Officials in order to help answer the most urgent questions raised by the official declaration regarding the pandemic's end. Scientific experts provided objective state-of-the-art information about the efficacy and cost-effectiveness of H1N1 pandemic influenza vaccination, the implementation of effective vaccination strategies and, obviously, an assessment of the pandemic potential of different influenza virus strains (including H1N1 and H5N1).

The Fourth Influenza Workshop for Public Health Officials was held on 17 September 2010 in Brussels. More than 20 public health officials representing 15 different countries attended the meeting, demonstrating their need for state-of-the art and unbiased data about influenza.

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	Prof. Bruno Lina	Prof. Kristin Nichol	Dr Ted van Essen
Erasmus MC Rotterdam	*University of Lyon*	*University of Minnesota*	*Utrecht University Medical Centre*

ESWI is a partnership organization with a clear mission: to reduce 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.

PANDEMIC SECTION

THE MEXICAN FLU PANDEMIC: NOT A CLOSED CASE

The 2009 influenza pandemic's origin, spread, effects and the reaction to it across the globe are still an unfolding story. This raises many questions for the international healthcare community about how to prepare for the next pandemic. What we do know, however, is that the current one turned out to be less virulent than expected, though that is no justification for complacence.

"It is debatable whether this pandemic is over or not," warns Prof. Ab Osterhaus, Professor of Virology at Rotterdam's Erasmus Medical Centre, and chairman of ESWI. "We all need to examine whether we did the right thing and whether there are conclusions to be drawn yet. But this pandemic is still around and mutations – potentially deadly ones – are still a possibility. We cannot say: 'Oh, it's now over.' We have to be prepared, we have to expect the next one."

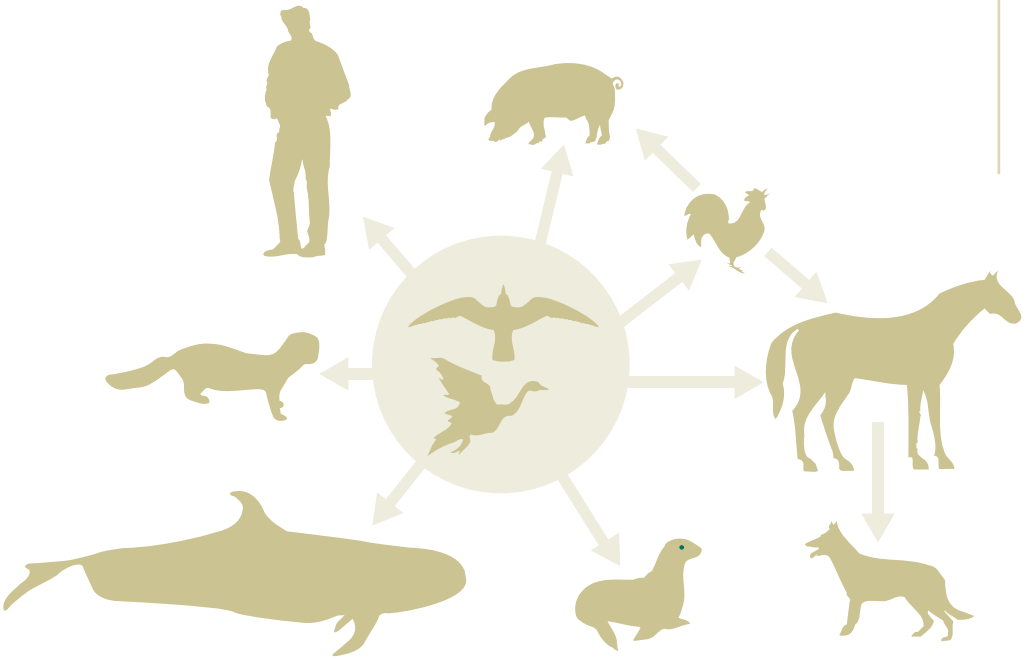
WHERE DID THE PANDEMIC MEXICAN FLU COME FROM?

Despite the ever-more sophisticated tools of modern science, we still don't know exactly how the pandemic virus jumped from its animal hosts to humans. Or how the genomes of two different virus strains – one in Asia and one in North America – merged to produce what the world now knows as the H1N1 Flu pandemic.

The medical research community is still unsure how the H1N1 avian virus propagated itself. It could have been transmitted in several ways, starting from wild fowl and moving to either domestic fowl or pigs, and then from them to humans – or even straight to humans. (see diagram)

"It's very puzzling," said Osterhaus. "Could the Eurasian pig virus have mixed with the North American pig virus to produce the Mexican flu? First of all, pig meat does not trade between Asia and America. And second, the old dogma that humans can only be infected with a virulent influenza virus via pigs is simply not true. The viruses may start out as low-pathogenic ones but when they pass into domestic poultry via the H5 and H7 strains they can mutate into high-pathogenic ones that can go straight to humans."

Thus, the pig-to-human transmission of the Mexican flu was not likely in his view. "I think it probably occurred via human transmission: by someone or something that traveled from Asia or Europe, carrying the infection to Mexico where it spread from there to the United States and thence by air travel to around the world," he observed.



"Virulent influenza can use multiple pathways to reach its human target."

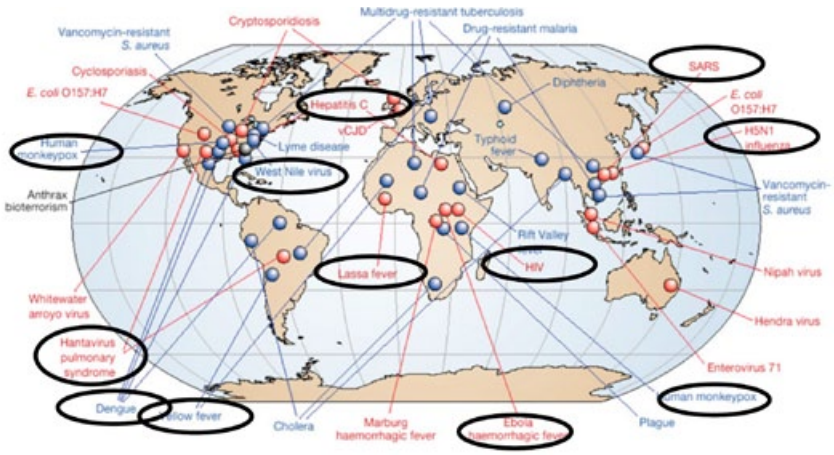
THE IMPORTANCE OF PERVASIVE AND RAPID PANDEMIC SURVEILLANCE

The ability of health officials around the world to detect and notify influenza outbreaks is strong and growing. The rapidity by which the 2009 pandemic virus was spotted and tracked shows how responsive this network can be. But it needs more investment and more effort to make it a true "one world, one health" surveillance tool for the globe that functions in real time as much as possible.

"There's been a lot of talk and criticism of WHO and whether it was right to declare the Mexican flu pandemic given the virus' low pathology, but such criticism is absolutely ridiculous," Osterhaus told the workshop. "The severity of the flu was not the issue, though it was perceived that way. The trigger for WHO's decision was the virus' transmissibility. A pandemic is a pandemic, regardless of its virulence." Just as important as WHO's decision to declare the pandemic, however, was the international cooperation for monitoring the spread of the virus. "With good surveillance collaboration you can nip a pandemic in the bud," he observed.

THE IMPACT OF VIRUSES ON PUBLIC HEALTH

- EMERGING AND RE-EMERGING PATHOGENS -



Source: D.M. Morens et al. Nature 430:242-9, 2004

Noting today's network of surveillance around the world, Osterhaus pointed to the 50 flu centers under WHO's aegis in Europe and the need to invest in that capability. "I would like to make a plea for more investment in the surveillance of humans and animals, of which pig surveillance is particularly important. I'm glad to see that the WHO is now focusing on this, as is the United States," he said. "However, we need to ensure there is even a stronger surveillance system in the future by doubling or tripling its size. If we had identified the Mexican flu virus just three months earlier, the pandemic vaccine would have been available that much earlier too, with all the avoided costs."

As an example, he reminded his audience that the mortality and years-of-life-lost associated with H1N1 infection in the US is estimated as high as 2 million years. "That alone is enough to justify vaccination," he said.

PANDEMIC PREPARATION AND RESPONSE: VACCINATE OR NOT?

Public authorities, the medical establishment and virology researchers are divided over the ideal approach to vaccines to protect their populations against influenza, whether of the pandemic or seasonal variety. Is there a "priming" effect of seasonal vaccines that provides some immunological protection against a subsequent pandemic?

Though the results are still preliminary, a comparison of the 2009 pandemic vaccination strategies in two regions of Europe reveals interesting parallels about their outcome, says Prof. Bruno Lina, Professor of Virology at the University of Lyon, France.

CASE 1: THE RESULTS OF SCOTLAND'S VACCINATION APPROACH

A recent analysis of statistics linked to Scotland's pandemic vaccination campaign presents a strong argument in favour of vaccination. Known as the VIPER study[1], it was carried out by Scottish universities to determine the effectiveness of vaccination in reducing emergency admission to hospital for all patients. The study extracted information from the patient databases of 41 general practitioners across Scotland during the pandemic's second peak of October-December 2009. This revealed a 12-percent uptake of the adjuvanted vaccine for Scotland's population as a whole.

Even after the results were adjusted to reflect the population's age, sex, at-risk co-morbidity rates, etc., the outcome was striking. "The effectiveness was 100 percent. No one who was vaccinated got the flu or was hospitalised," Lina told the workshop. "Together these two studies strongly suggest that vaccination reduces the risk of flu and pneumonia while reducing mortality."

1 Simpson CR, Ritchie LD, Robertson C, Sheikh A, McMenamin J. Vaccine effectiveness in pandemic influenza - primary care reporting (VIPER): an observational study to assess the effectiveness of the pandemic influenza A (H1N1)v vaccine. Health Technol Assess. 2010;14:313-46.

CASE 2: THE RESULTS OF GERMANY'S VACCINATION APPROACH

"The German government's preparations and response to the pandemic was quite consistent and well funded. Thus, it provided a good foundation to observe the effects of the country's national strategy," observes Lina.

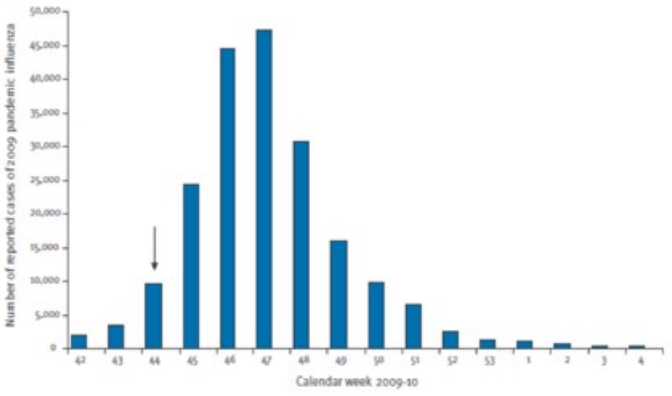
A recent study by German researchers[1] could thus rely on a consistent foundation for sampling. It was carried out across all 16 Länder (regions) of the country. Moreover, Germany had sufficient stocks in place to react quickly by administering adjuvanted vaccines at the very beginning of the pandemic's second wave.

The study examined nearly 46,000 laboratory-confirmed cases of pandemic influenza to determine the vaccine's effectiveness in two age-groups: 14-59 years and 60 years or above. The extrapolated results? The vaccine's efficacy was more than 95 percent in the 14-59 age group and more than 80 percent in the elderly.

The statistics from that study "are really straightforward—no doubt about that," said Lina. "The difference between those who were vaccinated versus those who were not were so stark that we could estimate the vaccine's effectiveness at more than 95 percent in the 14-59 age group and about 83 percent in the over-60 group. These figures are similar to those obtained with seasonal flu vaccinations."

1 Wichmann O, Stöcker P, Poggensee G, Altmann D, Walter D, Hellenbrand W, Krause G, Eckmanns T. Pandemic influenza A(H1N1) 2009 breakthrough infections and estimates of vaccine effectiveness in Germany 2009-2010. Euro Surveill. 2010;15(18):pii=19561.

DYNAMIC OF THE EPIDEMIC WAVE IN GERMANY



Wichmann O et al, Eurosurveillance, 2010

SEASONAL SECTION

SEASONAL VACCINATION: THE MYTHS & THE BENEFITS

Scientific and medical opinion is still not uniform about the interplay between seasonal and pandemic viruses, nor how seasonal vaccination plays into the picture – although evidence is growing that the latter can mitigate the effects of a pandemic virus. This depends on the rapidity by which the viral strains are identified, isolated and converted into vaccines – and, of course, on available resources and the economics of public health policy options.

Overcoming viral resistance is one thing, but getting around the public's resistance to vaccination is another. Myths persist about the efficacy of seasonal vaccination and its imputed side-effects, while medical opinion remains mixed about the sensitive issues of vaccinating young children, pregnant women and other at-risk groups. Towering over all these issues are the tough allocation-of-resource decisions that public policymakers must make.

FLU SHOTS:
APPROPRIATE FOR THE YOUNG? AND WHAT ABOUT THE SIDE-EFFECTS? JUST THE FACTS, PLEASE.

There is some evidence to suggest that vaccinating small children and young adults for seasonal flu may increase their resistance to a pandemic strain. National health policies across OECD countries split sharply on the issue, however, while public myths persist about the alleged side-effects of influenza vaccines, antivirals and adjuvants in general.

What are the pros and cons of vaccinating children for seasonal flu? "If you vaccinate children for seasonal flu, then it is my opinion that you should do the same for pandemic flu: then they are protected," Ab Osterhaus told the workshop. "Theoretically, one could argue that young children vaccinated with seasonal flu and subsequently challenged with H1N1 [Mexican pandemic virus] are more vulnerable – that the fact that they were exposed to the vaccine might make them slightly more susceptible to the pandemic virus. But there have not been enough studies conducted yet to draw any firm conclusions about this."

Bruno Lina agreed. Referring to the VIPER study, he said its researchers reported that some young age groups, which had previously received seasonal vaccines, were more likely to get pandemic flu. "However, it is very difficult to assess whether this was related to their seasonal vaccination," he stressed. "Many children have already been exposed to flu before they get vaccinated, so they may have been 'primed' with one sero-type or another," he said.

"On the one hand, there is the theory that a person's antibodies may be set to protect against the seasonal virus but not a pandemic one, but there are other arguments that asset the opposite: that this enables an antibody to adapt itself slightly better to meet the challenge of a pandemic. There's no crystal clear view yet," said Lina.

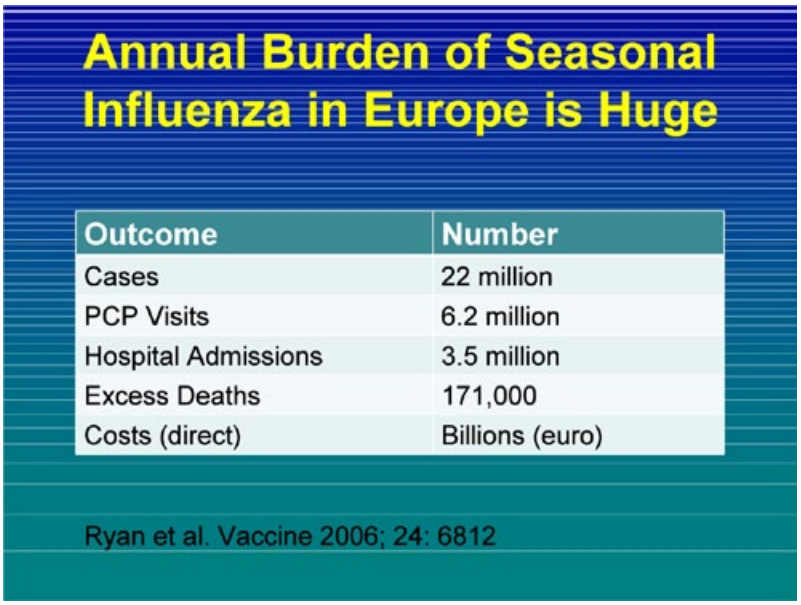
As for perceptions about the side-effects of seasonal vaccines, Osterhaus poured cold water on "groundless media-driven public fears" that antivirals and other medicines were behind post-prophylactic suicides in Japan or incidences of narcolepsy in France. "It is too early to draw any final conclusion, but if there was any real linkage or serious symptoms breaking out, we would have heard about it by now," he said.

Seasonal flu shots for children – a pointed issue.

THE ECONOMICS OF VACCINATION: WHICH RATIONALE IS BEST?

Allocating resources for public health purposes is obviously a touchy subject, and the prioritisation behind influenza vaccines is no exception. Such policy clearly has economic-impact-vs-mortality implications that public health officials should not shy away from assessing, argues Dr. Kristin Nichol, Professor of Medicine at the University of Minnesota.

"Seasonal flu in the total disease profile is just the tip of the iceberg of the total disease burden," she told the workshop. "The underlying bits are: exacerbations of chronic illnesses such as heart disease or diabetes and secondary problems such as staph infections. These all lead to misery, absenteeism, physician visits, antibiotic use, hospitalization and deaths. And when all is added up, the cost for a country is huge."



According to US flu statistics for 2007, for example, seasonal influenza caused 31 million outpatient visits and a loss for 44 million productivity days, leading to a staggering loss for the economy of $87 billion. "Seasonal flu is a big deal and we shouldn't overlook its economic impact," she stated.

So does seasonal flu intervention deliver true value for the resources expended? It does, according to Nichol, who pointed to three different methodologies for allocating resources to vaccines.

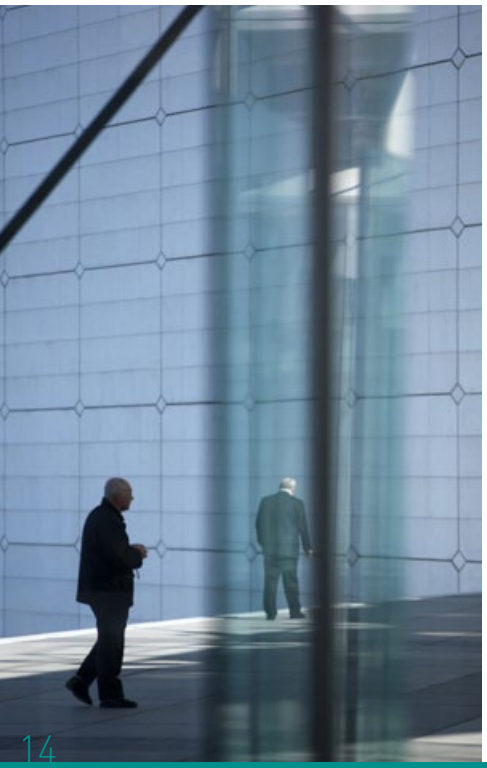
The first is cost-effectiveness analysis, based on avoided costs and deaths. The second is straightforward cost-benefit analysis, based on the net savings of vaccination, and the third is cost-utility analysis, based on quality-adjusted life year calculations. Of the latter, Nichol said "I don't necessarily agree with this, as its notion of quality is a bit odd when you are treating the disease because it doesn't reflect all the direct and indirect costs such as absenteeism."

Whatever the model used, awareness of the cost-benefit assumptions that lie behind any seasonal vaccination strategy is imperative, she said. "Simply put: if you want to maximise economic savings, then target the working population; if you want to avoid deaths, then target the older 65-age group. These are not easy choices but, as researchers and health economists, we have an obligation to explain the options for policymakers."

SEASONAL VACCINATION: "GOING DUTCH" TO GET ALL VACCINATION STAKEHOLDERS ON BOARD

Defining a national vaccine objective is one thing; attaining it is another kettle of fish, as the saying goes. A successful uptake of vaccination depends on the obvious such as available stockpiles and budgetary resources but also on invisible factors. These include public perceptions and, critically, the attitude of a country's health care workers (HCWs) and general practitioners (GPs) – and whether they have "ownership" of the issue.

Creating ownership among HCWs and GPs for vaccination is not always evident, but the Netherlands has managed to achieve it to a considerable degree, according to Dr. Ted van Essen of Utrecht University's Medical Centre.



Noting that Dutch policy is to vaccinate all its at-risk members of society – some 5.2 million people out of a total population of 16.5 million – van Essen said 72 percent of these received one vaccination, while an impressive 64 percent got a second booster shot during the Mexican flu pandemic's peak month of November 2009.

What accounts for the high uptake rate? It's a combination of premeditated policy choices, he said.

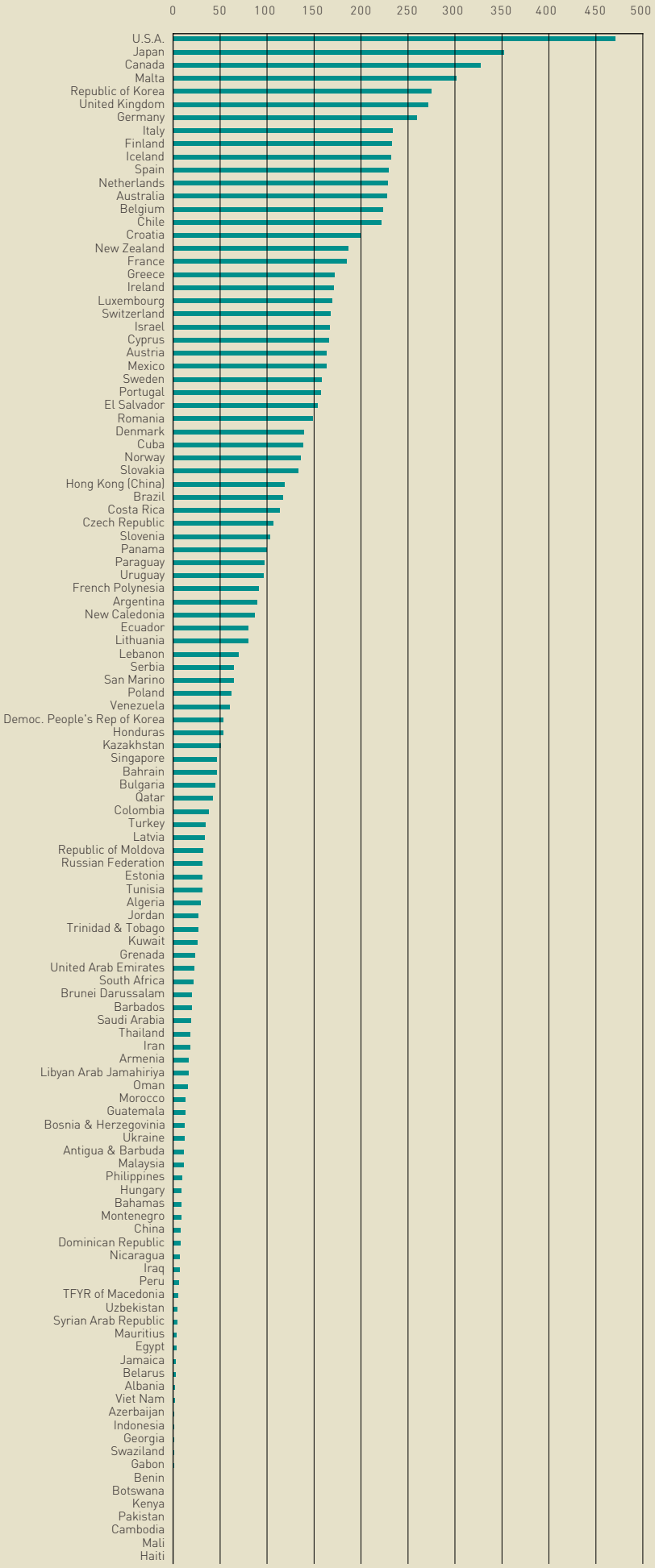
For example, Dutch authorities try to make one professional – the GP – ultimate accountable for educating and encouraging his patients. "It is essential that the Dutch GP sends postcard invitations and flyer information [about the benefits of vaccination] to his patients," van Essen told the workshop. "Also, the government offers a fee for the service so the GP gets 10 euros per vaccine. Giving money to the GP helps as an incentive."

Other Dutch factors that help are:

- the maintenance of good electronic medical records across offering selection criteria (age, risk code, patient medication, etc.)
- special vaccination hours that make it easy for the public to come to clinics
- free vaccinations for patients at-risk
- a centralised government contract for vaccines
- easy paper work for the GP and HCWs
- use of feedback from the public and GPs to track results

"If you throw in all the seasonal vaccinations about the same time, you're looking at 11 million vaccinations that took place in six weeks. For our country's, that a very satisfactory rate," he said.

DOSES OF SEASONAL INFLUENZA VACCINE DISTRIBUTED PER 1,000 POPULATION IN 2007



HIGH RISK GROUPS

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

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

IFPMA IVS, 2008

c/o Link Inc
Tolstraat 9
2000 Antwerpen,
Belgium
phone + 32 3 232 93 42
fax + 32 3 232 17 04
info@eswi.org
www.eswi.org
www.flucentre.org