Multinational Influenza Seasonal Mortality Study Newsletter
Spring 2007

MISMS Americas Meeting

Save the date!
MISMS Asia Meeting
Hanoi, Vietnam
August 13th – August 15th, 2007
The MISMS Asia meeting will feature research describing national and regional influenza mortality and virus circulation patterns. Presentations will be suitable for epidemiologists, virologists, computational biologists, and public health officials with interest in influenza.

The first regional Multinational Influenza Seasonal Mortality Study (MISMS) meeting was held in Buenos Aires, Argentina in early February. Fifty people attended, including 30 individuals from universities and public health institutions in nine countries in the region and 20 individuals from the Pan-American Health Organization, National Institutes of Health (NIH), US Department of Defense, Centers for Disease Control and Prevention (CDC), and vaccine companies. The meeting began with two days of presentations that highlighted MISMS research results and the progress that has been made in characterizing influenza epidemiology in Central and South America. Topics on the agenda included the methodology used by NIH and CDC to describe influenza epidemiology, vaccine issues, influenza genomics, and surveillance activities, including presentations of national influenza epidemiology and virology research.

Following the presentation portion of the meeting, many of the participants stayed for a 3-day long workshop during which many received technical assistance with their own country's influenza morbidity and mortality data and/or genomic analysis. NIH staff worked with individuals and small groups and assisted them with analysis and interpretation of their national data or demonstrated the techniques using sample data and programs. In addition, assistance was provided with manuscript preparation. The workshop also provided a networking opportunity for scientists to share their expertise and develop relationships that will allow for better regional collaboration. While the workshop technically ended at 1 pm on Friday, it was so popular that some participants continued working together until 7 pm in the evening.

Overall, the meeting strengthened existing collaborations and facilitated the formation of new collaborations, and the participants evaluated the meeting positively. We look forward to an equally successful meeting in Vietnam in August.

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

Participants in MISMS Argentina meeting, February 2007

Guest researcher spotlight

Jong-Won Kang, South Korea

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). In the past, visiting fellows for the MISMS program have come from France, Italy, Taiwan, and Brazil. Here we spotlight Dr. Kang, a researcher from South Korea who will spend a year at the Fogarty International Center, learning techniques to analyze the impact of influenza on Korean mortality.

Dr. Kang received his MD from the Seoul National University in 1991. He became interested in public health during his second year of medical school and followed his medical training with an MPH in infectious disease epidemiology at the School of Public Health, also at Seoul National University. His Masters thesis dealt with the impact of a cigarette price increase on smoking and mortality in Korean men. He obtained his doctorate in Preventive Medicine in 1999, and has since worked as a professor and researcher at the Chungbuk National University College of Medicine. His recent research has involved such disparate topics as cancer epidemiology, menopause, and the effects of video games on hormone levels and musculoskeletal disorders in young Korean men.

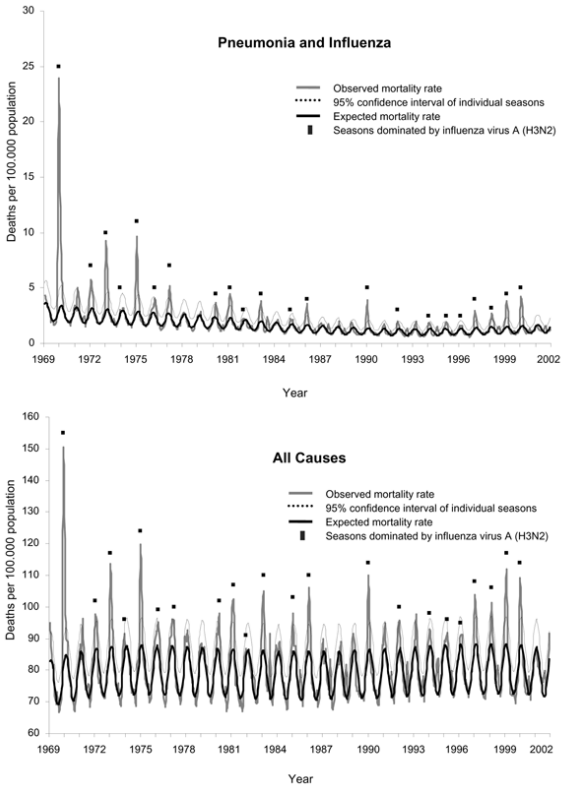
Dr. Kang received funding from the Chungbuk National University to spend a year at NIH learning and applying analytical techniques to Korean mortality data from 1991-2005. He will look at cause-specific (influenza, pneumonia, all respiratory diseases, all cardiovascular diseases, diabetes, cerebrovascular disease, ischemic heart disease, hypertension and cancer) and all-cause mortality by age groups and over time. In Korea he found himself working on many projects and tasks at once, so he appreciates being able to focus on influenza full-time at Fogarty and looks forward to documenting his research results in a manuscript.

In addition to all of the traditional essentials that one packs when moving half a world away, Dr. Kang and his family packed a year's supply of nori (a type of seaweed), fearing that they would be unable to purchase this in the United States. Happily, he has discovered that he can find most of the Korean ingredients they need at Korean and Asian grocery stores, including nori. Their children (8 and 10) are enjoying their time in elementary school, and his wife is keeping busy taking English classes at the local library. When they return to Korea in December 2007, Dr. Kang hopes to continue his research in the prevention and control of infectious diseases and to continue collaborations with MISMS and Fogarty.

Study highlights

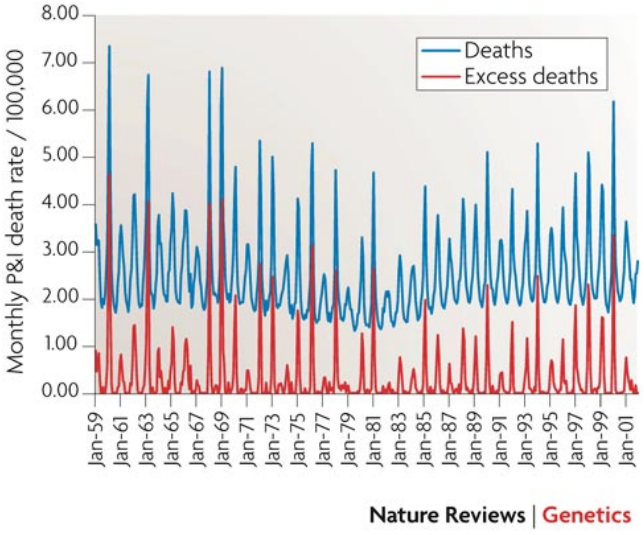
Collaborators in the MISMS project have published a number of articles and presented at international meetings. Below is a sample of the manuscripts that have been published.

Rizzo C, Bella A, Viboud C, Simonsen L, Miller MA, Rota MC, Salmaso S, and degli Atti MLC. (2007) Trends for influenza-related deaths during pandemic and epidemic seasons, Italy, 1969-2001. EID, Vol. 13, No. 5, May 2007.



Abstract: Age-specific patterns of death from influenza vary, depending on whether the influenza season is epidemic or pandemic. We assessed age patterns and geographic trends in monthly influenza-related deaths in Italy from 1969 through 2001, focusing on differences between epidemic and pandemic seasons. We evaluated age-standardized excess deaths from pneumonia and influenza and from all causes, using a modified version of a cyclical Serfling model. Excess deaths were highest for elderly persons in all seasons except the influenza A (H3N2) pandemic season (1969–70), when rates were greater for younger persons, confirming a shift toward death of younger persons during pandemic seasons. When comparing northern, central, and southern Italy, we found a high level of synchrony in the amplitude of peaks of influenza-related deaths.

Nelson MI and Holmes EC. (2007) The evolution of epidemic influenza. Nature Reviews Genetics, 196, vol. 8, March 2007.



Recent developments in complete-genome sequencing, antigenic mapping and epidemiological modelling are greatly improving our knowledge of the evolution of human influenza virus at the epidemiological scale. In particular, recent studies have revealed a more complex relationship between antigenic evolution, natural selection and reassortment than previously realized. Despite these advances, there is much that remains to be understood about the epidemiology of influenza virus, particularly the processes that determine the virus's strong seasonality. We argue that a complete understanding of the evolutionary biology of this important human pathogen will require a genomic view of genetic diversity, including the acquisition of polymorphism data from within individual hosts and from geographical regions, particularly the tropics, which have been poorly surveyed to date.

Read more about the MISMS Project here:
http://www.fic.nih.gov/news/publications/newsletters/ghmapr2007.pdf

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Brinkhof MWG, Spoerri A, Birrer A, Hagman R, Koch D, Zwahlen M. Influenza-attributable mortality among the elderly in Switzerland. (2006) Swiss Med Wkly 136: 302-309.

Background: Influenza infections are considered responsible for a substantial burden of disease and mortality in the elderly, especially during wintertime. However, death certificates indicating influenza as the cause of death might only partly reflect the mortality attributable to influenza.

Methods: We estimated influenza-attributable mortality for the Swiss resident population of age 60 and older from 1969 to 1999 by Poisson regression modeling of all cause and influenza mortality, and examined long-term trends by age and gender. In sensitivity analyses we additionally used data on official pneumonia deaths, as well as clinical diagnosis of influenza-associated illnesses from the Swiss Sentinel Network.

Results: For the 30 successive respiratory seasons (July of a given year to June of the next year) from 1969/70 to 1998/99 the estimated total number of influenza-attributable deaths in the Swiss population of 60+ was 24 800 (95% confidence interval: 21 000 to 28 600), about 2 times the official count of influenza deaths. Influenza-attributable mortality rate declined from 1969 to 1999, but the yearly number of influenza-attributable deaths nevertheless stabilized at around 600 to 700 in the nineties due to aging of the population. The oldest-aged groups persistently showed the highest influenza mortality rate. Influenza-attributable mortality estimates were substantially higher when using the general practice influenza indicator (by 66%) or the combined cause-of-death category pneumonia and influenza (by 169%).

Conclusions: Only counting official influenza deaths underestimated influenza-attributable mortality in Switzerland by a factor of two to three. Despite a gradual decline in age-specific influenza-attributable mortality rates in the years 1969 to 1999, we estimated an average annual number of 830 deaths in the elderly Swiss resident population. The elderly remain the primary target group for influenza vaccination to reduce influenza-attributable mortality.

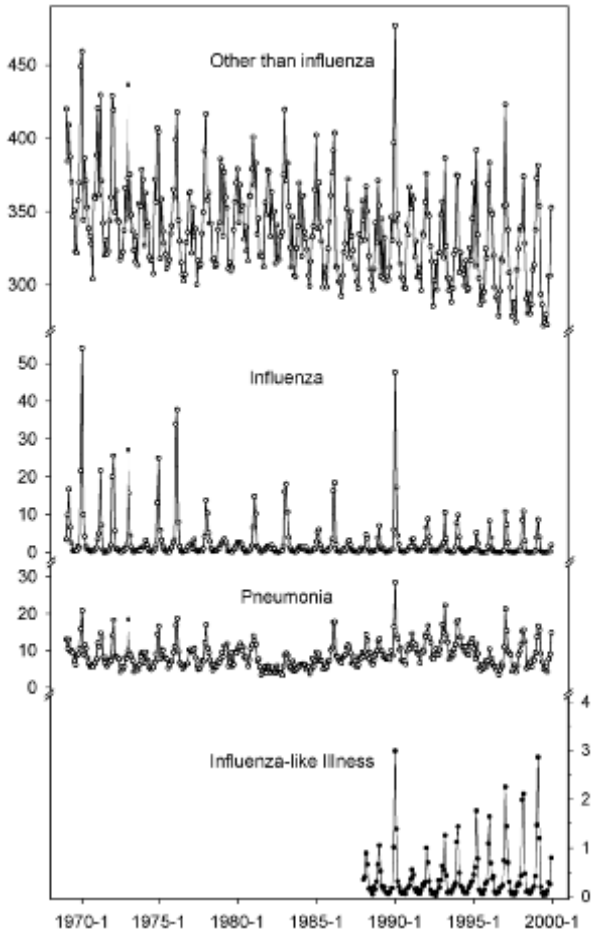


Figure1
Monthly mortality rates for all cause mortality excluding official influenza deaths, influenza mortality, pneumonia mortality (open symbols) and monthly proportion of general practice consultations for influenza-like illness (ILI) from the Swiss Sentinel Surveillance System, for Switzerland and the population of age 60 and older, 1969–1999.

Going to Options VI in June?

We plan to host an informal meeting at Options and will send out the meeting details soon. If you are interested in learning more about possible collaborations, please let us know.

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

MISMS related Publications

Disease burden studies in the tropics and temperate climates:

1. Alonso, WJ, Viboud C, Simonsen L, Hirano EW, Daufenbach LZ, Miller MA. Seasonal Patterns of Influenza in Brazil: traveling wave from the Amazon to the Sub-Tropics. 2006, Am J Epidemiol. In Press.
2. Dushoff J, Plotkin JB, Viboud C, Earn DJ, Simonsen L. Mortality due to influenza in the United States--an annualized regression approach using multiple-cause mortality data. *Am J Epidemiol*. 2006 Jan 15;163(2):181-7. Epub 2005 Nov 30.
3. Rizzo C, Viboud C, Montomoli E, Simonsen L, Miller MA. Influenza-related mortality in the Italian elderly: No decline associated with increasing vaccination coverage. Vaccine. 2006 Oct 30;24(42-43):6468-75. Epub 2006 Jul 7.
4. Viboud C, Alonso WJ, Simonsen L. Influenza in Tropical Regions. *Plos Med*. March 2006. 3:4:e89.
5. Simonsen, L., Taylor, R., Viboud, C., Dushoff, J., Miller, M. 2006. US flu mortality estimates are based on solid science. *Bmj* 332(7534): 177-8.
6. Dushoff J. Assessing influenza-related mortality: Comment on Zucs et al. *Emerg. Themes Epidemiol.*, 2:7, 2005.
7. Dushoff J, J. B. Plotkin, S. A. Levin, and D. J. D. Earn. Dynamical resonance can account for seasonality of influenza epidemics. Proc Natl. Acad. Sci. USA, 101:1691516916, 2004..
8. Reichert TA, Simonsen L, Sharma A, Pardo SA, Fedson DS, Miller MA. Influenza and the winter increase in mortality in the United States, 1959-1999. *Am J Epidemiol*. 2004 Sep 1;160(5):492-502.
9. Viboud C, Pakdaman K., Boëlle P-Y., Myers M., Wilson M. L., Valleron A-J., Flahault A. Association of influenza epidemics with global climate variability 2004. Eur J Epidemiol 19(11): 1055-9.
10. Simonsen L, Blackwelder WC, Reichert TA, Miller MA. Estimating deaths due to influenza and respiratory syncytial virus. JAMA. 2003 May 21;289(19):2499-500

Transmission dynamics of influenza virus and disease:

11. Viboud C, Tam T, Fleming D, Handel A, Miller M, Simonsen L. Transmissibility and mortality impact of epidemic and pandemic influenza: Comparison of the deadly 1951 epidemic with surrounding seasons. Vaccine, 2006 Jun 9; [Epub ahead of print]
12. Viboud C, Tam T, Fleming D, Miller M, Simonsen L. 1951 influenza epidemic, England and Wales, Canada and the United States. Emerg Infect Dis 2006 Apr;12(4):661-8
13. Viboud C, Bjørnstad O, Smith DL, Simonsen L, Miller MA, Grenfell B. Synchrony, waves, and spatial hierarchies in the spread of influenza. Science Apr 21;312(5772):447-51. Epub 2006 Mar 30.
14. Viboud C, Miller MA, Grenfell B, Bjørnstad O, Simonsen L. Air travel and the spread of influenza: Important Caveats. PLos Med Nov 2006;3(11):e503.
15. Viboud C, Boëlle PY, Cauchemez S, Lavenu A, Valleron AJ, Flahault A., Carrat F. Risk factors of influenza transmission in households. *Br J Gen Pract* 2004;54(506): 684-9.
16. Viboud C, Boëlle P-Y., Pakdaman KP., Carrat F, Valleron A-J., Flahault A. Correlations over time and space of influenza epidemics in the USA, France and Australia: 1972-97. *Emerging Infectious Diseases*. *Emerg Infect Dis* 2004;10(1): 32-9.
17. Cauchemez S, Carrat F, Viboud C, Valleron AJ, Boëlle PY. A Bayesian MCMC approach to study transmission of influenza: application to household longitudinal data. *Stat Med* 2004; 23(22): 3469-87.
18. Viboud C, Boëlle P-Y., Carrat F., Valleron A-J., Flahault A. Prediction of the spread of influenza epidemics by the method of analogues. *American Journal of Epidemiology* 2003. 158:10; 996-1006.

Vaccine impact and control studies on various target populations including indirect effects:

19. Le Menach A, Vergu E, Grais RF, Smith DL, Flahault A. Key strategies for reducing spread of avian influenza among commercial poultry holdings: lessons for transmission to humans. Proceedings of the Royal Society of London, B, Biological Sciences. DOI: 10.1098/rspb.2006.3609.
20. Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: A quantitative review. *Vaccine*. 2006 Feb 20;24(8):1159-69. Epub 2005 Sep 19.
21. Simonsen L, Reichert TA, Viboud C, Blackwelder WC, Taylor RJ, Miller MA. Impact of Influenza Vaccination on Seasonal Mortality in the US Elderly Population. *Archives of Internal Medicine* 2005;165(3):265-72.
22. Simonsen L, Viboud C, Blackwelder WC, Taylor RJ, Miller MA. Researchers defend influenza vaccine study.*Infectious Diseases News*, Aug 2005 (Guest Editorial)
23. Reichert TA. The Japanese program of vaccination of schoolchildren against influenza:implications for control of the disease. *Semin Pediatr Infect Dis*. 2002 Apr;13(2):104-11.

Influenza virus evolutionary patterns:

24. Koelle K, Cobey S, Grenfell B, Pascual M. Epochal evolution shapes the phylodynamics of interpandemic influenza A (H3N2) in humans. Science. 2006 Dec 22;314(5807):1898-903
25. Holmes EC, Lipman DJ, Zamarin D & Yewdell JW. Comment on “Large Scale Sequence Analysis of Avian Influenza Isolates”. *Science* 15 Sept 2006; 313:1573b.

26. Chen R & Holmes EC. Avian influenza virus exhibits rapid evolutionary dynamics. *Molecular Biology and Evolution* 2006 Dec;23(12):2336-41.
27. Kuiken T, Holmes EC, McCauley J, Rimmelzwaan GF, Williams CS & Grenfell BT. Host species barriers to influenza virus infections. *Science* 2006 312: 394-397.
28. Wolf YL, Viboud C, Holmes EC, Koonin EV, Lipman DJ. Long Intervals of Stasis Punctuated by Bursts of Positive Selection in the Seasonal Evolution of Influenza A Virus. Biology Direct, October 26, 2006.
29. S. A. Levin, Dushoff J, and J. B. Plotkin. Evolution and persistence of influenza A and other diseases. Math. *Bioscience*, 188:1728, 2004.
30. J. B. Plotkin and Dushoff J. Codon bias and frequency-dependent selection on the hemagglutinin epitopes of influenza A virus. *Proc. Natl. Acad. Sci.* USA, 100:71527157, 2003.
31. D. J. D. Earn, Dushoff J, and S. A. Levin. Ecology and evolution of the flu. 2002. *Trends Ecol. Evol.* 17:334-40, 2002.
32. J. B. Plotkin, Dushoff J, and S. A. Levin. Hemagglutinin sequence clusters and the antigenic evolution of influenza A virus. 2002. *Proc. Natl. Acad. Sci*. USA, 99:6263-68.

Pandemic influenza and other topics:

33. Reichert TA. Preparing for the next influenza pandemic: lessons from multinational data. *Pediatr Infect Dis J*. 2005 Nov;24(11 Suppl):S228-31. Review.
34. Viboud C, Grais RF, Lafont BA, Miller MA, et al. "Multinational impact of the 1968 Hong Kong influenza pandemic: evidence for a smoldering pandemic." *J Infect Dis*. 2005; 192(2): 233-48.
35. Simonsen L, Viboud C, Taylor R. Influenza vaccination in elderly people. Lancet. 2005 Dec 17;366(9503):2086.
36. Simonsen L, Olson DR, Viboud C, Heiman E, Miller MA, Reichert TA. In: Pandemic influenza and mortality: past evidence and projections for the future. In: Institute of Medicine's Pandemic Influenza: Assessing Capabilities for Prevention and Response. Forum on Microbial Threats series, (2004). 1-26-46.

MISMS overview

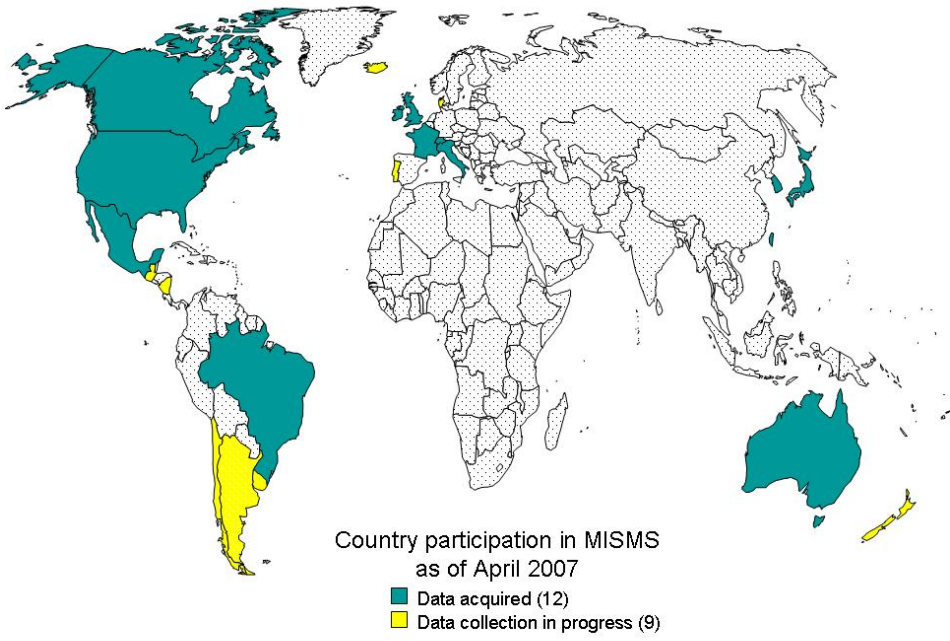
The Multinational Influenza Seasonal Mortality Study (MISMS) is an international collaborative effort to analyze national and global mortality patterns associated with influenza virus circulation.
MISMS has 4 specific aims:

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 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



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