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Surveillance of illness associated with pandemic (H1N1) 2009 virus infection among adults using a global clinical site network approach: the INSIGHT FLU 002 and FLU 003 Studies

The INSIGHT Influenza Study Group*

Abstract

The novel pandemic influenza A (H1N1) 2009 virus spread rapidly around the world in 2009. The paucity of prospective international epidemiologic data on predictors of clinical outcomes with pandemic (H1N1) 2009 virus infection stimulated the INSIGHT network, an international network of community and hospital-based investigators, to commence two worldwide clinical observational studies to describe pandemic (H1N1) 2009 virus activity.

The purpose of these two studies was to estimate the percent of adult patients with illness due to laboratory-confirmed pandemic (H1N1) 2009 virus infection that experience clinically significant outcomes and to study factors related to these outcomes.

Enrollment commenced in October 2009 and will continue until August 2011: as of the end of 2010, 62 sites in 14 countries in Australasia (12 sites), Europe (37) and North America (13) have enrolled 1365 adult patients, with 1049 enrollments into the FLU 002 outpatient study and 316 into the FLU 003 hospitalization study.

These “in progress” INSIGHT influenza observational studies may act as a model for obtaining epidemiological, clinical and laboratory information in future international disease outbreaks.

Keywords

Influenza; pandemic (H1N1) 2009 virus; INSIGHT; international observational studies

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Introduction

The world was alerted to descriptions of the first infections with a novel influenza A virus of swine origin in south-western USA and Mexico in April and May 2009; on June 11, 2009, the World Health Organization declared that a pandemic was underway.^{1–4} Although of uncertain origin, the pandemic (H1N1) 2009 virus was a quadruple reassortment of North American and Eurasian swine, avian and human influenza A gene segments.⁵

By late 2010, there have been two pandemic waves: the first (“spring”) wave in the northern hemisphere coincided with declining seasonal influenza activity, whereas the first southern hemisphere wave coincided with the onset of the usual winter influenza and respiratory virus season. The monovalent pandemic (H1N1) 2009 vaccine became available in some countries in October or November 2009, during or just after the peak of the second (“fall”) northern hemisphere wave. Both the monovalent pandemic (H1N1) 2009 and the “seasonal” trivalent vaccine (including a pandemic (H1N1) 2009 virus component) were available prior to the second southern hemisphere wave.

It was quickly recognized that the highest activity of pandemic (H1N1) 2009 was in children, adolescents and younger adults, reflected in presentations to emergency departments or general practices, hospitalisation rates, admissions to intensive care and deaths.^{6, 7} This was in contrast to seasonal influenza, where severe disease is most concentrated in the elderly.^{8–11} A number of risk factors for severe disease were identified - pregnancy, morbid obesity, and other medical conditions (eg. diabetes, cardio-respiratory disease, immunosuppression) known to place individuals at high risk of complications from seasonal influenza.^{12–17} Various indigenous populations also were at increased risk of complications from pandemic (H1N1) 2009 influenza.^{18–20} However, between one-quarter to one-half of people admitted to intensive care, or who died, had no known risk factor.^{6, 13, 21–23}

Nucleic acid testing (NAT) on respiratory tract samples is the laboratory test of choice for confirmation of pandemic (H1N1) 2009 virus infection.⁶ Rapid antigen tests such as direct immunofluorescence or rapid influenza diagnostic tests have poor to moderate sensitivity to detect the pandemic strain compared to seasonal influenza A viruses.^{24, 25} In severely ill patients with lower respiratory tract disease requiring intensive care and ventilation or extracorporeal membrane oxygenation, NAT sensitivity was improved when lower respiratory tract samples were collected.²⁶ Clinically relevant pandemic (H1N1) 2009-specific serological testing is limited by the technical difficulties of the hemagglutination inhibition or microneutralization assays, including the presence of cross-reacting antibodies from prior seasonal influenza A (H1N1) virus infections or (perhaps) vaccination, the need for paired acute and convalescent sera to detect significant rises in virus-specific antibody to occur, and the difficulties of interpreting results.

The neuraminidase inhibitors (NIs) oseltamivir or zanamivir are recommended as soon as possible for antiviral treatment of pandemic (H1N1) 2009 influenza; early use is important in individuals with underlying risk factors or hospitalized. Intravenous peramivir and zanamivir, although limited in availability, can be used in seriously ill patients where administration of oral or inhaled drugs is problematic. Unlike most seasonal A/H1N1 strains isolated during 2008–2009, the pandemic (H1N1) 2009 virus is sensitive to the NIs. The neuraminidase H275Y mutation that confers resistance to oseltamivir has been detected occasionally in pandemic (H1N1) 2009, most commonly in viruses identified from immunosuppressed patients who were treated with oseltamivir (or in individuals who had received oseltamivir chemoprophylaxis prior to clinical onset); these strains are zanamivir sensitive.⁶

Although there are many clinical and laboratory reports of pandemic (H1N1) 2009 activity, there is a paucity of prospective international epidemiologic data on predictors of clinical outcomes with pandemic (H1N1) 2009 virus infection. To address these issues, the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) network has commenced two worldwide observational studies to describe pandemic (H1N1) 2009 activity from October 2009 until August 2011. The purpose of the first study, the INSIGHT H1N1v Outpatient Study (FLU 002), is to describe adult participants in geographically diverse locations who present for medical treatment with influenza-like illness (ILI) and who have laboratory-confirmed pandemic influenza A (H1N1) 2009 virus infection and their clinical course over a 14-day period following enrollment. The purpose of the second study, the INSIGHT H1N1v Hospitalization Study (FLU 003), is to describe the characteristics and outcomes over a 60 day follow-up of adult participants in geographically diverse locations with pandemic influenza A (H1N1) 2009 (or seasonal influenza) and who are hospitalized with influenza-related complications.

The INSIGHT Global Clinical Trial Network

The mission of the INSIGHT is “to define optimal strategies for the management of HIV and other infectious diseases through a global clinical research network”. INSIGHT has collaborated with several hundred sites in both northern and southern hemispheres, as well as in high, middle and low-income countries. Through these collaborations, INSIGHT has completed enrollment and analyzed the two largest HIV treatment trials to date,^{27, 28} and has commenced recruitment to another large HIV treatment study, START (Strategic Timing of AntiRetroviral Treatment). While these sites have been engaged because of their HIV interest, many are situated within institutions with diverse clinical services and have investigators with broad interest in other areas of infectious diseases. In addition, some sites have regional responsibilities, or their institutions include national infectious disease reference centres. Thus, the INSIGHT infrastructure, which includes a core statistical data management center and operations structure at the University of Minnesota, and four coordinating centers in the USA, Europe and Australia, was ideally suited for influenza studies.

The emergence of the pandemic (H1N1) 2009 virus prompted the rapid development of two protocols by the INSIGHT Study Group. They were designed to cover the spectrum of both mild outpatient disease and more serious disease requiring hospitalization, and took advantage of the international network of community and hospital-based investigators already in place.

Study Objectives

Table 1 lists the objectives of the FLU 002 Outpatient and the FLU 003 Hospitalization Studies. The general purpose of these studies was to estimate the percent of adult patients with illness due to laboratory-confirmed pandemic (H1N1) 2009 virus infection that experience severe complications and to study factors associated with severe and fatal complications.

Study Design, Data Collection Plan and Sample Size Considerations

Sites were chosen for FLU 002 and FLU 003 in geographically diverse areas. The studies were designed so that sites could open and then cease enrolling depending on the current local burden of pandemic (H1N1) 2009 virus activity as reported by public health authorities (e.g., CDC and WHO reporting of local influenza activity: the definitions of significant local influenza activity varied). Once sites are activated, suspected influenza-infected individuals are then consecutively enrolled. Table 2 summarizes the data collection plan for each study.

For both studies, serum and respiratory tract samples are collected and shipped to the central specimen repository for testing and storage. The central determination of influenza A and subtype is reported back to the clinical site, but is not part of the medical record or used for diagnosis, prognosis or treatment. Influenza RNA from clinical specimens where pandemic (H1N1) 2009 virus detected by NAT was directly sequenced by the J. Craig Venter Institute (JCVI, Rockville, Maryland, USA), with full and partial genome assemblies deposited in the National Center for Biotechnology Information GenBank (NCBI, Bethesda, Maryland, USA).

Serum and respiratory tract specimens are stored for future viral research, following review and approval by the Protocol Team and the NIAID. Results of research tests on stored specimens will not be given to participants or their clinicians, but aggregate results will be made available.

FLU 002 - H1N1v Outpatient Study

At designated clinical sites, consenting participants aged 18 years with ILI are consecutively enrolled (Figure 2). At enrollment, demographics, height and weight and vital signs, date of ILI onset and symptom duration, use of NIs in the last 14 days, medical history (including underlying illnesses, pregnancy, smoking, current medications, influenza (seasonal and pandemic (H1N1) 2009) from 2008 and pneumococcal vaccination history, antiviral and other treatments prescribed at enrollment, and reason for seeking care are recorded (Table 2).

If available, the results of oropharyngeal and nasal swab for local influenza NAT, chest radiographic reports, and local laboratory tests performed as part of standard of care are recorded. Oropharyngeal and nasal swabs for central laboratory characterization of influenza viruses and serum (for future substudies) are collected at enrollment and stored.

Following enrollment, patients are given a diary to record symptoms, days of work or school missed, and medications used. Each participant is contacted 14 days later and the following collected: duration of ILI symptoms based on patient diary, NI and other medications prescribed, number of days of work or school missed due to ILI, number of household contacts and number who developed ILI, chest radiograph report, hospitalization (including duration, intensive care requirements, oxygen and ventilation requirements) and vital status.

It was projected that 5000 participants with laboratory-confirmed pandemic (H1N1) 2009 virus infection would be needed to identify 100 cases who required hospitalization and developed severe and/or complicated influenza within 14 days after enrollment. To obtain 5000 participants with pandemic (H1N1) 2009 virus infection, it was estimated that approximately 10,000 participants with ILI would have to be enrolled. Assuming that the percent of patients who die or who are hospitalized in the first 14 days is 2%, then with 5,000 patients with laboratory-confirmed pandemic (H1N1) 2009 virus infection it was calculated that we would be able to estimate this percent within $\pm 0.5\%$ (exact 95% confidence interval: 1.6 to 2.4%). With 100 severe cases of influenza (e.g., death or hospitalization within 14 days of enrollment), the power is 80% at the 0.05 level of significance (2-sided) to detect odds ratios ranging from 1.8 to 2.7 for risk factors having a prevalence between 50% and 5%.

FLU 003 - H1N1v Hospitalization Study

Patients aged 18 years with a confirmed or suspected diagnosis of influenza A who are hospitalized with severe and/or complicated influenza A are enrolled (Figure 3). This includes patients already hospitalized at the study site or who have been previously seen at

another hospital where the diagnosis of influenza A was made, or patients enrolled in FLU 002 who are hospitalized and meet the eligibility criteria. During specified times of known influenza activity, consecutive patients are enrolled.

The FLU 003 data collection plan is outlined in Table 2. Briefly, for patients without a confirmed influenza A diagnosis at enrollment, nasal and oropharyngeal swabs (or other suitable specimens e.g., lower respiratory tract sample) are obtained for local influenza NAT. Nasal and oropharyngeal swabs (and additional sampling from lower airways in case of respiratory distress) are obtained simultaneously at enrollment and sent to the central laboratory for influenza NAT and stored. Serum is collected at enrollment and at day 28.

All consenting participants have the following collected at enrollment: complications that define eligibility; demographics, height, weight and vital signs; date of ILI onset, symptom duration, earliest contact with the health system for current illness; use of NIs to prevent or treat influenza in the preceding 14 days; medical history and underlying medical conditions, smoking history, and current medications; influenza (seasonal and pandemic (H1N1) 2009) from 2008 and pneumococcal vaccination history; and antiviral, antibacterial and other treatments prescribed at enrollment. Also recorded are local laboratory test results for influenza A, including at enrollment; chest radiograph findings; and other local laboratory tests performed as part of standard of care.

The status of each participant is assessed at 28 and 60 days after enrollment by telephone or clinical review, irrespective of whether the diagnosis of influenza A is confirmed. These assessments include a report on influenza recovery, hospitalization duration, number of days in intensive care, on mechanical ventilation, and on dialysis, pregnancy outcome and vital status. Death causes are coded using the 10th Revision of the International Classification of Disease (ICD-10) and the Medical Dictionary for Regulatory Activities (MedDRA).

The goal of FLU 003 was to enrol sufficient individuals to observe 100 deaths among pandemic (H1N1) 2009 virus-infected patients. With this number of events, power is 80% to detect relative risks of 2.30 and 1.89 for dichotomous risk factors for death, assuming risk factor prevalences of 10% and 25%. It was estimated that the 60-day case fatality proportion would be 10% among pandemic (H1N1) 2009 virus-infected patients; therefore the original sample size was set at 1000 participants with laboratory-confirmed infection.

Results

Enrollments into the two studies commenced in October 2009 during the second northern hemisphere pandemic wave, and before the second southern hemisphere wave. The studies will continue until August 2011. To demonstrate the feasibility of these studies, preliminary results of enrollment characteristics are presented. As of the end of 2010, 62 sites in 14 countries in Australasia (12 sites), Europe (37) and North America (13) have enrolled 1365 adult patients: 1049 were enrolled into FLU 002 and 316 into FLU 003. The characteristics of the first 1288 patients enrolled and analysed (by October 1, 2010) are shown in Table 3. A central laboratory-confirmed diagnosis of influenza A (H1N1) 2009 has been made, to date, in 47.4% of enrollments in FLU 002 and 55.6% in FLU 003.

Less than one-third of the targeted number of primary outcomes for each protocol has been recorded. For FLU 002, 22 (5.6% of the pandemic (H1N1) 2009 NAT positive individuals) of the 100 deaths or hospitalizations in 14 days that were the protocol target have occurred; for FLU 003, 20 of the predicted 100 deaths in the 60-day follow-up period have occurred. While based on small numbers, the currently observed 60-day case-fatality proportion for laboratory-confirmed influenza (H1N1) 2009 infection in FLU 003 is very close to the 10% case fatality estimated in the protocol.

Discussion

The emergence of the pandemic (H1N1) 2009 virus in early 2009 activated international and national pandemic plans, based on escalation of the World Health Organization pandemic phases. Appropriate responses required knowledge of the clinical and laboratory features of the novel pandemic strain; rational use of antiviral agents, infection control measures, laboratory tests, and use of hospital and intensive care resources, depended on this information.

Geographic variation in virus activity, and risk factors for severe infection, were noted in the first year of the pandemic. For example, the first northern hemisphere pandemic wave occurred in autumn, when other respiratory virus activity was limited. In contrast, the first southern hemisphere wave occurred at the peak of the usual respiratory virus activity, further contributing to the load on the medical system and complicating identification of pandemic (H1N1) 2009 virus-specific clinical activity.

It is also difficult to know what will happen in the subsequent pandemic waves. It has been recognized in previous pandemics that later waves may be more severe than early waves.²⁹ It is also possible that as time progresses, the virulence of the pandemic (H1N1) 2009 virus may change, in particular having increased severity in older individuals compared to its current impact on adolescents and younger adults. Evidence from the first southern hemisphere wave suggested that seasonal strains were displaced by the pandemic (H1N1) 2009 virus:³⁰ whether this continues in subsequent waves is uncertain.³¹

Studies of the viral genetic, antigenic and pathogenic features are needed to understand current (and future) vaccine effectiveness, and to assist vaccine design. Although a pandemic vaccine was available after the first and second waves, vaccine efficacy in future waves will depend on understanding the genetic and antigenic drift of this virus. Antigenic drift among circulating pandemic (H1N1) 2009 virus strains is expected in the future, but the rate and impact of drift cannot be predicted. The WHO Global Influenza Surveillance Network and other groups undertake international antigenic and genetic studies (including antiviral drug resistance) of circulating influenza viruses, although matching data about clinical severity and demographic information is usually absent.

Many studies have published on the clinical features of pandemic (H1N1) 2009 virus infections, including in intensive care admissions, hospitalizations, in adults and children, in pregnant women, in the morbidly obese, and (to a lesser extent) in the community. However, studies are usually limited to one institution, region or country: international clinical studies using common data collection methods are unavailable. It is important for local planning and vaccine delivery to establish if underlying risk factors for severe disease vary from country to country. Global studies are also required to monitor for antiviral drug resistance in the context of known anti-influenza therapy and clinical outcomes.

For these reasons, two clinical observational studies were rapidly developed to assess the clinical features of community and hospitalized patients with influenza around the world using the INSIGHT network of HIV trials centres. Understanding the local influenza activity that determines opening of clinical sites for enrolment may vary between regions. However, the use of a central laboratory will reduce regional variability in laboratory confirmation of infection. Substudies utilizing stored specimens that take advantage of the international comparative aspects of these studies are also likely to provide data not necessarily available in more localized projects. These include laboratory studies (eg. genetic analyses of influenza detected in enrolled subjects, serological measures, comparisons of central versus local laboratory testing, identification of bacterial or viral co-infections) where disease severity details are available for comparison. Integration and analyses of epidemiological,

virological, and clinical data will help inform public health and clinical management of influenza.

These simple observational studies may act as a model for obtaining epidemiological, clinical and laboratory information in future international respiratory disease outbreaks.

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Figure 1.
Flow Diagram for FLU 002 Outpatient Study

Figure 2.
Flow Diagram for FLU 003 Hospitalization Study

Table 1**Study Objectives**

<u>FLU 002</u>	<ol style="list-style-type: none"> 1 Characterize individuals who develop influenza-like illness, influenza A and H1N1v in terms of demographics, co-morbid conditions, prior influenza vaccination (seasonal and H1N1v), and use of antivirals overall, and according to type of clinical site. 2 Describe the clinical course and treatment provided for participants with H1N1v. 3 For those with H1N1v, to estimate the percent who are hospitalized and develop severe and/or complicated influenza within 14 days after enrollment. 4 For those with H1N1v, to study risk factors, (e.g., patient and viral characteristics, geographic location) for severe disease. 5 Establish a repository of oropharyngeal and nasal samples to determine a precise diagnosis, to molecularly characterize the virus, including subtype, antigenic and genetic analyses, and to identify known signature mutations associated with antiviral drug resistance, mutational evolution, and additional reassortment. 6 Establish a repository of serum to study biomarkers related to severity of influenza. 7 Compare the characteristics and outcomes of patients with H1N1v with seasonal influenza A.
<u>FLU 003</u>	<ol style="list-style-type: none"> 1 Characterize individuals who are hospitalized with influenza A and H1N1v in terms of demographics, comorbid conditions, prior influenza (seasonal and H1N1v) and pneumococcal vaccination, and use of antivirals. 2 For those with H1N1v, to estimate the percent who die and who develop a composite outcome of death, a requirement for intubation or dialysis, or prolonged hospitalization (duration of hospitalization >7 days) within 28 and 60 days after enrollment. 3 For those with H1N1v to study risk factors, (e.g., patient and viral characteristics, geographic location) for mortality and the composite outcome of death, a requirement for intubation or dialysis, or prolonged hospitalization (duration of hospitalization >7 days). 4 Establish a repository of oropharyngeal, nasal and lower airway samples to determine a precise diagnosis; to molecularly characterize the virus, including subtype, antigenic and genetic analyses; and to identify known signature mutations for antiviral drug resistance, mutational evolution, and additional reassortment. 5 Establish a repository of serum to study biomarkers related to severity of influenza and the immune response to the virus. 6 Compare the characteristics and outcomes of patients with H1N1v with seasonal influenza A.

Table 2

Data Collection for the FLU 002 and FLU 003 Studies

	FLU 002		FLU 003		
	Baseline (clinic visit)	Follow-up Day 14	Baseline (hospitalization)	Follow-up Day 28	Day 60
Data collected					
Targeted medical history	X		X		
ILI symptoms	X		X		
Antiviral medications	X	X	X	X	X
Vital signs	X		X		
Laboratory test results	X		X		
Complications		X	X	X	X
Local influenza test results	X		X		
Hospital and Vital Status		X		X	X
Hospital procedures/treatments		X	X	X	X
Specimens collected					
Respiratory tract	X		X		
Serum	X		X	X	

Table 3

Baseline Characteristics by Study as of October 2010 (enrollment ongoing).

	FLU 002	FLU 003	Total
Baseline Characteristics	(N=984)	(N=304)	(N=1288)
Age, median years	31	46	34
Interquartile range	24 – 43	35 – 59	25 – 47
Gender, % female	54.3	49.2	53.1
Pregnant*, % of women	2.1	12.8	4.4
Race, %			
Asian	33.5	10.3	28.0
Black	6.8	4.0	6.1
White	54.4	81.5	60.8
Other	5.3	4.3	5.1
BMI, median	23.9	25.8	24.3
Interquartile range	21.1 – 27.2	23.1 – 29.9	21.5 – 28.0
Duration of symptoms, median days	2	5	2
Interquartile range	1 – 3	3 – 8	1 – 4
Complications Defining Eligibility to FLU 003 (%)			
Respiratory distress requiring supplemental O ₂		83.1	
Exacerbation of pre-existing medical condition		30.1	
Circulatory collapse requiring vasopressor support		9.3	
Acute renal failure		7.9	
Acute liver failure		1.3	
Complications of pregnancy		2.3	
Other severe organ dysfunction		5.6	
Central Laboratory Results	(N=858)	(N=277)	(N=1135)
PCR Results by Central Laboratory, %			
Influenza A, H1N1	45.6	53.8	47.6
Influenza A, Other	1.8	1.8	1.8
Influenza A negative	52.0	43.0	49.8
Indeterminate	0.7	1.4	0.9

* At time of enrollment or 14 days prior to enrollment.