



Multinational Influenza Seasonal Mortality Study Newsletter Winter 2009

MISMS Europe Meeting

The Multinational Influenza Seasonal Mortality Study (MISMS) is an international collaborative effort led by the Fogarty International Center – Division of International Epidemiology and Population Studies (FIC-DIEPS) to analyze disease patterns associated with influenza virus circulation. Following on the success of previous American and Asian regional meetings in February and August 2007, a European meeting was held in September 2008 in Vilamoura, Portugal, following the third European Influenza Conference where the DIEPS staff and collaborators presented their research. Participants to the MISMS Portugal meeting included influenza epidemiologists, virologists, computational biologists, and public health officials.

Save the date!

MISMS Africa Meeting & Workshop
Dakar, Senegal
April 21-25, 2009

The MISMS Africa general meeting will feature research describing national and regional patterns in disease burden and evolutionary dynamics of avian and human influenza virus. Following the meeting, a technical workshop describing methodological approaches 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 workshop.



Participants in MISMS Europe Meeting, September 2008



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. There were over 50 participants at the meeting, from universities, research and public health institutions throughout the Americas, Europe, Africa, and the Middle East. The topics on the agenda included influenza evolutionary patterns and genomics of avian and human influenza viruses, vaccine and control strategies issues, international surveillance activities, as well as statistical methods for estimation of influenza disease burden. The speakers included NIH staff, scientists US Centers for Disease Control and Prevention (CDC), and researchers from various academic institutions and foreign public health agencies. Participants were actively engaged in the presentations, debating a wide variety of influenza-related issues (link to the program of the European meeting: <http://origem.info/misms/Vilamoura/>).

Following the presentations, a 2½-day long workshop was held during which participants received hands-on technical training in the analysis of influenza morbidity and mortality data, as well as influenza genomic data. NIH staff sat with individuals and small groups and assisted them with data cleaning, formatting, analysis, and demonstrated the techniques using sample data and programs prepared at NIH. Finally, the workshop provided the opportunity for networking so that scientists from different countries could share their experiences and knowledge and establish relationships that will allow for better regional and international collaborations.

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 Senegal in April 2009.

Guest Researchers Spotlight

1. Martha Nelson, National Institutes of Health, USA
2. Baltazar Nunes, Instituto Nacional de Saude Dr. Ricardo Jorge, Portugal

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, South Africa, Australia, Portugal and the US -- here we spotlight researchers from the US and Portugal who began their visit the NIH/Fogarty staff in Summer 2008.

1. Dr. Martha Nelson joins Fogarty as a post-doctoral researcher from the Pennsylvania State University, where she recently completed her Ph.D. on the genomic evolution of the human influenza A virus. Martha's research uses phylogenetic analysis to study influenza virus evolution and migration patterns and understand the links between viral evolution, spatial spread, and epidemiology. In collaboration with Fogarty researchers, Martha's dissertation work described the evolutionary relationships between hundreds of whole-genome influenza virus sequences sampled from different geographic





localities around the world over restricted timescales. In particular, her research examined the extent of genetic diversity circulating over different spatial-temporal scales, patterns of virus persistence and global migration (see highlighted paper below), the evolutionary basis for the spread of adamantane resistant influenza viruses, and the occurrence of unusually severe epidemics.

When asked about the future direction of the field of influenza virus research, Martha emphasized the importance of “an integrated understanding of viral evolution that includes all genome segments, antigenic data, clinical outcomes data, and viral sequences from tropical regions that historically have not been well sampled.”

2. Mr. Baltazar Nunes spent 3 months at Fogarty over the summer 2008 where he developed various statistical models to estimate influenza-associated mortality in Portugal from 1980-2005. It was Baltazar’s goal to use his time here to refine his knowledge and skills in classical time series methods, such as ARIMA modeling, as well as to meet “experienced and skilled researchers in the field of influenza epidemiology with whom I can learn and discuss ideas.”



Baltazar earned his BS in Statistics and Operation Research in 1997, and a Masters degree in Probabilities and Statistics in 2003, both from University of Lisbon. Upon graduation, Baltazar began working at the Center for Epidemiology and Biostatistics of the Portuguese National Institute of Health Dr. Ricardo Jorge. His early work included modeling the effect of heat waves on daily mortality, and developing an early warning system currently used by the Portuguese Authorities (Heat/Health Early Warning System, ICARO). Baltazar’s current research covers many aspects of influenza epidemiology, including: analysis of the molecular evolution of influenza B, developing preparedness scenarios for pandemic influenza burden and statistical methods to estimate excess deaths attributed to seasonal influenza epidemics. When questioned about the most important public health concern in Portugal and the rest of the world, Baltazar notes that, “The most important public health concern in Portugal is cerebrovascular disease - Portugal presents one of highest stroke mortality rates at the 15-EU group. Globally, I think that the most important public health problem is the lack of access to health care in the developing countries.” Some of Baltazar’s most memorable experiences from his time at Fogarty include lunches overlooking the Rose Garden, being in the Washington, DC metropolitan area during the 2008 presidential elections, and taste of American coffee.



Study Highlights

Collaborators in the MISMS project have published a number of articles and presented at international meetings between August 2007 and January 2009. Below is a sample of 3 of these studies. Two studies focus on the analysis of historical epidemiological data associated with the 1918-19 pandemic, and the third describes the evolutionary patterns and spatial spread of seasonal influenza A viruses in the US.

HISTORICAL DATA ANALYSIS AND PANDEMIC PREPAREDNESS (1)

Barry JM, Viboud C, Simonsen L. **Cross-Protection between Successive Waves of the 1918-1919 Influenza Pandemic: Epidemiological Evidence from US Army Camps and from Britain.** *J Infect Dis.* 2008 Nov 15;198(10):1427-34.

BACKGROUND: The current worst-case scenario for pandemic influenza planning is based on the catastrophic 1918-1919 pandemic. In this article, we examine the strength of cross-protection between successive waves of the 1918-1919 pandemic, which has remained a long-standing issue of debate.

METHODS: We studied monthly hospitalization and mortality rates for respiratory illness in 37 army camps, as well as the rates of repeated episodes of influenza infection during January-December 1918 in 8 military and civilian settings in the United States and Britain.

RESULTS: A first wave of respiratory illness occurred in US Army camps during March-May 1918 and in Britain during May-June, followed by a lethal second wave in the fall. The first wave was characterized by high morbidity but had a lower fatality rate than the second wave (1.1% vs. 4.7% among hospitalized soldiers; [Formula: see text]). Based on repeated illness data, the first wave provided 35%-94% protection against clinical illness during the second wave and 56%-89% protection against death.

CONCLUSIONS: Exposure to influenza in the spring and summer of 1918 provided mortality and morbidity protection during the fall pandemic wave. The intensity of the

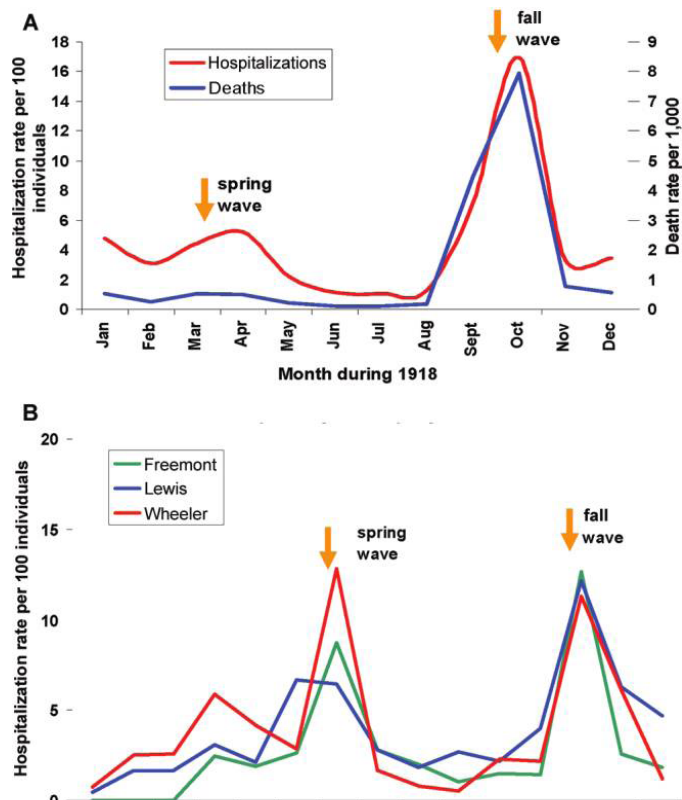


Figure 1: Morbidity and mortality from respiratory illness in US Army training camps. *A*, Monthly rates of hospitalizations and deaths among enlisted men in US Army training camps, January-December 1918 (total for all 37 camps). *B*, Monthly rates of hospitalization for October 1917- December 1918 for the 3 US Army training camps that experienced the most pronounced spring wave of illness, relative to the amount of illness in



first wave may have differed across US cities and countries and may partly explain geographical variation in pandemic mortality rates in the fall. Pandemic preparedness plans should consider that immune protection could be naturally acquired during a first wave of mild influenza illnesses.

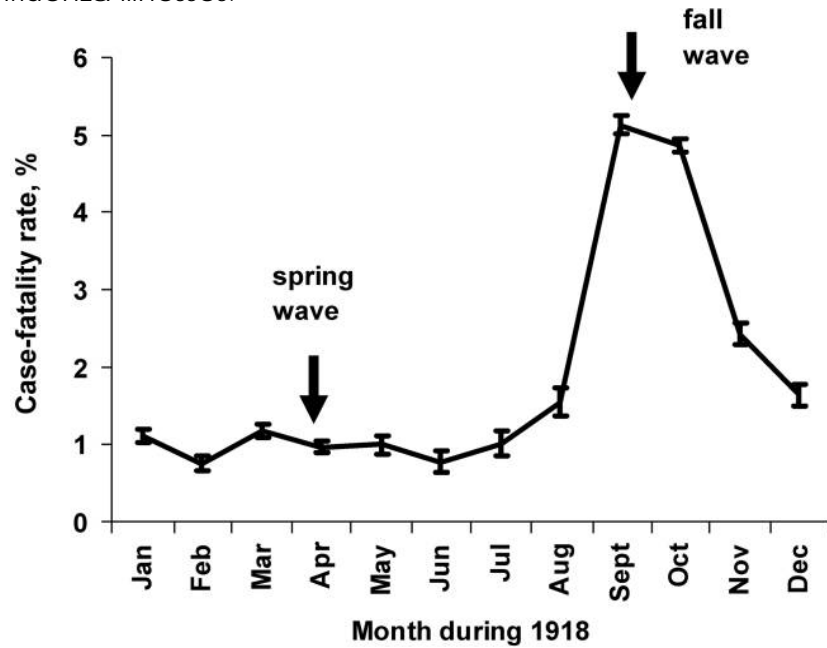


Figure 2: Monthly case-fatality rate among individuals hospitalized for respiratory illness, for all enlisted men in US Army camps, 1918. Black bars, 95% confidence intervals. Arrows point to the time of the spring and fall pandemic waves; note the lack of elevation above the background case-fatality rate in the spring and the large elevation above the

HISTORICAL DATA ANALYSIS AND PANDEMIC PREPAREDNESS (2)
 Richard SA, Sugaya N, Simonsen L, Miller MA, Viboud C. **A Comparative Study of the 1918 Influenza Pandemic in Japan: Mortality Impact and Implications for Pandemic Planning.** *Epidemiol & Infection*. 2009. In Press.

ABSTRACT: Historical studies of influenza pandemics can provide insight into transmission and mortality patterns, and may aid in planning for a future pandemic. Here, we analyze historical vital statistics and quantify the age-specific mortality patterns associated with the 1918-1920 influenza pandemic in Japan, the US, and the UK. All three countries showed

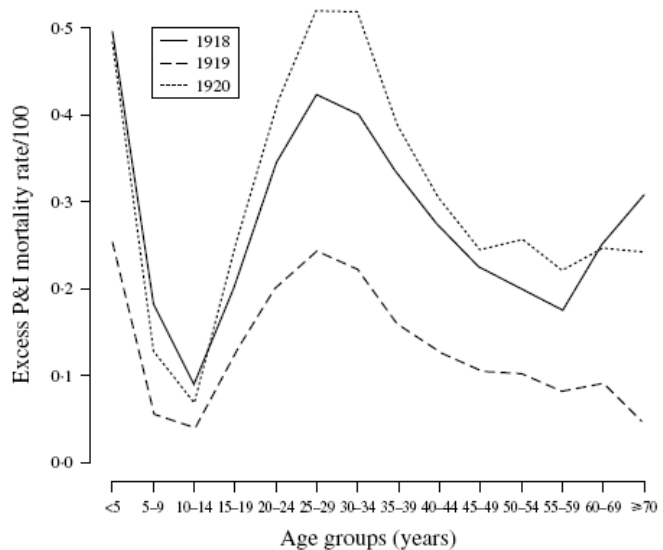


Fig. 4. Age patterns of excess pneumonia and influenza (P&I) mortality rates in Japan, by year, 1918–1920. Excess mortality estimates are calculated with the annual approach (subtracting mortality in pandemic years 1918–1920 from average baseline mortality in surrounding years 1915–1917 and 1921–1923).



highly elevated mortality risk in young adults relative to surrounding non-pandemic years. By contrast, the risk of death was low in the very young and very old. In Japan, the overall mortality impact was not limited to the winter of 1918-1919, and continued during the winter of 1919-1920. Mortality impact varied as much as 3-fold across the 47 Japanese prefectures, and differences in baseline mortality, population demographics, and density could not explain these variations. Our study highlights important geographical variations in timing and mortality impact of historical pandemics, in particular between the Eastern and Western hemispheres. In a future pandemic, vaccination in one region could save lives even months after the emergence of a pandemic virus in another region.

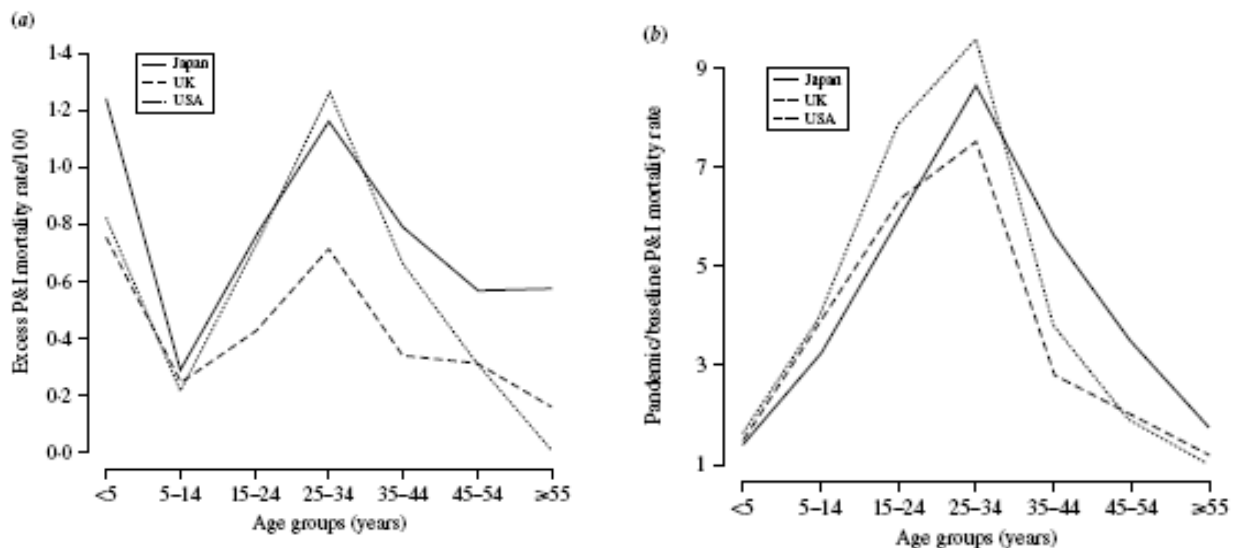


Figure 1a. Comparison of age-specific excess P&I mortality rates during pandemic years 1918-1920 in Japan, the UK, and the US. Estimates are calculated using the annual method. Figure 3b. Ratio of P&I mortality during 1918-1920 pandemic years to baseline P&I mortality in 1915-1917 and 1921-1923, for Japan, the UK, and the US. Extreme age groups (children <5 and people over 55) were less affected than young adults, relative to non-pandemic influenza seasons.

GENOMICS AND EVOLUTION

Nelson MI, Edelman L, Spiro DJ, Boyne AR, Bera J, Halpin R, Sengamalay N, Ghedin E, Miller MA, Simonsen L, Viboud C, Holmes EC. **Molecular epidemiology of A/H3N2 and A/H1N1 influenza virus during a single epidemic season in the United States.** *PLoS Pathog.* 2008 Aug 22;4(8):e1000133.

ABSTRACT: To determine the spatial and temporal dynamics of influenza A virus during a single epidemic, we examined whole-genome sequences of 284 A/H1N1 and 69 A/H3N2 viruses collected across the continental United States during the 2006-2007 influenza season, representing the largest study of its kind undertaken to date. A phylogenetic analysis revealed that multiple clades of both A/H1N1 and A/H3N2 entered and co-circulated in the United States during this season, even in localities that are distant from major metropolitan areas, and with no clear pattern of spatial spread. In addition, co-circulating clades of the same subtype exchanged genome segments through reassortment, producing both a minor clade of A/H3N2 viruses that appears to



have re-acquired sensitivity to the adamantane class of antiviral drugs, as well as a likely antigenically distinct A/H1N1 clade that became globally dominant following this season. Overall, the co-circulation of multiple viral clades during the 2006-2007 epidemic season revealed patterns of spatial spread that are far more complex than observed previously, and suggests a major role for both migration and reassortment in shaping the epidemiological dynamics of human influenza A virus.

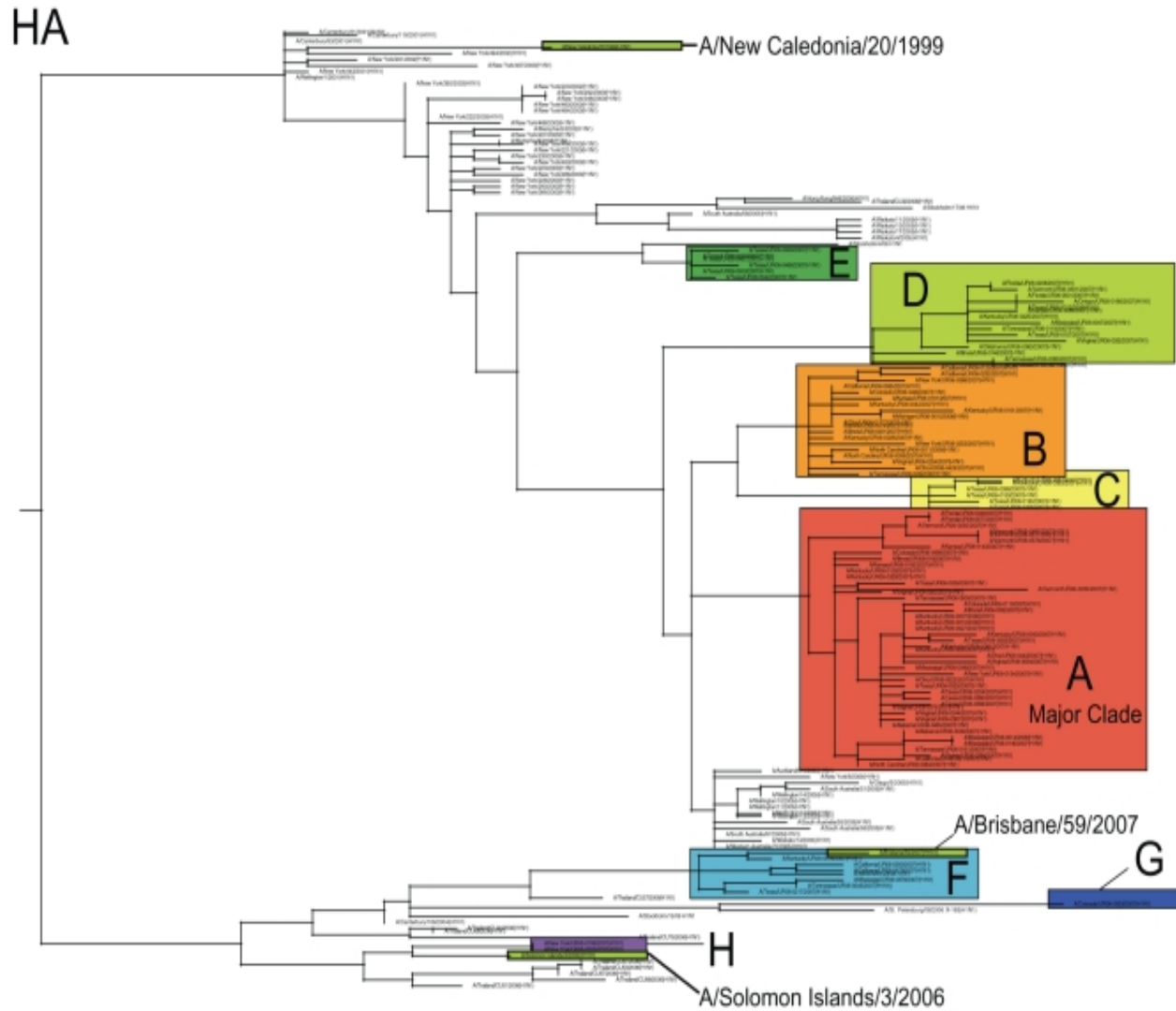


Figure 1: Phylogenetic relationships of the HA gene segment of 100 A/H1N1 influenza viruses sub-sampled from all eight clades that co-circulated in the United States during the 2006–2007 influenza season, 67 global isolates from 2001–2006, and the A/H1N1 component of the influenza vaccine used from the years 2000–2001 to 2006–2007 (A/New Caledonia/20/1999), the A/H1N1 strain selected for the 2007–2008 vaccine (A/Solomon Islands/3/2006), and the 2008–2009 A/H1N1 vaccine component, (A/Brisbane/59/2007), estimated using an ML method.



MISMS related Publications

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

Influenza virus evolutionary patterns

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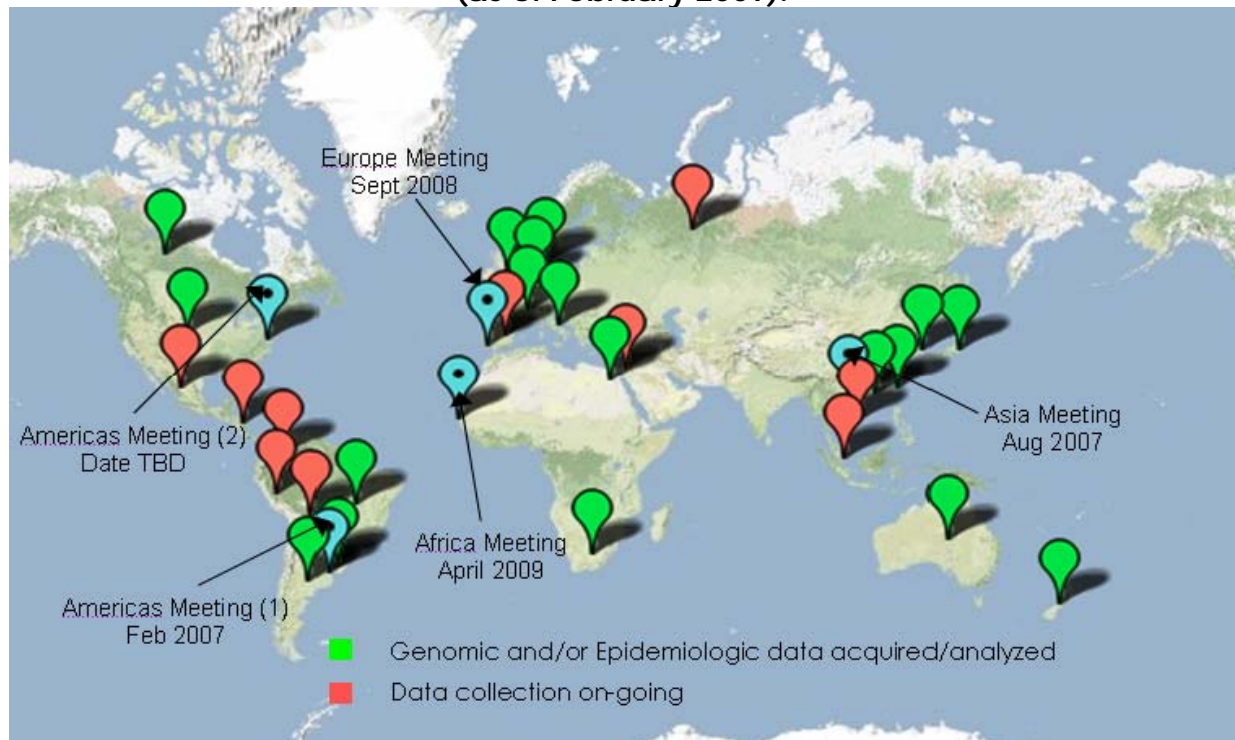
MISMS Overview

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 February 2009):



<http://origem.info/misms/>

