Multinational Influenza Seasonal Mortality Study Newsletter
Summer 2008

MISMS Asia Meeting

The Multinational Influenza Seasonal Mortality Study (MISMS) is an international collaborative effort to analyze national and global mortality patterns associated with influenza virus circulation. Following on the success of the previous South American regional meeting in February 2007, the Fogarty International Center – Division of International Epidemiology and Population Studies (FIC-DIEPS) organized an Asian regional MISMS meeting in August 2007 for influenza epidemiologists, virologists, computational biologists, and public health officials. The meeting was co-hosted by the Vietnam National Institute of Hygiene and Epidemiology (NIHE) and held at NIHE's facilities in Hanoi, Vietnam.

Save the date!

MISMS Europe Meeting & Workshops
Vilamoura, Portugal
September 17th - September 20th, 2008

The MISMS Europe meeting will feature research describing national and regional influenza mortality and virus circulation and evolution patterns. Following the meeting, a workshop describing the methodology to evaluate vital statistics, virological, genomic and economic data to describe influenza disease burden and inform policy will be held. All are invited to attend the general meeting and introductory workshop, to be held in Room Gemini III, Tivoli

Participants in MISMS Asia Meeting, August 2007

Please contact ficmisms@mail.nih.gov with any questions about the MISMS project

The first 2 days of the meeting consisted of presentations that highlighted MISMS research results and the local and regional progress that has been made in characterizing influenza epidemiology in Asia, with particular emphasis on distinguishing between influenza seasonality in tropical and temperate regions. There were over 100 participants at the meeting, from universities, research and public health institutions in 17 countries and territories in Asia and Europe. The topics on the agenda included influenza genomics, vaccine and control strategies issues, international surveillance activities, as well as statistical methods for estimation of influenza disease burden. The speakers included NIH staff, as well as scientists from the US CDC, WHO, AFRIMS and representatives from the CDCs and Ministries of Health of many countries. Participants were actively engaged in the presentations, debating a wide variety of influenza-related issues.

Following the presentations, a 2-day long workshop was held during which participants received hands-on technical training in the analysis of influenza morbidity and mortality data. NIH staff sat with individuals and small groups and assisted them with data cleaning, formatting, analysis of their epidemiological data, or demonstrated the techniques using sample data and programs prepared at NIH. Additionally, Dr. Wladimir Alonso demonstrated some of the possible applications of Google Earth for visualization of climatological and mortality data. Finally, the workshop provided the opportunity for networking among the different country scientists so that they could share their experiences and knowledge, developing relationships that will allow for better regional and international collaborations (link to the program of the Asian meeting: http://origem.info/misms/Hanoi/)

Overall, the Fogarty staff deepened existing collaborations and developed new ones, and the participants evaluated the meeting positively, both for the information and analytical tools they were provided by the speakers and FIC staff, as well as the new relationships they developed that will encourage new and fruitful partnerships in the region. We look forward to an equally successful meeting in Portugal in September 17-20, following the ESWI Third European Influenza Conference.

Guest Researchers Spotlight

1. Cheryl Cohen, National Institute for Communicable Diseases, South Africa
2. Anthony Newall, University of New South Wales, Australia

The Fogarty International Center's MISMS program utilizes a number of collaborative mechanisms, including the support of visiting fellows who perform research at the National Institutes of Health (NIH) Bethesda campus. Recent guest researchers have come from France, Italy, Taiwan, Brazil, Japan, and South Korea -- here we spotlight researchers from South Africa and Australia who have been visiting the NIH/Fogarty staff between May and September 2008.

1. Dr. Cheryl Cohen, a researcher from South Africa, used her time with Fogarty to learn new analytic skills to estimate the excess mortality associated with influenza in South African seniors. This study is important because there is no estimate of the mortality burden of influenza anywhere in Africa so far. Additionally, Dr. Cohen came to Fogarty

intending to evaluate the impact of influenza in HIV-infected individuals, using South Africa as a case study.

Dr. Cohen received her Bachelor of Medicine and Bachelor of Surgery in 1997 and her Diploma in Tropical Medicine and Hygiene in 2000 from the University of the Witwatersrand, South Africa. She also received a Master of Science in Epidemiology from the London School Hygiene and Tropical Medicine in 2005. Dr. Cohen's interest in epidemiology was a natural way for her to merge all of her interests, bringing together her clinical and microbiology knowledge to work on public health projects at the micro and macro levels. She notes that, "epidemiology is really about making sense of the world and describing underlying patterns in the distribution of disease".

After completing her masters in epidemiology, Dr. Cohen began work at the National Institute for Communicable Diseases, in Johannesburg, as head of the Epidemiology and Surveillance Unit. Additionally, she is also the editor of the Communicable Diseases Surveillance Bulletin and serves as a member of several committees and working groups with agendas of promoting public health in South Africa. When questioned as to what she believes is the most important public health issue for South Africa, she responds, "the biggest issue in South Africa is inequity with regard to access to health care as well as basic services, such as water and sanitation, and this inequity extends globally as well. Poor and marginalized people are still less likely to have the burden of their diseases measured and consequently have resources allocated to combat them. In South Africa there is great awareness of the role of equity and the challenges faced by the poor, so hopefully this will improve."

2. The second visiting scholar whom we will showcase is Dr. Anthony Newall, a health economist. Dr. Newall graduated from the University of Sydney, Australia, with a MPH and PhD on the economic evaluation of vaccines. After graduation, he worked as research fellow at the National Centre for Immunisation Research and Surveillance (NCIRS), Westmead, New South Wales, and he is currently a lecturer in health economics at the University of New South Wales in Sydney and an honorary fellow at the NCIRS. Presently, most of Dr. Newall's research is focused on the economic evaluation of prevention strategies for infectious diseases, seasonal and pandemic influenza in particular.

The goals of Dr. Newall's visits to Fogarty included modeling the influenza-attributable mortality burden in Australia in different age groups, so as to enable a fuller understanding of the uncertainty in the disease burden attributable to influenza. Like Dr. Cohen, Dr. Newall also looked forward to learning new epidemiological techniques and building relationships to enable future collaborations.

When asked what he sees as the most important public health concern in Australia and the world, he responded that, "As a health economist, I would say an important challenge to Australia and the world is to ensure efficiency in health spending. Given the rising cost of healthcare there is an increasing need to reform

health spending patterns and apply accountability to decision making. To do the most 'good' we need to consider what interventions provide relative value for money, not just which are effective."

Study Highlights

Collaborators in the MISMS project have published a number of articles and presented at international meetings between August 2007 and September 2008. Below is a sample of the manuscripts that have been published, by area of research.

PUBLIC HEALTH POLICY

Miller MA, Viboud C, Olson DR, Grais RF, Rabaa MA, Simonsen L. **Prioritization of influenza pandemic vaccination to minimize years of life lost.** *J Infect Dis.* 2008 Aug 1;198(3):305-11.

Table 1. Mortality per 100,000 population, estimated no. of prevented deaths, and years of life lost prevented per vaccine dose, by age group and relative risk.

Influenza pandemic scenario, age group	Deaths: Rate per 100,000 population	Deaths: Prevented per 100,000 vaccine doses, range	Years of life lost: Rate per 10,000 population	Years of life lost: Prevented per 10,000 vaccine doses, range	Relative risk*
1918					
<45 years	563	**394–507**	3209	**2246–2888**	**28–68**
45–64 years	210	147–189	992	694–893	8.8–21
≥65 years	150	26–80	192	33–102	Reference
All ages	434	294–383	2344	1628–2102	. . .
1957					
<45 years	6.4	4.5–5.8	36	25–32	0.2–0.4
45–64 years	45	32–41	131	**92–118**	**0.6–1.6**
≥65 years	315	**54–167**	347	**59–184**	**Reference**
All ages	53	17–33	96	44–70	. . .
1968					
<45 years	4.2	2.9–3.8	23	16–21	0.2–0.6
45–64 years	41	29–37	110	**77–99**	**1.1–2.8**
≥65 years	151	**26–80**	167	28–89	Reference
All ages	30	11–21	60	32–48	. . .

NOTE. Scenarios are based on the 1918 experience in New York City and the 1957 and 1968 pandemic experiences in the United States [11, 23, 25]. Vaccination was assumed to prevent 70%–90% of deaths in persons <65 years old and 17%–53% of deaths in persons ≥65 years old [14]. Results for age groups with the highest vaccine benefits are shown in boldface. See also the sensitivity analysis in table 2.

* The relative risk was calculated as the ratio of the prevented no. of years of life lost per vaccine dose in younger age groups to that in seniors.

BACKGROUND: How to allocate limited vaccine supplies in the event of an influenza pandemic is currently under debate. Conventional vaccination strategies focus on those at highest risk for severe outcomes, including seniors, but do not consider (1) the signature pandemic pattern in which mortality risk is shifted to younger ages, (2) likely reduced vaccine response in seniors, and (3) differences in remaining years of life with age.

METHODS: We integrated these factors to project the age-specific years of life lost (YLL) and saved in a future pandemic, on the basis of mortality patterns from 3 historical pandemics, age-specific vaccine efficacy, and the 2000 US population structure.

RESULTS: For a 1918-like scenario, the absolute mortality risk is highest in people <45 years old; in contrast, seniors (those >or=65 years old) have the highest mortality risk in the 1957 and 1968 scenarios. The greatest YLL savings would be achieved by targeting different age groups in each scenario; people <45 years old in the 1918 scenario, people 45-64 years old in the 1968 scenario, and people >45 years old in the 1957 scenario.

CONCLUSIONS: Our findings shift the focus of pandemic vaccination strategies onto younger populations and illustrate the need for real-time surveillance of mortality patterns in a future pandemic. Flexible setting of vaccination priority is essential to minimize mortality.

GENOMICS AND EVOLUTION

Rambaut A, Pybus OG, Nelson MI, Viboud C, Taubenberger JK, Holmes EC. **The genomic and epidemiological dynamics of human influenza A virus.** *Nature*. 2008 May 29;453(7195):
615-9.

Abstract: The evolutionary interaction between influenza A virus and the human immune system, manifest as 'antigenic drift' of the viral haemagglutinin, is one of the best described patterns in molecular evolution. However, little is known about the genome-scale evolutionary dynamics of this pathogen. Similarly, how genomic processes relate to global influenza epidemiology, in which the A/H3N2 and A/H1N1 subtypes co-circulate, is poorly understood. Here through an analysis of 1,302 complete viral genomes sampled from temperate populations in both hemispheres, we show that the genomic evolution of influenza A virus is characterized by a complex interplay between frequent reassortment and periodic selective sweeps. The A/H3N2 and A/H1N1 subtypes exhibit different evolutionary dynamics, with diverse lineages circulating in A/H1N1, indicative of weaker antigenic drift. These results suggest a sink-source model of viral ecology in which new lineages are seeded from a persistent influenza reservoir, which we hypothesize to be located in the tropics, to sink populations in temperate regions.

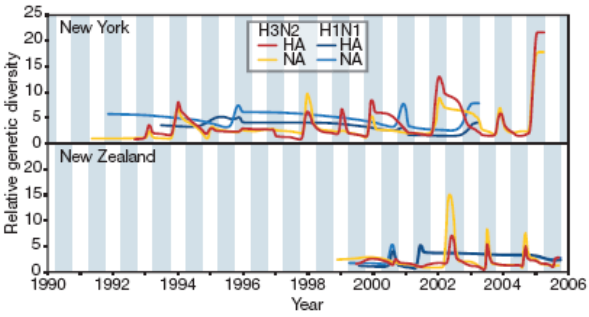

Figure 1 | Population dynamics of genetic diversity in influenza A virus. Bayesian skyline plots of the HA and NA segments for the A/H3N2 and A/H1N1 subtypes in New York state (top) and New Zealand (bottom). The horizontal shaded blocks represent the winter seasons. The *y*-axes represent a measure of relative genetic diversity (see Methods for details). The shorter timescale of New Zealand skyline plot is due to the shorter sampling period.

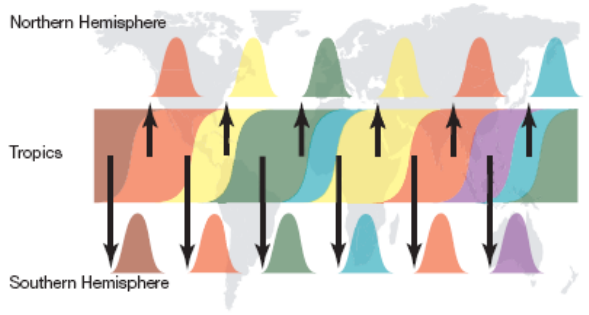

Figure 2 | A 'source–sink' model for the evolution of influenza A virus. Viral genetic and antigenic diversity (shown by different colours) is continuously generated in a reservoir, or 'source' population, perhaps represented by the tropics, before being exported to 'sink' populations in the Northern and Southern Hemispheres as shown by the arrows. The continuous transmission of influenza A virus in the source population, and hence its larger effective population size, allows natural selection for antigenic diversity to proceed more efficiently than in the sink populations that are afflicted by major seasonal bottlenecks.

HISTORICAL DATA ANALYSIS AND PANDEMIC PREPAREDNESS

Andreasen V, Viboud C, Simonsen L. **Epidemiologic characterization of the 1918 influenza pandemic summer wave in Copenhagen: implications for pandemic control strategies**. *J Infect Dis*. 2008 Jan 15;197(2):270-8.

BACKGROUND: The 1918-1919 A/H1N1 influenza pandemic killed approximately 50 million people worldwide. Historical records suggest that an early pandemic wave struck Europe during the summer of 1918.

METHODS: We obtained surveillance data that were compiled weekly, during 1910-1919, in Copenhagen, Denmark; the records included medically treated influenza-like illnesses (ILIs), hospitalizations, and deaths by age. We used a Serfling seasonal

regression model to quantify excess morbidity and mortality, and we estimated the reproductive number (R) for the summer, fall, and winter pandemic waves.

RESULTS: A large epidemic occurred in Copenhagen during the summer of 1918; the age distribution of deaths was characteristic of the 1918-1919 A/H1N1 pandemic overall. That summer wave accounted for 29%-34% of all excess ILIs and hospitalizations during 1918, whereas the case-fatality rate (0.3%) was many-fold lower than that of the fall wave (2.3%). Similar patterns were observed in 3 other Scandinavian cities. R was substantially higher in summer (2.0-5.4) than in fall (1.2-1.6) in all cities.

CONCLUSIONS: The Copenhagen summer wave may have been caused by a precursor A/H1N1 pandemic virus that transmitted efficiently but lacked extreme virulence. The R measured in the summer wave is likely a better approximation of transmissibility in a fully susceptible population and is substantially higher than that found in previous US studies. The summer wave may have provided partial protection against the lethal fall wave.

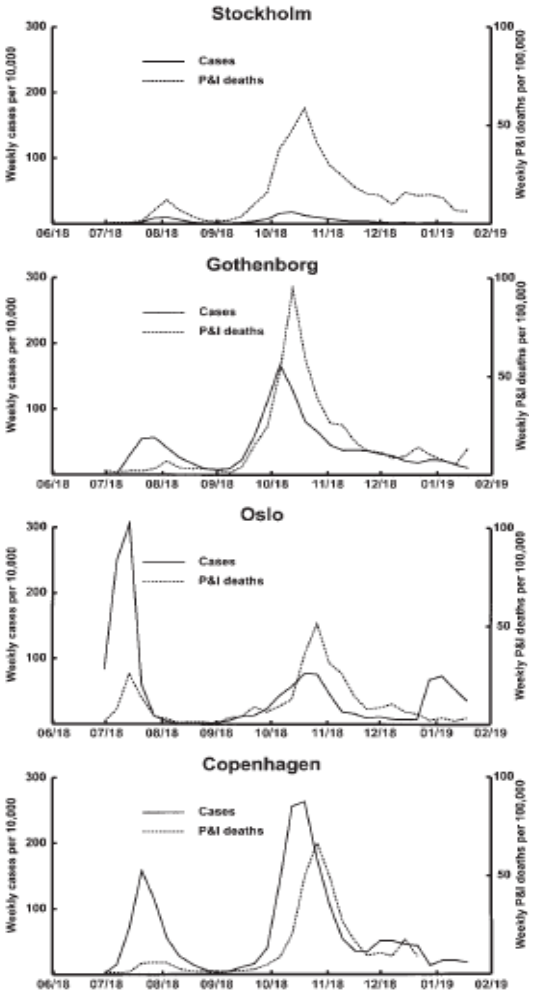

Figure 2. Scandinavian 1918 summer wave—weekly incidence of cases of influenza illness and respiratory deaths in 4 Scandinavian cities, during 1918–1919. Mortality data from Stockholm, Oslo, and Gotenborg are based on data reported by Low [8] and depict pneumonia and influenza (P&I) mortality; data from Copenhagen are based on all respiratory deaths, including bronchitis (nearly 90% of deaths during the 1918 fall wave in Copenhagen were coded to bronchitis).

Table 1. Morbidity and mortality impact of 3 influenza pandemic waves in Copenhagen, 1918–1919.

	1918 summer wave (12 weeks: 23 June–8 September 1918)	1918 fall wave (12 weeks: 15 September–1 December 1918)	1918–1919 winter wave (24 weeks: 8 December–27 April 1919)	Sum of 3 waves
Excess influenza illnesses[a]	480	1170	710	2360
Excess influenze hospitalizations[a]	40	80	60	180
Excess all-cause hospitalizations[a]	40	80	50	170
Excess all-cause deaths[a]	1.7	27	12	41
Case-fatality rate, %[b]	0.35	2.3	1.7	1.7

NOTE. Data are no. of cases/10,000 individuals, unless otherwise indicated. Estimates are excess rates per 10,000, based on Serfling seasonal regression model.

[a] In excess of seasonal baseline, as derived from Serfling seasonal regression model.
[b] Calculated as ratio of all-cause excess deaths:excess influenza illnesses.

Table 4. Estimates of reproduction number (R), by wave, in Copenhagen.

	1918 summer wave		1918 fall wave	
Data type	R_{short} (2.6 days)	R_{long} (4 days)	R_{short} (2.6 days)	R_{long} (4 days)
Cases of clinical influenza	2.2–2.4	2.8–3.0	1.22–1.24	1.29–1.33
Hospitalizations	2.8–4.0	3.6–5.4	1.2–1.3	1.3–1.4
Excess respiratory deaths[a]	NA	NA	1.4[b]	1.6[b]
Excess all-cause deaths[a]	NA	NA	1.5[b]	1.8[b]

NOTE. R is based on 2 serial-interval parameter values—short duration (2.6 days) [4] and long duration (~4 days) [1]. Ranges represent 95% confidence intervals. NA, not available.

[a] R for the summer wave could not be estimated with precision, when mortality data were used, because there were few deaths.
[b] The method for R estimation based on excess mortality does not allow for computation of confidence intervals.

MISMS related Publications

(These papers available at: http://origem.info/FIC/Bibliography.html)

VIRAL EVOLUTON

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INFLUENZA

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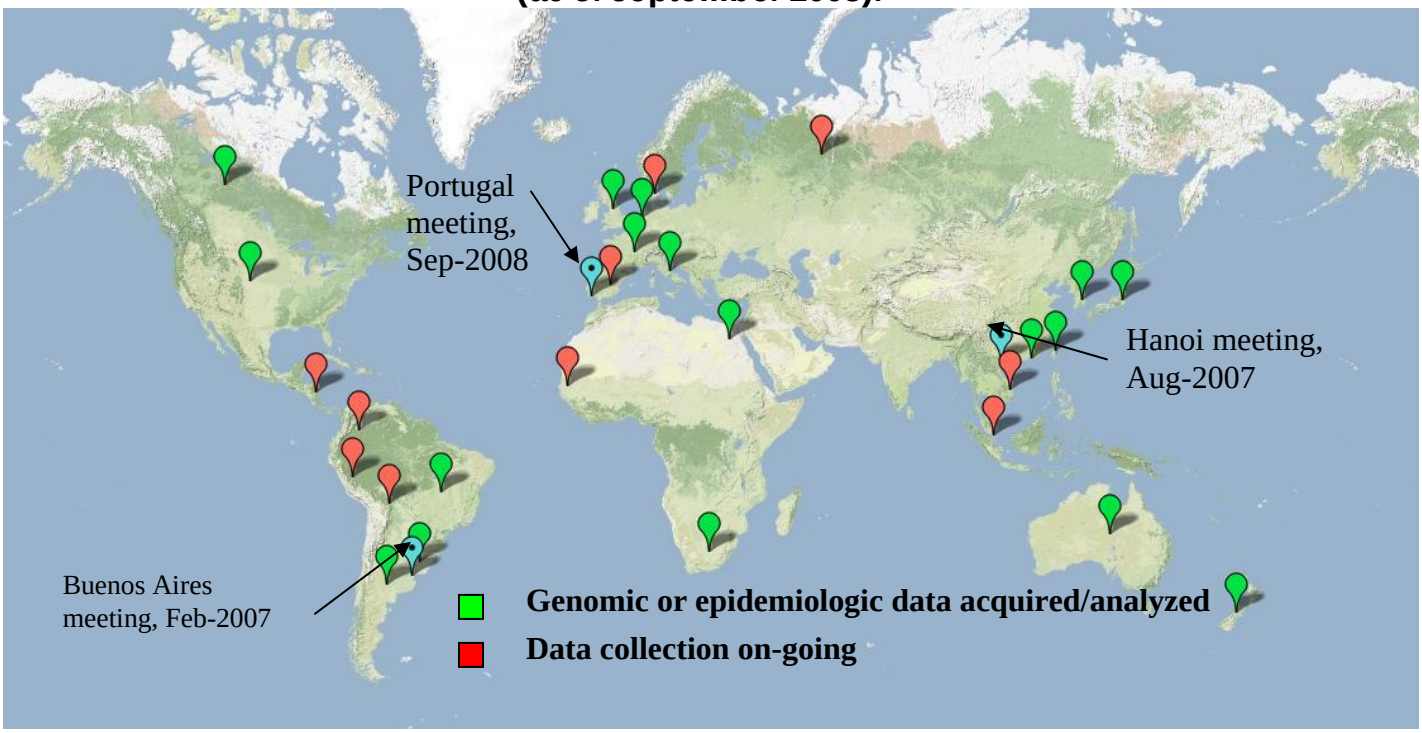
MISMS Overview

The Multinational Influenza Seasonal Mortality Study (MISMS) is an international collaborative effort to analyze national and global mortality patterns associated with influenza virus circulation.

MISMS has 4 specific aims:

1. To describe synchrony in seasonal variations of various causes of mortality associated with influenza, by state, country, and region.
2. To describe long-term temporal trends and inter-annual variations in influenza mortality patterns, both within and amongst countries, and their association with changes in circulating subtypes of influenza virus, antigenic and genomic characteristics, population factors, and vaccine coverage.
3. To explore the seasonal patterns and burden of influenza mortality in tropical countries, and understand the global circulation of influenza viruses - to achieve this goal, new methods for estimating mortality impact in tropical countries need to be developed.
4. To develop a world map of influenza mortality burden and seasonal patterns.

Global map of participation in MISMS and regional meetings (as of September 2008):



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