

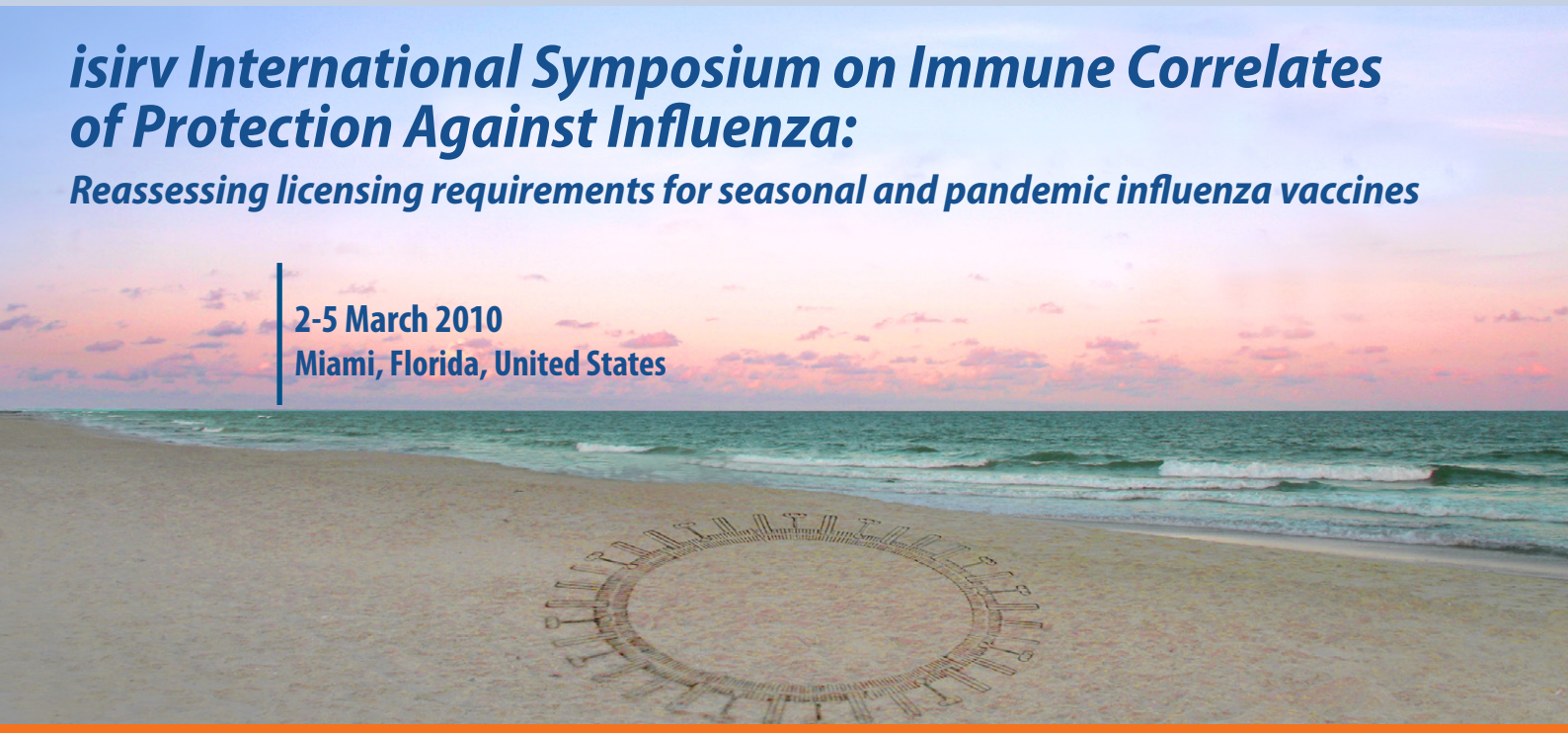


# Respiratory Virus Report

spring 2009

**isirv International Symposium on Immune Correlates  
of Protection Against Influenza:**  
*Reassessing licensing requirements for seasonal and pandemic influenza vaccines*

2-5 March 2010  
Miami, Florida, United States



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Robert Webster eulogizes Australian researcher Graeme Laver, who made major contributions to our current understanding of influenza ecology and antigenic drift, and to the development of subunit vaccines and influenza antiviral drugs

## SPECIAL BULLETIN

**In response to the ongoing influenza A (H1N1) outbreak, isirv has posted two new resource lists on its website. These lists will facilitate access to current guidance and background information relative to this new public health threat.**

**isirv is committed to providing accurate information to its membership. Visit [www.isirv.org](http://www.isirv.org) for more information and authoritative sources of key professional information on the influenza A (H1N1) outbreak.**

# Highlights of the isirv International Symposium on Viral Respiratory Disease Surveillance

by John Watson, MB BS, MSc, FRCP, FFPH



The surveillance symposium was a great success. Pilar Perez Brena of the National Centre for Microbiology at the Instituto de Salud Carlos III, welcomed delegates to the “charming, mysterious, and warm” city of Seville, Spain. The city, and the Melia Sevilla Hotel, provided an ideal setting for the meeting, and a comfortable venue for networking with colleagues from around the globe.

Over 170 delegates from 43 countries representing various government, academic institutions, and commercial organisations participated in the two and a half day meeting, a new initiative developed and organised by **isirv**. Significant financial support for the symposium was provided by the US Centers for Disease Control and Prevention, the US Armed Forces Health Surveillance Center, the US Department of Health and Human Services, Roche, sanofi pasteur, bioMérieux, the US National Institutes of Health, and TIB MOLBIOL.



Entrance at Plaza de Espana, Seville  
Credit: Marge Tamas

Unlike most scientific meetings, the Surveillance Symposium was run like a WHO meeting, with lectures followed by structured discussions to produce action-oriented meeting outcomes. A total of 30 lectures on national and global approaches to

viral respiratory disease surveillance, seasonal and pandemic influenza surveillance, and viral respiratory pathogens other than influenza were presented. Three stimulating keynote lectures were also delivered. David Heymann of the WHO spoke on “Recognizing the Next SARS and the Role of Surveillance,” Ilaria Capua of the Istituto Zooprofilattico Sperimentale delle Venezie addressed “Influenza at the Human-Animal Interface: The Need for Collaborative Surveillance and Research,” and Thomas Brieseman of Columbia University presented “Respiratory Pathogen Discovery: A Staged Strategy and Recent Developments.” All of the presentations were warmly received.



John Watson opening the symposium  
Credit: Greg Gray



Panelists for “Seasonal Influenza Activity Surveillance,” from left to right, Andrea Ammon (chair), Caroline Brown, Ousmane Diop, Krongkaew Supawat, Akhilesh Chandra Mishra, Talat Mokhtari Azad  
Credit: Greg Gray

## Highlights of the isirv International Symposium on Viral Respiratory Disease Surveillance, Continued

by John Watson, MB BS, MSc, FRCP, FFPH

John.Watson@HPA.org.uk



Conversation during a break  
Credit: Marge Tamas

The principal recommendations from Dr Heymann's superb keynote address are to recognize the existence of many types of surveillance systems and to use them all. Dr Capua's keynote showed there are significant gaps at the interface of animal and human disease surveillance that will require collaboration

to overcome. Dr Briese described a highly sophisticated laboratory system for detecting novel viral respiratory pathogens, and invited the audience to collaborate with his institution.

Panel discussions following each of the 6 symposium sessions were instrumental in developing prioritised lists of interventions that could be implemented to improve viral respiratory disease surveillance. The questions and answers during the panels were highly informative, and did much to reveal the nature and depth of the gaps in current disease surveillance systems. A number of points were repeatedly addressed by the symposium participants.

With regard to influenza, it is clear that much more can be done to improve seasonal surveillance. Although much planning work for pandemic influenza has already been done, risk communication during a pandemic will be a major challenge in view of the discontinuation of major newspapers and other media outlets in a number of cities around the world. With regard to respiratory viruses other than influenza, there is a lack of understanding of their epidemiology and even of their existence, but considerable impact of infection with these agents, in hospital and community settings.

During this meeting, 8 significant themes for future research were identified and are shown below. Appropriate follow-up activities to the Surveillance Symposium will be discussed with the Scientific Programme Committee and the WHO.



Lance Jennings describing the symposium proceedings  
Credit: Greg Gray

### Themes for future research identified at the isirv International Symposium on Viral Respiratory Disease

1. Case definition standardization
2. Specimen collection and transport
3. Effective pandemic plan exercises
4. Effective pandemic plan communication
5. Mathematical modeling of disease burden
6. Motivating surveillance development in different parts of the world
7. Collaboration of the private healthcare sector in surveillance
8. Better, faster, cheaper multipathogen diagnosis

### Notable and quotable comments from the Surveillance Symposium:

"The most important lesson learned from the SARS outbreak is to build a surveillance culture in which disease reporting is *expected* and *respected*."—David Heymann, WHO

"Discussion must lead to action or nothing will change."—Wenqing Zhang, WHO

"We need to find out more about what we don't fully understand."—Lance Jennings, University of Otago, on the need for research into respiratory viruses other than influenza

"Stamp collecting!"—Arnold Monto, University of Michigan, describing critics' perspective on diagnosing respiratory viruses other than influenza

"Subtyping viruses is not just an academic exercise."—Tracy DuVernoy, US Armed Forces Health Surveillance Center, countering the critics' perspective

"Thailand has a remarkable system for outbreak follow-up."—Douglas Holtzman, Gates Foundation

"Why didn't we think of that before?"—Dan Miller, US HHS, on the most common refrain after pandemic simulation exercises

### Key Themes in Surveillance System Development—Joe Bresee

- Look for opportunities for expanding or improving surveillance
- Address pandemic/avian influenza surveillance
- Capture multiple outcomes to be successful
- Only collect data needed for action
- Recognise that needs of countries will differ
- International cooperation on surveillance systems is critical for influenza

### Selected Surveillance Symposium Evaluation Results

Percentage of respondents planning to use information learned at symposium where they work	97%
Percentage of respondents who believe information learned from the symposium will improve the quality of their work	97%
Top research priority	Developing low-cost disease surveillance technologies
Most important new information learned at symposium	Disease burden of noninfluenza respiratory viruses, especially adenovirus
Most memorable speaker	Ilaria Capua

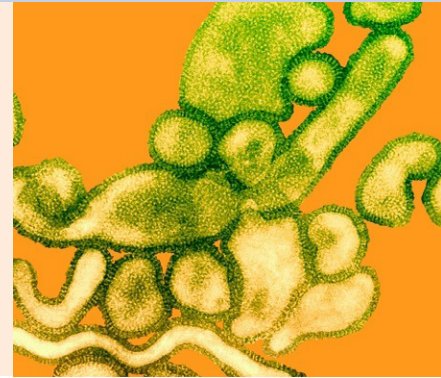
*Professor Watson was Chair for the isirv International Symposium on Viral Respiratory Disease Surveillance, and is the Chair of isirv. He is also Deputy Director, Respiratory and Systemic Infections Department, at the Health Protection Agency Centre for Infections, UK.*

# In the Loop



## Recent publications and news items of special interest to isirv members

by Marge Tamas  
[marge.tamas@intmedpress.com](mailto:marge.tamas@intmedpress.com)



### CLINICAL MEDICINE

United States influenza management guidelines now recommend rimantadine-oseltamivir combination therapy for first-line treatment in the absence of diagnostic testing for influenza subtypes.

Source: Centers for Disease Control and Prevention. CDC issues interim recommendations for the use of influenza antiviral medication in the setting of oseltamivir resistance among circulating influenza A (H1N1) viruses, 2008-09 influenza season. 19 December 2008. <http://www2a.cdc.gov/HAN/Archive/Sys/viewMesgV.asp?AlertNum=00279>.

### EMERGING INFECTIOUS DISEASES

Isolated case of influenza A(H9N2) infection reported in Hong Kong, first since March 2007.

Source: Schnirring L. Hong Kong reports baby has H9N2 virus. CIDRAP News. 30 December 2008. <http://www.cidrap.umn.edu/cidrap/content/influenza/avianflu/news/dec3008influenza.html>.

### EPIDEMIOLOGY

Guillain-Barre syndrome occurs in temporal proximity to influenza infection.

Source: Sivadon-Tardy V, Orlikowski D, Porcher R, et al. Guillain-Barre syndrome and influenza virus infection. *Clin Infect Dis*. 2009;48:48-56.

### PANDEMIC PLANNING

The Global Viral Forecasting Initiative (GVFI) monitors the human-animal interface for zoonoses.

Source: Wise J. New initiative launched to track emergent pandemics. *Lancet Infect Dis*. 2009;9:13.

### VACCINES

Neutralizing antibodies show promise for a universal seasonal and pandemic influenza vaccine.

Source: Sui J, Hwang WC, Perez S, et al. Structural and functional bases for broad-spectrum neutralization of avian and human influenza A viruses. *Nat Struct Molec Biol*. 2009;16:265-273.

### VIROLOGY

SARS research aided by electron microscopy images used to create 3-D model of coronavirus.

Source: Bosch BJ, et al. Utrecht University. *Proc Nat Acad Sci*. 2009. 5 January 2009.

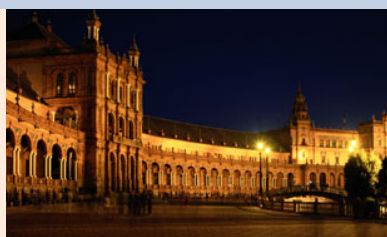
Korean Influenza Sequence and Epitope Database (ISED) now available online.

Source: Kim T. Korean database to help combat flu epidemics. <http://www.koreatimes.co.kr/www/news/include/print.asp?newsIdx=37325>.

Influenza A(H5N1) may replicate in human neutrophils.

Source: Zhao Y, Lu M, Lau LT, et al. Neutrophils may be a vehicle for viral replication and dissemination in human H5N1 avian influenza. *Clin Infect Dis*. 2008;47:1575-1578.

Mrs Tamas, Senior Medical Writer at International Medical Press, edits the quarterly **isirv** Respiratory Virus Report and was the rapporteur for the **isirv** Surveillance Symposium.



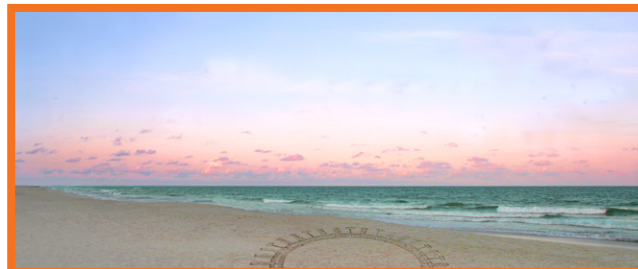
## isirv Conference Activities Update



**isirv International Symposium on Respiratory Virus Transmission and Community Mitigation**  
3-5 November 2009  
Vancouver, British Columbia, Canada

by Lance Jennings, QSO, PhD  
lance.jennings@cdhbc.govt.nz

The Mitigation Symposium, a logical follow-on to the Surveillance Symposium, will weigh the evidence supporting various tools and strategies for community mitigation, including nonpharmaceutical interventions, vaccines, and antiviral agents for viral respiratory disease. It will emphasise addressing practical challenges associated with community mitigation actions called for in pandemic response plans to viral respiratory disease outbreaks. Audience participation through panel discussions, which were so vital to the success of the Surveillance Symposium, will be a prominent feature of the Mitigation Symposium. Jonathan Van-Tam, MBE, DM, FFPH, FRIPH, Professor of Health Protection at the University of Nottingham, UK, is chairing the Mitigation Symposium. This meeting has been moved from September to November of 2009 to avoid a scheduling conflict with a major CDC meeting. Further details about the meeting are available at [www.isirv.org](http://www.isirv.org). Inquiries regarding participation in or support of this Symposium may be directed to Lynne Pryor at [Lynne.pryor@meetintegress.com](mailto:Lynne.pryor@meetintegress.com).



**isirv International Symposium on Immune Correlates of Protection Against Influenza**  
2-5 March 2010  
Miami, Florida, United States

by Lars R Haaheim  
lars.haaheim@gades.uib.no

**isirv** is pleased to announce its next scientific meeting, the International Symposium on Immune Correlates of Protection Against Influenza. This meeting will consider the benefits and limitations of the current licensing requirements for seasonal and pandemic influenza vaccines. The meeting will critically review the evidence, benefits, and limitations of current laboratory procedures and discuss alternative or supplementary methods to identify immune correlates of protection. This topic is especially important in the development of vaccines against viruses with pandemic potential, specifically the newly emerged A(H1N1) pandemic virus, as well as influenza A(H5N1), and is also relevant for the evaluation of seasonal influenza vaccines. Dr Lars R Haaheim and Dr Jackie Katz serve as the meeting chairs. Further details about this meeting will be published as they become available at [www.isirv.org](http://www.isirv.org).

Day 1	Day 2	Day 3
Practical Challenges in Community Mitigation Actions (dinner and panel discussion)	Tools and Strategies for Community Mitigation: Weighing the Evidence (lectures and panel discussions)	New Developments in Vaccines and Antiviral Agents for Viral Respiratory Diseases  Applying Pandemic Influenza Plans to Seasonal Influenza and Other Viral Respiratory Disease Outbreaks



**Options for the Control of Influenza VII**  
**3-6 September 2010**  
**Hong Kong**

by Lynne Pryor  
[lynne.pryor@meetintegress.com](mailto:lynne.pryor@meetintegress.com)

The *Options VII* committee members have been confirmed, and work is proceeding apace on the programme. Dr Malik Peiris, Professor in the Department of Microbiology at The University of Hong Kong and Scientific Director of the HKU-Pasteur Research Center, is chairing the meeting. Dr Yi Guan, Director of the State Key Laboratory of Emerging Infectious Diseases Department of Microbiology at The University of Hong Kong is the Conference Scientific Chair. Dr Gavin Smith, Research Assistant Professor at the State Key Laboratory of Emerging Infectious Diseases, Department of Microbiology at The University of Hong Kong, is the Conference Communications Liaison. Based on feedback from *Options VI* participants, *Options VII* will be shortened by 1 day and will take place in Hong Kong, 3-6 September 2010. Both oral and poster abstracts will be accepted for presentation after blinded review by the scientific programme committee. The meeting proceedings will be produced by Blackwell, publisher of the **isirv** journal, *Influenza and Other Viruses*. Visit [www.controlinfluenza.com](http://www.controlinfluenza.com) for the latest updates on *Options VII*.

Launched in 1985, *Options for the Control of Influenza* has grown into the largest international conference exclusively devoted to influenza, covering every imaginable topic from basic science to health care policy. Whatever your domain of expertise – science, human medicine, animal medicine, public health policy, industry or media – *Options for the Control of Influenza VII* will provide comprehensive scientific guidance for all disciplines involved in influenza prevention, control and treatment, including seasonal and pandemic planning.

## Other events of interest



**The Lancet Conferences—Influenza in the Asia-Pacific:  
From Strategy to Operation**  
**21–23 August 2009**  
**Qingdao, China**

*The Lancet* and *The Lancet Infectious Diseases* have joined forces to develop a conference that will enable leaders in their fields to present and discuss management of influenza with key health administrators, experts from the medical and scientific communities, and industry representatives. We hope the meeting will provide valuable insight into fundamental public health and operation strategies to bring about change within the Asia-Pacific.

Members of **isirv** are being offered a 40% discount off the registration fee. To take advantage of this offer enter promotional code "IDS" when you register.

For more information, please visit  
[www.AsiaFlu.TheLancetConferences.com](http://www.AsiaFlu.TheLancetConferences.com).



### Obituary: William Graeme Laver PhD, FRS (1929-2008)

by Robert G Webster, PhD, FRS  
[robert.webster@stjude.org](mailto:robert.webster@stjude.org)

Graeme Laver, one of Australia's greatest influenza research scientists, died after collapsing en route to an influenza meeting in Portugal in September 2008. Graeme was born in Victoria, educated at Ivanhoe Grammar School and graduated from the University of Melbourne in biochemistry. He received his PhD in biochemistry at the University of London before returning to the John Curtin School of Medical Research at the Australian National University (ANU) in 1958.

After the Burnet School at the Walter and Eliza Hall Institute in Melbourne changed its focus from influenza to immunology, the influenza research program moved with Frank Fenner's group to ANU, where it was anchored by Stephen Fazekas de St Groth. There the pioneering influenza work of Sir Macfarlane Burnet continued, with Graeme Laver as biochemist and Stephen Fazekas as the mathematical modeler of virus neutralization. I (Rob Webster) joined the group in 1959 to carry on the virus neutralization studies.

To elucidate the subunit structure of influenza viruses, Graeme gently dissociated the lipid bilayer of the virus with the mild detergent sodium deoxycholate and established the basis for the first Australian subunit influenza. Before that accomplishment, only intact inactivated influenza vaccines had been used in Australia and they were considered undesirably reactogenic. Studies first in rabbits and then in children established the proof of principle for the vaccine. The ANU paid Laver and myself 10 shillings each for the patent rights. Australian subunit influenza vaccines have been further improved, but the fundamental principle established by Laver remains the same: that the proteins must be kept in their native conformation for the vaccine to be effective. Further studies with Robin Valentine of the

National Institute of Medical Research at Mill Hill, London, established the morphology of the hemagglutinin (HA) and neuraminidase (NA) subunits by electron microscopy, and later work with Nick Wrigley produced the first electron microscopy images of antigen-antibody complexes.

After the emergence of the Asian influenza pandemic in 1957 the influenza community, led by Martin Kaplan of the World Health Organization (WHO), began searching for the origins of influenza pandemics. During a fishing trip to the Southeast coast of Australia, near Bateman's Bay, New South Wales, Laver and I found the beaches littered with dead mutton birds (*Puffinus pacificus*). Knowing that A/Tern/South Africa/61 (H5N3) influenza virus had been isolated from seabirds, we speculated that the mutton birds might have been killed by an influenza virus. In 1970, serological studies of mutton birds on the Great Barrier Reef of Australia found the first evidence of human N2 neuraminidase-inhibiting antibodies, and in 1973 influenza viruses were isolated for the first time from wild migratory seabirds. These findings provided the first links in the chain of evidence that subsequently showed that the migratory aquatic birds of the world are the natural reservoirs of all influenza A viruses.

Studies on the structure of influenza virus neuraminidase began with Graeme's keynote paper in 1978 on crystallization of the heads of the human N2 neuraminidase molecule (*Virology*. 1978; 96:78-87.). These and subsequent studies culminated in the resolution of the three-dimensional structure of the neuraminidase, with Peter Colman and Jose Varghese. With this information, Mark von Itzstein was able to design the first structure-based anti-influenza drug, zanamivir (Relenza®). Further development using NA crystals provided by Graeme led to the development of the orally available anti-influenza drug oseltamivir (Tamiflu®).

The WHO Global Influenza Surveillance Network was established in 1952 to keep up with antigenic drift in influenza viruses and to recommend changes in vaccine strains to stay abreast of antigenic variation. However, there was no fundamental understanding of the mechanisms involved until Graeme Laver began peptide mapping of the hemagglutinin (HA) molecule and provided evidence of multiple antigenic determinants on HA spikes (*Virology*. 1974;59:230-244.). The advent of monoclonal antibodies by Georges Kohler and Caesar Milstein and their use to select influenza virus escape mutants, together with sequence analysis of the HA molecules (*Virology*. 1979;98:226-237.), established that a single amino acid change in the HA would allow the influenza virus to escape neutralization. Antigenic mapping of the HA and NA molecules soon followed and, ultimately, establishment of the antibody binding domains



and visualization of the epitopes on the NA subunits (*Nature*. 1987;326:358-363.). Thus, the mechanism of antigenic drift in influenza and the epitopes involved were elucidated thanks to the seminal work of the Laver laboratory.

Graeme Laver had a sense of adventure in all aspects of his life, from family to friends to research, and was always a free spirit who was willing to challenge bureaucracy when they "got it wrong." He was an avid skier, mountaineer, gardener and axeman. In later life, his scientific passion was the production of perfect crystals of NA through studies in zero gravity on the Russian MIR space station and crystallization chambers set up in every laboratory he visited. Some of the most beautiful crystals were the N9 neuraminidase of an influenza virus isolated from a noddy tern on the Great Barrier Reef. Photographs of these crystals appeared on the covers of many scientific journals, and Graeme and photographer Julie Macklin were awarded the Nikon "Small World" prize in 1987. In addition to influenza, Graeme made contributions to our knowledge about adenoviruses, sialidases, and paramyxoviruses. His multiple scientific achievements were recognized by his election to the Royal Society of London in 1987 and by co-receipt of the Australia Prize with Peter Colman in 1996.

In its efforts to prepare for an influenza pandemic and to identify the best options for controlling seasonal influenza, the global community owes a very special debt to Graeme Laver. The current strategies for control of both pandemic and seasonal influenza, the stockpiles of anti-influenza drugs and pre-pandemic vaccines are products of his life's work. His final mission was to have anti-influenza drugs made available over the counter so that every household could have an immediate supply in the face of a pandemic. He argued that this option would have no effect on the emergence of resistance and could save millions of lives in the event of infrastructure failure. New Zealand has taken the lead in following his visionary advice.

*Robert G. Webster, PhD, FRS, is the Rose Marie Thomas Chair in the Division of Virology, Department of Infectious Diseases at St. Jude Children's Research Hospital in Memphis, Tennessee, USA.*

*Originally published in Influenza and Other Respiratory Viruses and reproduced here by kind permission of Alan Hampson.*

 **Voices of isirv**

The **isirv** board would like to broaden the society's reach to be of greatest interest to current and potential **isirv** members, and is keenly interested in your ideas for future events and newsletter articles. Is there a topic you'd like to write about for the newsletter? Do you have an idea for a meeting or satellite symposium? What are the most pressing issues in viral respiratory disease? Please send your thoughts to [marge.tamas@intmedpress.com](mailto:marge.tamas@intmedpress.com).

## About isirv

**isirv** is a scientific professional society to promote the prevention, detection, treatment, and control of influenza and other respiratory virus diseases. It will:

- Provide a forum for the exchange of information and for international collaboration
- Advocate for research and effective public health measures
- Promote relevant scientific and clinical training and education
- Organize scientific meetings and workshops on key topics and develop international consensus
- Support and develop partnerships with international bodies such as the WHO and other agencies

# isirv Membership Application

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First Name	Last Name	
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Current Position	Academic Title	
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Institution Name		
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**Please indicate your five main areas of interest (rate from '1' to '5', with 5 as the highest score):**

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|--|--|
| <input type="checkbox"/> Animal health/disease             | <input type="checkbox"/> Diagnostics, epidemiology, and surveillance |
| <input type="checkbox"/> Human health/disease              | <input type="checkbox"/> Vaccines                                    |
| <input type="checkbox"/> Zoonoses/ecology                  | <input type="checkbox"/> Immunology                                  |
| <input type="checkbox"/> Pandemic preparedness             | <input type="checkbox"/> Antivirals                                  |
| <input type="checkbox"/> Policy for control and prevention | <input type="checkbox"/> Viral structure & replication               |
| <input type="checkbox"/> Cost benefit and health economics | <input type="checkbox"/> Other? <input type="text"/>                 |

**Which virus(es) are your main interest?**

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**The Society's members will elect the officers of isirv.**

If proposed, would you accept nomination for election?

Please give any general suggestions you have on priorities for **isirv** activities for the first 1-2 years:

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Membership fees of €100 may be paid by cheque or bank transfer to the **isirv** account: Barclays Bank, Edgware Branch, 126 Station Road, Edgware, London, HA8 7RY. Sort code 20 29 41. Account #307 876 20. To register for **isirv** and pay online: visit [www.isirv.org](http://www.isirv.org). Payment confirmation will be mailed to the address provided on the membership form.

If using a cheque please print and mail a copy of this form together with payment to:

**Dr Geoffrey C Schild**  
**17 Sunnyfield, Mill Hill**  
**London NW7 4RD, UK**

Make the cheque payable to **isirv** and write the member's name legibly on the cheque. The amount of the cheque must match the annual membership fee.