Clinical Infectious Diseases

MAJOR ARTICLE

Using Clinical Research Networks to Assess Severity of an Emerging Influenza Pandemic

Lone Simonsen,[1,2] Elizabeth Higgs,[3] Robert J. Taylor,[4] Deborah Wentworth,[5] Al Cozzi-Lepri,[6] Sarah Pett,[7,8] Dominic E. Dwyer,[9] Richard Davey,[3] Ruth Lynfield,[10] Marcelo Losso,[11] Kathleen Morales,[4] Marshall J. Glesby,[12] Jozef Weckx,[13] Dianne Carey,[8] Cliff Lane,[3] and Jens Lundgren[1]; for the INSIGHT FLU002 and FLU003 Study Groups

[1]Rigshospitalet and Faculty of Health Sciences, University of Copenhagen and [2]Department of Science and Environment, Roskilde University, Denmark; [3]National Institutes of Allergy and Infectious Diseases, National Institutes of Health, and [4]Sage Analytica, Bethesda, Maryland; [5]Division of Biostatistics, University of Minnesota, Minneapolis; [6]University College, and [7]Medical Research Council Clinical Trials Unit and Clinical Research Group, University College, London, United Kingdom; [8]The Kirby Institute, University of New South Wales, and [9]Centre for Infectious Diseases and Microbiology Laboratory Services, Institute for Clinical Pathology and Medical Research, Westmead Hospital and University of Sydney, Australia; [10]Minnesota Department of Health, St. Paul; [11]Hospital J.M. Ramos Mejía, Buenos Aires, Argentina; [12]Weill Cornell Medical College, New York, New York; and [13]Testumed Vereniging zonder winstoogmerk, Tessenderlo, Belgium, for the International Network for Strategic Initiatives in Global HIV Trials FLU002 AND FLU003 Study Groups

Background. Early clinical severity assessments during the 2009 influenza A H1N1 pandemic (pH1N1) overestimated clinical severity due to selection bias and other factors. We retrospectively investigated how to use data from the International Network for Strategic Initiatives in Global HIV Trials, a global clinical influenza research network, to make more accurate case fatality ratio (CFR) estimates early in a future pandemic, an essential part of pandemic response.

Methods. We estimated the CFR of medically attended influenza (CFR_{MA}) as the product of probability of hospitalization given confirmed outpatient influenza and the probability of death given hospitalization with confirmed influenza for the pandemic (2009–2011) and post-pandemic (2012–2015) periods. We used literature survey results on health-seeking behavior to convert that estimate to CFR among all infected persons (CFR_{AR}).

Results. During the pandemic period, 5.0% (3.1%–6.9%) of 561 pH1N1-positive outpatients were hospitalized. Of 282 pH1N1-positive inpatients, 8.5% (5.7%–12.6%) died. CFR_{MA} for pH1N1 was 0.4% (0.2%–0.6%) in the pandemic period 2009–2011 but declined 5-fold in young adults during the post-pandemic period compared to the level of seasonal influenza in the post-pandemic period 2012–2015. CFR for influenza-negative patients did not change over time. We estimated the 2009 pandemic CFR_{AR} to be 0.025%, 16-fold lower than CFR_{MA}.

Conclusions. Data from a clinical research network yielded accurate pandemic severity estimates, including increased severity among younger people. Going forward, clinical research networks with a global presence and standardized protocols would substantially aid rapid assessment of clinical severity.

Clinical Trials Registration. NCT01056354 and NCT010561.

Keywords. severity; pandemic influenza; case fatality ratio; clinical research; pandemic preparedness.

In 2009, uncertainty about the emerging pH1N1 virus' clinical severity hindered the early global response. Although the rapid spread of the virus around the world fulfilled the traditional pandemic definition, its global mortality impact in the end proved to be smaller than any 20th century pandemic [1, 2]. However, its relative mildness was not known in the early months of the outbreak. The earliest estimate of the case fatality ratio (CFR) was on par with the rating for the catastrophic 1918 pandemic, and a June 2009 assessment put it in the 1957 pandemic range (Table 1)[3].

An evaluation of the 2009 pandemic response ordered by the World Health Organization's (WHO) Director General [4] found that a systematic way to assess both transmissibility and clinical severity—also known as its "seriousness" [5]—is needed in the early phase of a future pandemic to assess the level of threat accurately and to mobilize resources appropriately. CFR is one important measure of clinical severity; others include the risk of admission to the intensive care unit (ICU) and the need for mechanical respiratory support. A WHO task force is currently developing the data inputs and study designs needed to generate timely estimates of clinical severity [6]. The Centers for Disease Control and Prevention has proposed a scheme for comparing pandemic and seasonal influenza graphically, plotting attack rates against clinical severity [7].

In 2009, UK Public Health England spearheaded what has become a standard first-line approach to assessing the clinical severity of a pandemic, known as the "First Few Hundred" (FF100) [8]. These and similar studies gather data on the earliest cases that come to medical attention through outpatient facilities and hospitals and provide important descriptive data

Received 25 August 2017; editorial decision 26 January 2018; accepted30 April 2018; published online May 8, 2018.

Correspondence: L. Simonsen, University of Copenhagen, Universitetsvej 1, 4000 Roskilde, Roskilde, Denmark (lsimonsen2@gmail.com).

Clinical Infectious Diseases® 2018;67(3):341–9

DOI: 10.1093/cid/ciy088

Table 1. Evolution of the Estimated Case Fatality Ratio Over Time

Report	Date of Publication	Setting	Estimated Case Fatality Ratio (%)	Severity
World Health Organization report [9]	May 2009	Early outbreaks Mexico	2	1918-like
Fraser et al [10]	June 2009	First wave Mexico	0.4	1957-like
Castro-Jiménez et al [11]	July 2009	First wave Colombia	3.8	1918-like
Baker et al [12]	July 2009	New Zealand first complete season	0.1	1968-like
Presanis et al [13]	September 2009	First wave in 2 US cities	0.04	1968-like
Van Kerkhove et al [14]	January 2013	Global estimate for first season, CONCISE Network	0.02	Seasonal

See also Wong et al [3].

about symptoms, risk factors, and risk of progression to severe illness or death [15–21]. These data can in turn be combined with other data on population attack rates to forecast national and global hospitalization and mortality estimates using a pyramid modeling strategy [13, 22].

Standard FF100 studies, however, lack historic controls in the form of a baseline from recent seasonal influenza seasons. They are also subject to selection bias, as the first cases that come to attention are likely to be more severe [23]. Unless an FF100 study is set in an existing surveillance system or ongoing clinical research data collection scheme, there is no obvious seasonal influenza baseline against which to compare the clinical severity of the pandemic virus. Moreover, unless the pandemic is severe, an FF100 study in the outpatient setting alone will not have the statistical power to accurately estimate the CFR unless many thousands of patients are enrolled.

Global clinical research networks that study mild and severely ill influenza patients could be used to overcome many of these problems. Two ongoing clinical cohort studies of influenza are conducted under the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) umbrella, sponsored by the National Institutes of Health. Since 2009, INSIGHT has undertaken 2 cohort studies—1 outpatient (FLU002) and 1 inpatient (FLU003)—specifically to address gaps in clinical research on the emerging influenza pandemic, including factors linked to disease progression and severe outcomes [24]. INSIGHT annually enrolls hundreds of patients with suspected or confirmed influenza, with intake sites in 12 countries. At these sites, experienced teams use a standardized protocol to collect extensive clinical data, perform long-term follow-up (at 28 and 60 days for inpatients, 14 days for outpatients), and bank patient samples for further study. Several articles on influenza have been published using INSIGHT data, including protocol descriptions and preliminary data [24], an exploration of biomarkers of influenza case severity [25], patient outcomes after pH1N1 infection [26], and phylogeography of the pH1N1 virus [27].

We used INSIGHT data collected in the pandemic period (2009–2011) to retrospectively demonstrate how clinical research networks can provide essential early insights into pandemic clinical severity and other epidemiological parameters. To "leverage" the CFR computation, we multiplied the conditional probability of progression from outpatient to hospitalization by that of progression from hospitalization to death. To underscore the importance of having baseline data, we compared the estimated pH1N1 clinical severity to that of seasonal influenza types and subtypes and noninfluenza respiratory patients in the post-pandemic period (2012–2015). Our CFR estimates were in reasonable agreement with final global CFR estimates based on excess mortality estimates from time series of nationwide vital statistics data and seroepidemiology data—final estimates of a type that would only be available several years after the next pandemic emerges [1, 2, 16]. Here, we discuss what it would take to move a clinical research network like INSIGHT from routine research operation into emergency mode to generate timely and robust clinical severity assessments.

METHODS

INSIGHT FLU002 and FLU003 protocols

The National Institute of Allergy and Infectious Diseases (NIAID)–funded INSIGHT network initially focused solely on HIV but expanded first to include pH1N1 and then all influenza types and subtypes and emerging respiratory pathogens such as Middle East respiratory syndrome and severe acute respiratory syndrome. Sites, located in 5 of 6 world regions (Figure 1), consecutively enroll adult patients aged ≥18 years with suspected influenza. FLU002 recruits patients who present at a physician's office or clinic with influenza-like illness (ILI), defined as fever with either cough or sore throat. FLU003 recruits patients with known or suspected influenza who require hospitalization. At enrollment, patient medical history and demographic information are recorded, and blood and oropharyngeal swabs are analyzed and stored. Testing for influenza is done both locally and at an INSIGHT central laboratory. All patients are followed up, regardless of influenza test result, at 14 days after enrollment in FLU002 and at 28 and 60 days in FLU003.

We extracted INSIGHT data on demographics, illness onset, medical history, and vital status at follow-up visit from the protocol databases. We defined the pandemic period as the first 2 seasons, October 2009 through September 2011, and the post-pandemic influenza period as October 2012 through September 2015 (last 3 complete INSIGHT seasons, skipping the 2011–2012 season as a transition). Patients who were lost

Figure 1. Map of International Network for Strategic Initiatives in Global HIV Trials influenza protocol patient intake sites. Blue markers indicate FLU002 outpatient sites and red markers indicate FLU003 inpatient sites.

to follow-up were treated as missing and removed from the analysis.

We identified 9 relevant case series in the literature reporting data on patients aged >18 years. After excluding studies with fewer than 100 patients or with a specialty population (such as high-risk patients), we chose 2 outpatient studies, 1 set in the United States [28] and 1 in the United Kingdom [8], and 2 inpatient studies [18, 20], both set in the United States, for comparison with FLU002 and FLU003 pH1N1 laboratory-confirmed patients during the pandemic period (Table 2).

We calculated the medically attended CFR (CFR_{MA}) from the probability that a medically attended ILI (FLU002) patient would progress to hospitalization by day 14 and the probability that a hospitalized (FLU003) patient would die by day 60:

$$CFR_{MA} = P(H \mid ILI_{MA}) \times P(D \mid H),$$

where H = hospitalization and D = death

To estimate CFR among all infected persons (CFR_{AR}), we used findings from a UK health behavior survey that found that 25% of patients aged ≥18 years with ILI sought care for their illness [29] and a UK serology study that found that 25% of influenza-infected adults aged 25–64 years were symptomatic [30]. Assuming that the nonmedically attended and asymptomatic influenza cases would not progress to severe illness, we have:

$$CFR_{AR} = CFR_{MA} \times P(ILI_{MA} \mid ILI) \times P(ILI \mid infection) = CFR_{MA} \times 0.0625,$$

where "infection" is defined as a person who responded immunologically.

The 95% confidence intervals (CIs) on the CFR estimate were generated from the variance of the product of the 2 proportions, P(H/ILI) × P(D/H), using the delta method or a first-order Taylor series expansion. We assumed the 2 proportions were independent. In small samples with large variability, this may not be a good approximation. In some cases, negative values for the CIs may be obtained.

Data analysis was done using SAS, version 9.4, and Excel. The FLU 002 and FLU 003 protocols were approved by the institutional review boards or institutional ethics committees at the University of Minnesota and at each of the participating clinical sites. All patients (or their proxies) gave signed informed consent prior to enrollment.

RESULTS

Descriptive Comparison of INSIGHT Patient Findings to Findings from Other FF100 Studies

During the pandemic period (October 2009 through September 2011), 559 ILI and 384 hospitalized patients tested influenza pH1N1 positive. Of these, 99.6% of pH1N1-infected FLU002 outpatients were aged 18–64 years compared to only 88% of the FLU003 inpatients. During the post-pandemic period (October 2012 through September 2015), 704 ILI and 245 hospitalized patients were pH1N1 positive; of these, 96% of ILI outpatients and 81% of hospitalized patients were aged 18–64 years. In the pandemic period about 1/2 of outpatients and 2/3 of inpatients were from European sites, while during the post-pandemic

Table 2. Findings on Clinical Symptoms, Demographics, and Underlying Illness from FLU003 and FLU002 Protocols

Inpatient Studies (Ward and Intensive Care Unit Combined)					Outpatient Studies		
Study	Country	United States		Global	United States	United Kingdom	Global
	First Author	Jain [18]	Louie [20]	INSIGHT 003	Dawood [28]	McLean [8]	INSIGHT 002
	(N) adults (unless noted)	150	744	282	642 (L)	392 (M)	559
	Adult median age, y (range)	41 (18–86)	39 (18–92)	48 (19–87)	…	…	30 (18–73)
Major symptoms (%)	Fever	100	87	…	94	94	…
	Cough or sore throat	93	88	…	92	85	…
	Gastrointestinal symptoms	26	34	…	25	28	…
	Myalgia	51	41	…	…	80	…
	Headache	45	22	…	…	84	…
	Shortness of breath	73	66	…	…	44	…
Comorbidities (%)	At least 1 comorbidity	83	>72	55	4	11	16
	Pregnant (of women in study)	11	13	10	…	1	2
	Immunosuppression	19	20	11	0.4	1	1
	Human immunodeficiency virus only	…	15	4	…	…	8
	Cardiovascular disease	20	19	14	0.4	1.0	0.4
	Chronic obstructive pulmonary disease	15	16	11	2.5	8	0.7
	Asthma	27	21	17			
	Diabetes	25	15	11	…	1.3	2
Other factors (%)	Influenza vaccination	44	…	23	…	10	14
	Obesity (BMI >30)	55	58	25	…	…	16
	Morbid obesity (BMI ≥40)	26	25	5	…	…	2
	Smoker (ever)	24	…	59	…	…	21
Progression of illness (%)	Hospitalized	100	100	100	9	6	5
	Died	9	15	9	0.5	0	0.2
	Intensive care unit	29	34	26	3	…	0.2
	Chest X-ray infiltrate	39	68	…	4	0.8	0.7
	Mechanical ventilation	22	31	22	2	0.8	0.2
	Sepsis	12	…	6	…	…	0
Treatment (%)	Antiviral use	79	81	80	7	92	20
	Antibiotic use	82	…	83	…	11	…
	Corticosteroid use	39	…	33	…	…	…

Data are for the pandemic period October 2009 through September 2011 and select studies that either presented or allowed extraction of similar findings for adults aged ≥18 years.
Abbreviations: BMI, body mass index; INSIGHT, International Network for Strategic Initiatives in Global HIV Trials.

period, after the network expanded to sites in 5 world regions, these figures were 1/3 of outpatients and 2/5 of inpatients.

We found that demographic and clinical characteristics of INSIGHT pandemic period pH1N1 patients were similar to those described in published FF100-like studies of adult pH1N1 patients [26] with respect to mean age, prevalence of symptoms and underlying diseases, mortality rates, and other characteristics (Table 2).

CFR Estimates

CFR_{MA} in the Pandemic Period 2009–2011

Five percent of pH1N1-confirmed ILI patients were hospitalized, and 8.7% of pH1N1-positive inpatients died (Table 3, Figure 2). This yielded a pH1N1 CFR_{MA} of 0.4% (0.2%–0.7%) both for all adults and for adults aged 18–64 years. The CFR_{MA} for patients aged ≥65 years could not be established with confidence due to the small number of older outpatients in the study. As a nonhistoric control, the all-ages CFR_{MA} of influenza test–negative patients was 0.1% during the pandemic period, albeit with wide CIs. It was not possible to establish a seasonal influenza comparison for the pandemic period because non-pH1N1 influenza cases (H3N2, B) in the pandemic period were rare.

CFR_{MA} in the Post-Pandemic Period 2012–2015

The CFR_{MA} for pH1N1 cases in the post-pandemic period was 0.09% for patients aged 18–64 years, 5-fold lower than the value for the pandemic period and comparable to the influenza-negative patients of the same age. We could not reliably assess pH1N1 CFR_{MA} for the ≥65 years age group due to small numbers in the post-pandemic period; however, CFR_{MA} was 0.4% for seniors aged ≥65 years positive for any influenza virus in the post-pandemic period vs 0.04% for younger adults positive for any influenza virus. For the post-pandemic period (any

Table 3. Estimated Case Fatality Ratio among Medically Attended Cases

Period	Age	Viral Subtype	N (Outpatient)	N (Inpatient)	P (H|ILI)	P (D|H)	Case Fatality Ratio/% (95% Confidence Interval)
Pandemic (2009–2011)	All ages	pH1N1	541	358	0.052	0.087	0.45 (0.23, 0.67)
		H3N2	273	31	0.004	0.065	*
		B	33	12	0.061	0.000	*
		Negative	971	117	0.031	0.043	0.13 (0.01, 0.25)
	18–64	pH1N1	539	313	0.052	0.083	0.43 (0.21, 0.65)
		H3N2	254	14	0.000	0.000	*
		B	31	8	0.065	0.000	*
		Negative	924	84	0.025	0.024	*
	65+	pH1N1	2	45	0.000	0.111	*
		H3N2	19	17	0.053	0.118	*
		B	2	4	0.000	0.000	*
		Negative	47	33	0.149	0.091	*
Post-pandemic (2012–2015)	All ages	pH1N1	667	218	0.019	0.046	0.09 (0.02, 0.16)
		H3N2	1345	424	0.009	0.047	0.04 (0.01, 0.07)
		B	639	185	0.020	0.070	0.14 (0.04, 0.25)
		Negative	4089	422	0.018	0.107	0.19 (0.12, 0.26)
	18–64	pH1N1	639	174	0.019	0.046	0.09 (0.01, 0.16)
		H3N2	1248	191	0.006	0.016	0.01 (0.00, 0.02)
		B	602	118	0.017	0.042	0.07 (0.00, 0.14)
		Negative	3778	244	0.016	0.057	0.09 (0.04, 0.14)
	65+	pH1N1	28	44	0.036	0.045	*
		H3N2	97	233	0.041	0.073	*
		B	37	67	0.081	0.119	*
		Negative	311	178	0.039	0.174	0.67 (0.24, 1.1)

Data are for the pandemic and post-pandemic periods, computed as the product of the risk of FLU002 influenza-like illness outpatients getting hospitalized and the FLU003 hospitalized patients having died at day 60.
Abbreviations: P (D|H), probability of death given hospitalization; P (H|ILI) , probability of hospitalization given influenza-like illness.
*Case fatality rate not calculated when fewer than 100 outpatients or inpatients contained in any stratum.

subtype), we also estimated the conditional probabilities and the CFR_{MA} by region (Table 4).

Converting CFRMA to CFRAR

Because the final WHO CFR estimate from the 2009 pandemic was based on attack rates as revealed by serology data, we sought to convert our medically attended CFR to one based on the attack rate. To do so, we used data from a study that indicated that approximately 25% of all cases are asymptomatic [29] and from survey data that indicate that approximately 25% of adult ILI cases sought medical attention [30]. We found the CFR_{AR} to be 0.03% (0.01%–0.04%; Table 5), or 16-fold lower than the CFR_{MA}.

DISCUSSION

WHO has recently expanded its pandemic definition to include clinical severity. This means that rapid and accurate estimates of pandemic clinical severity are needed to characterize the threat level and guide the global response. Our analysis combining data from inpatient and outpatient INSIGHT cohorts demonstrates how preestablished global research networks could immediately begin rigorous studies to estimate the CFR, a key parameter of clinical severity of an emerging pandemic.

Assessments of the clinical severity in the 2009 pandemic became less dire as time passed [3]. The earliest estimate of CFR, an FF100-like case series of hospitalized patients in Mexico, was a disturbing 2% of influenza-positive patients. However, as studies of the first (summer) wave in the United States, the complete southern hemisphere 2009 season in New Zealand, and further studies from Mexico were completed, it became clear that the pandemic would be relatively mild (Table 1).

Several factors contributed to the early confusion in 2009. The most important was probably selection bias toward sicker patients in the earliest FF100-type case series studies [3]. Another factor was simply that studies reported on different types of CFR—either as a proportion of medically attended cases (CFR_{MA}) or as a proportion of all infected individuals (CFR_{AR}). Most early assessments were of the CFR_{MA} type, but these were not directly comparable.

Our method, retroactively applied to INSIGHT databases, yielded a CFR_{MA} estimate of 0.4%. Using literature values that indicated that the probability of symptomatic people seeking medical treatment was 25% [29] and that the probability of infected individuals being asymptomatic was also 25% [30], our CFR_{MA} value would be equivalent to a CFR_{AR} of .025%, which

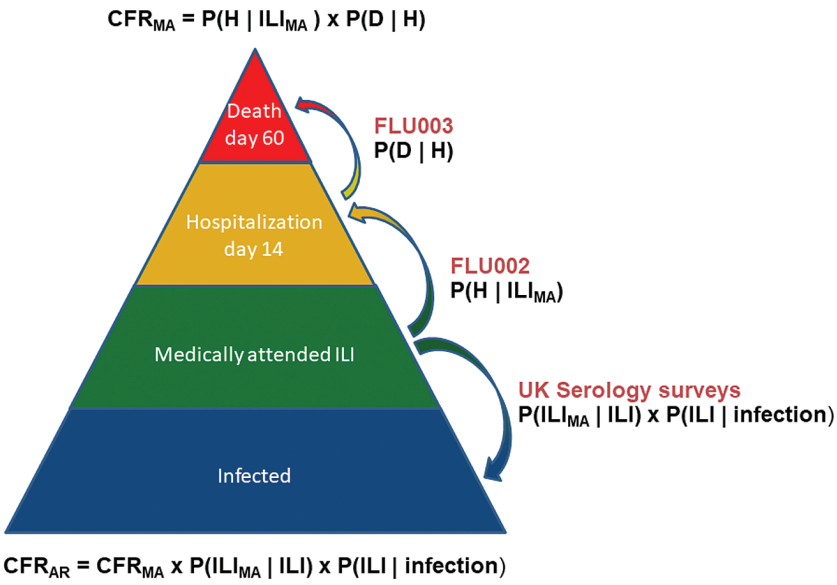

Figure 2. A schematic representation of the pyramid modeling approach used to estimate the 2009 pandemic case fatality ratio among medically attended cases from probabilities of disease progression from International Network for Strategic Initiatives in Global HIV Trials outpatient (FLU002) and inpatient (FLU003) data. Modeling was also done for 18–64 and 65+ year age groups separately due to known differences in attack rates and preexisting immunity. Abbreviations: AR, all infected persons; CFR, case fatality ratio; ILI, influenza-like illness; MA, medically attended; P (D|H), probability of death given hospitalization; P (H|ILI) , probability of hospitalization given influenza-like illness.

is in reasonable agreement with the final global WHO CFR_{AR} estimate of 0.02% [1, 2, 16].

In addition to an absolute measurement of CFR, data from previous seasons can provide a relative comparison of pandemic to seasonal influenza severity; even if the absolute estimate of CFR is uncertain, it would be useful to know if an emerging pandemic has a CFR far higher than previous seasonal influenza experiences. Thus, we also estimated CFRs for influenza patients from seasonal influenza epidemics 2012–2015, as a surrogate for pre-pandemic baseline seasons.

Age greatly influences both seasonal and pandemic clinical severity estimates. In all 4 influenza pandemics since 1900, mortality was higher than normal in younger people and lower than normal in seniors, sometimes dramatically so [31]. In the post-pandemic period (2012–2015) we found that the CFR_{MA} of pH1N1 for patients aged 18–64 years had fallen 5-fold from the pandemic period value, becoming similar to that of A/H3N2 and B. This suggests that the emerging virus had settled into a seasonal epidemic pattern due to accumulated population immunity. Moreover, in the post-pandemic period patients aged ≥65 years with any influenza virus had a CFR_{MA} approximately 10-fold higher than patients aged <65 years. These results corroborate a previous metaanalysis of FF100 studies that concluded that age is an important confounder of CFR estimates for pH1N1 pandemic influenza [3]. They also show how important it is to take into account both the age group and the type of CFR being calculated when comparing across regions and time.

It is also possible that discrepancies in early assessments of CFR may in fact have reflected true geographical differences. For example, a comprehensive study of 2009 pandemic mortality that applied a uniform methodology to different regions found the mortality impact in Central and South American countries

Table 4. Numbers of Patients Who Test Positive for Influenza, Probabilities of Progression to Hospitalization and Death, and Medically Attended Case Fatality Ratio by International Network for Strategic Initiatives in Global HIV Trials Geographic Region in the Post-Pandemic Period

	Positive for Any Influenza (N)		Probabilities		
Region	FLU002	FLU003	P(H|ILI)	P(D|H)	Medically Attended Case Fatality Ratio (95% Confidence Interval)
Asia	616	116	0.010	0.009	0.01% (–0.01, 0.03)
Australia	10	106	0.000	0.010	*
Europe	678	280	0.028	0.068	0.19% (0.07, 0.31)
North America	183	233	0.044	0.034	0.15% (0.01, 0.29)
South America	1164	92	0.004	0.152	*
All regions	2651	827	0.014	0.052	0.07% (0.04, 0.11)

Abbreviations: P (D|H), probability of death given hospitalization; P (H|ILI) , probability of hospitalization given influenza-like illness

*Case fatality ratio not calculated when fewer than 100 outpatients or inpatients contained in any stratum.

Table 5. Conversion of Medically Attended Case Fatality Ratio (CFR) to CFR for All Infected Persons Estimates Using 2 UK Studies

Source	Measure	Parameter	Estimate	Lower Bound	Upper Bound
This study	CFR based on persons with medically attended ILI	CFR_{MA}	0.4%	0.2%	0.6%
Brooks-Pollock et al [28]; UK survey of healthcare-seeking behavior in adults	Probability of seeking medical care given ILI	$P(ILI_{MA}\|ILI)$	0.25	0.25	0.25
Hayward et al [29]; serology study	Probability of having ILI symptoms given H1N1pdm infection (based on antibody titers)	P(ILI|Inf)	0.25	0.25	0.25
Multiplying the 3 figures	CFR based on persons with influenza infection	CFR_{AR}	0.03%	0.01%	0.04%

Abbreviations: AR, attack rate; CFR, case fatality ratio; ILI, influenza-like illness; MA, medically attended.

was approximately 20-fold higher than in Europe [1]. This indicates that early reports of higher severity in Mexico than in New Zealand may not solely have been the result of ascertainment bias. Clinical severity can even increase substantially over time, as was seen in the 1918 influenza pandemic when a milder summer wave preceded the severe autumn waves [32].

The best way around the measurement problems that occur early in a pandemic would be to compute the same type of CFR with the same protocol in multiple geographical settings. If possible, estimates should be stratified by risk factors, such as pregnancy and chronic illness, and baseline data should be collected during seasonal epidemics. While some countries have created FF100 protocols since the 2009 pandemic, a global standard along the lines we have outlined here would be helpful.

We recognize limitations to our approach to computing CFR by multiplying conditional probabilities of disease progression. First, we used distinct groups of outpatients and inpatients who were recruited under different circumstances at different sites, often in different countries. It is therefore possible the 2 cohorts differed in age composition, health status, or other important respects that could bias the result. However, we argue that the approach, while not ideal, would nonetheless supply timely and useful data, especially if it could be compared to baseline seasons. We also note that the characteristics of the INSIGHT pH1N1 outpatients and inpatients in the pandemic period 2009–2011 are reassuringly similar in terms of age, symptoms, comorbidities, and outcomes to published UK and US FF100 studies of adult pH1N1 influenza outpatients and inpatients (Table 2). A second possible caveat—that INSIGHT inclusion criteria might have varied over time and explained the drop in CFR_{MA} over time—could be dismissed on the grounds that the influenza-negative patients did not have a significant drop in CFR_{MA} between the pandemic and post-pandemic period. This means that the measured decrease in pH1N1 clinical severity was real and not due to ascertainment or other bias.

CONCLUSIONS

Our retrospective analysis of 2009 pandemic clinical severity indicates that it is possible to use research networks to assess both the absolute magnitude of the clinical severity of a future pandemic and the relative increase compared to a seasonal influenza baseline. Even if the seroepidemiology and health-seeking behavior surveys needed to convert CFR_{MA} to CFR_{AR} could not be done rapidly, comparison of CFR_{MA} to previous seasons would reveal much about the relative magnitude of the emerging threat. To be useful in a prospective scenario, however, it would be necessary to ramp up the network's pace of operations from routine to emergency mode. For INSIGHT, that would mean, at a minimum, enhancing enrollment in sites located in areas initially affected by the emerging pandemic and increasing the tempo of laboratory processing of specimens and data analysis.

In addition to assessing clinical severity, global research networks could play other key roles in pandemic response including studies of comorbidity patterns, risk factors, hospital and ICU utilization, and mortality risk of hospitalized patients. Moreover, protocols that enroll children could be used to understand the pathogen in this key age group. Once a future pandemic outbreak begins, studies set in these networks could both characterize pathophysiology to optimize clinical management and provide a platform for rigorous clinical trials of new therapeutics. We suggest, therefore, that a specific role for clinical research networks carrying out ongoing rigorous research compliant with international standards be added to the international health regulations that govern international and national responsibilities for public health emergencies of international concern.

Notes

Acknowledgments. We thank and acknowledge all the patients who participated in this study.

Disclaimer. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Financial support. International Network for Strategic Initiatives in Global HIV Trials is funded by the National Institutes of Health (grant UOI-AI068641, SAIC-Frederick HHSN261200800001E). This study was funded through subcontracts (13XS134 and 16Q152) under Leidos Biomedical Corporation's prime contract (HHSN261200800001E and HHSN261201500003I) with the National Cancer Institute and the National Institute of Allergy and Infectious Diseases. The authors also acknowledge grant support from Danish National Research Foundation (grant 126) and the European Research Commission Horizon 2020 Research and Innovation Framework Program Marie Curie (grant 659437).

Potential conflicts of interest. L. S. and R. J. T. report earning consulting fees from Sage Analytica, LLC, during the conduct of the study. R. L. reports serving as co-editor on a book on infectious disease surveillance published by Wiley Blackwell, with royalties donated to the Minnesota Department of Health. All remaining authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Simonsen L, Spreeuwenberg P, Lustig R, et al. Global mortality estimates for the 2009 influenza pandemic from the GLaMOR project: a modeling study. PLoS Med. **2013**; 10.
2. Dawood FS, Iuliano AD, Reed C, et al. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. Lancet Infect Dis. **2012**; 12:687–95. doi: 10.1016/S1473-3099(12)70121–4.
3. Wong JY, Kelly H, Ip DKM, Wu JT, Leung GM, Cowling BJ. Case fatality risk of influenza A (H1N1pdm09): a systematic review. Epidemiology. **2013**; 24:830–41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24045719.
4. Report of the Review Committee on the Functioning of the International Health Regulations (2005) in relation to Pandemic (H1N1) 2009. **2011**;1–180.
5. Wong JY, Wu P, Nishiura H, et al. Infection fatality risk of the pandemic a(H1N1)2009 virus in Hong Kong. Am J Epidemiol. **2013**; 177:834–40.
6. World Health Organization. Pandemic Influenza Severity Assessment (PISA). 2017. Available at: http://www.who.int/influenza/surveillance_monitoring/pisa/en/.
7. Reed C, Biggerstaff M, Finelli L, et al. Novel framework for assessing epidemiologic effects of influenza epidemics and pandemics. Emerg Infect Dis **2013**; 19:85–91.
8. McLean E, Pebody RG, Campbell C, et al. Pandemic (H1N1) 2009 influenza in the UK: clinical and epidemiological findings from the first few hundred (FF100) cases. Epidemiol Infect. **2010**; 138:1531–41.
9. World Health Organization. Human infection with new influenza A (H1N1) virus: clinical observations from Mexico and other affected countries, May 2009. Wkly Epidemiol Rec. **2009**; 21:185–90.
10. Fraser C, Donnelly CA, Cauchemez S, et al. Pandemic potential of a strain of influenza A (H1N1): early findings. Science. **2009**; 324:1557–61. Available at: http://science.sciencemag.org/content/324/5934/1557.abstract.
11. Castro-Jiménez MA, Castillo-Pabón JO, Rey-Benito GJ, et al; Virology Group; Communicable Diseases Surveillance Group. Epidemiologic analysis of the laboratory-confirmed cases of influenza A(H1N1)v in Colombia. Euro Surveill **2009**; 14:19284.
12. Baker M, Wilson N, Huang Q, et al. Pandemic influenza A(H1N1)v in New Zealand: the experience from April to August 2009. Euro Surveill. **2009**; 14:1–6.
13. Presanis AM, De Angelis D, Hagy A, et al. The severity of pandemic H1N1 influenza in the United States, from April to July 2009: a Bayesian analysis. PLoS Med. **2009**; 6.
14. Van Kerkhove MD, Hirve S, Koukounari A, et al. Estimating age-specific cumulative incidence for the 2009 influenza pandemic: a meta-analysis of A(H1N1) pdm09 serological studies from 19 countries. Influenza Other Respir Viruses. **2013**; 7:872–86.
15. AlMazroa MA, Memish ZA, AlWadey AM. Pandemic influenza A (H1N1) in Saudi Arabia: description of the first one hundred cases. Ann Saudi Med **2010**; 30:11–4.
16. Domínguez-Cherit G, Lapinsky SE, Macias AE, et al. Critically Ill patients with 2009 influenza A(H1N1) in Mexico. JAMA. **2009**; 302:1880–7. Available at: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2009.1536. Accessed 8 March 2018.
17. Davey RT, Markowitz N, Beigel J, et al. INSIGHT FLU005: an anti-influenza virus hyperimmune intravenous immunoglobulin pilot study. J Infect Dis. **2016**; 213:574–78.
18. Jain S, Kamimoto L, Bramley AM, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. N Engl J Med. **2009**; 361: 1935–44. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19815859.
19. Khandaker G, Dierig A, Rashid H, King C, Heron L, Booy R. Systematic review of clinical and epidemiological features of the pandemic influenza A (H1N1) 2009. Influenza Other Respir Viruses **2011**; 5:148–56.
20. Louie JK, Winter K, Jean C, et al. Factors associated with death or hospitalization due to pandemic 2009 influenza A (H1N1) infection in California. **2009**; 302.
21. van Gageldonk-Lafeber AB, van der Sande MA, Meijer A, et al. Utility of the first few100 approach during the 2009 influenza A(H1N1) pandemic in the Netherlands. Antimicrob Resist Infect Control. **2012**; 1: 30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22995284.
22. Pelat C, Ferguson NM, White PJ, et al. Optimizing the precision of case fatality ratio estimates under the surveillance pyramid approach. Am J Epidemiol **2014**; 180:1036–46.
23. Lipsitch M, Donnelly CA, Fraser C, et al. Potential biases in estimating absolute and relative case-fatality risks during outbreaks. PLoS Negl Trop Dis. **2015**; 9:e0003846. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4504518&tool=pmcentrez&rendertype=abstract.
24. Dwyer DE. 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. Vaccine. **2011**; 29:56–62.
25. Davey RT, Lynfield R, Dwyer DE, et al. The association between serum biomarkers and disease outcome in influenza A(H1N1)pdm09 virus infection: results of two international observational cohort studies. PLoS One. **2013**; 8.
26. Lynfield R, Davey R, Dwyer DE, et al. Outcomes of influenza A(H1N1)pdm09 virus infection: results from two international cohort studies. PLoS One. **2014**; 9.
27. Holmes EC, Ghedin E, Halpin R a, et al. Extensive geographical mixing of 2009 human H1N1 influenza A virus in a single university community. J Virol. **2011**; 85:6923–29.
28. Dawood F, Jain S, Finelli L, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N. Engl. J. Med. **2009**; 360:2605–15. Available at: http://www.nejm.org/doi/abs/10.1056/NEJMoa0903810. Accessed 7 March 2018.
29. Brooks-Pollock E, Tilston N, Edmunds WJ, Eames KTD. Using an online survey of healthcare-seeking behaviour to estimate the magnitude and severity of the 2009 H1N1v influenza epidemic in England. BMC Infect Dis. **2011**; 11:68. Available at: http://www.scopus.com/inward/record.url?eid=2-s2.0-79952706157&partnerID=tZOtx3y1.
30. Hayward AC, Fragaszy EB, Bermingham A, et al. Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study. Lancet Respir Med. **2014**; 2:445–54. doi:10.1016/S2213-2600(14)70034–7.
31. Viboud C, Miller M, Olson D, Osterholm M, Simonsen L. Preliminary estimates of mortality and years of life lost associated with the 2009 A/H1N1 pandemic in the US and comparison with past influenza seasons. PLoS Curr. **2010**; 2:RRN1153.
32. 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**; 197:270–8.

The INSIGHT Influenza FLU 002 and FLU 003 Study Groups are as follows:

Community representatives: David Munroe, Claire Rappoport, Siegfried Schwarze. *Coordinating centers:* Copenhagen: Bitten Aagaard, Dejan Adzic, Jesper Grarup, Patricia Herrero, Per Jansson, Marie Louise Jakobsen, Birgitte Jensen, Karoline B. Jensen, Heidi Juncher, Jesper Kjær, Jens Lundgren, Paco Lopez, Amanda Mocroft, Mary Pearson, Begoña Portas, Caroline Sabin, Klaus Tillmann. London: Abdel Babiker, Nafisah Braimah, Yolanda Collaco-Moraes, Fleur Hudson, Ischa Kummeling, Filippo Pacciarini, Nick Paton. Statistical and Data Management Center–Minneapolis–Alain DuChene, Michelle George, Merrie Harrison, Kathy Herman, Eric Krum, Gregg Larson, Ray Nelson, Kien Quan, Siu-Fun Quan, Cavan Reilly, Terri Schultz, Greg Thompson, Nicole Wyman. Sydney: Anchalee Avihingsanon, Lara Cassar, Kanlaya Charoentonpuban, Sean Emery, Kobkeaw Laohajinda, Thidarat Jupimai, Isabel Lanusse, Alejandra Moricz, Ines Otegui, Kiat Ruxrungtham, Rose Robson. Washington: Elizabeth Finley, Fred Gordin, Adriana Sanchez, Michael Vjecha. Specimen repositories and laboratories: John Baxter, Shawn Brown (SAIC Frederick, Inc.), Elodie Ghedin (JCVI), Rebecca Halpin (JCVI), Marie Hoover (ABML). National Institute of Allergy and Infectious Disease: Beth Baseler (SAIC Frederick Inc.), Julia A. Metcalf. *Other experts:* Centers for Disease Control: Nancy Cox, Larisa Gubareva, Kathy Hancock, Jackie Katz, Alexander Klimov, Michael Shaw. Department of Health and Human Services: Lewis Rubinson. *FLU 002 clinical site investigators:* Argentina: Laura Barcan, Jorge Alberto Corral, Daniel Omar David, Hector Enrique Laplume, Maria Beatriz Lasala, Gustavo Daniel Lopardo, Marcelo H. Losso, Sergio Lupo, Eduardo Warley. Australia: Mark Bloch, Dominic E. Dwyer, Richard Moore, Sarah L. Pett, Norman Roth, Tuck Meng Soo, Emanuel Vlahakis. Austria: Heinz Burgmann. Belgium: Nathan Clumeck, Stephan De Wit, Eric Florence, KabambaKabeya, JozefWeckx. Chile: Carlos Perez, Marcelo J. Wolff. Denmark: Jan Gerstoft, Jens D. Lundgren, LarsØstergaard. Estonia: Kai Zilmer. Germany: Johannes R. Bogner, Norbert H. Brockmeyer, Gerd Faetkenheuer, Hartwig Klinker, Andreas Plettenberg, Juergen Rockstroh, Christoph Stephan. Greece: Anastasia Antoniadou, Georgios Koratzanis, Nikolaos Koulouris, Vlassis Polixronopoulos, Helen Sambatakou,

Nikolaos Vasilopoulos. Lithuania: Saulius Caplinskas. Peru: Alberto La Rosa, Fernando Mendo, Raul Salazar, Jorge Valencia. Poland: Elzbieta Bakowska, Andrzej Horban, Brygida Knysz. Portugal: Francisco Antunes, Manuela Doroana. South Africa: Nesri Padayatchi. Spain: David Dalmau, Eduardo Fernandez-Cruz, Jose Maria Gatell, Jesus Sanz Sanz, Vincent Soriano. Thailand: Ploenchan Chetchotisakd, Kiat Ruxrungtham, Gompol Suwanpimolkul. United Kingdom: Clifford L.S. Leen. United States: Calvin Cohen, David L. Cohn, Jack A. DeHovitz, Wafaa El-Sadr, Marshall Glesby, Fred M. Gordin, Sally Hodder, Norman Markowitz, Richard M. Novak, Robert Schooley, Gary L. Simon, Ellen Marie Tedaldi, Zelalem Temesgen, Joseph Timpone, Daniel Z. Uslan, Barbara Heeter Wade. *FLU 003 clinical site investigators:* Argentina: Laura Barcan, Jorge Alberto Corral, Daniel Omar David, Hector Enrique Laplume, Maria Beatriz Lasala, Gustavo Daniel Lopardo, Marcelo H. Losso, Eduardo Warley. Australia: Dominic E. Dwyer, Julian Elliott, Pam Konecny, John McBride, Sarah L. Pett. Austria: Heinz Burgmann. Belgium: Nathan Clumeck, Stephan De Wit, Philippe Jorens, KabambaKabeya. Chile: Marcelo J. Wolff. China: Tak Chiu Wu. Denmark: Jan Gerstoft, Lars Mathiesen, Henrik Nielsen, Lars Østergaard, Svend Stenvang Pedersen. Germany: Frank Bergmann, Johannes R. Bogner, Norbert H. Brockmeyer, Gerd Faetkenheuer, Hartwig Klinker, Juergen Rockstroh, Christoph Stephan. Greece: Anastasia Antoniadou, Georgios Koratzanis, Nikolaos Koulouris, Vlassis Polixronopoulos, Helen Sambatakou, Nikolaos Vasilopoulos. Norway: Anne Maagaard. Peru: Fernando Mendo, Raul Salazar

Poland: Elzbieta Bakowska, Andrzej Horban. South Africa: Nesri Padayatchi. Spain: David Dalmau, Vicente Estrada, Eduardo Fernandez-Cruz, Hernando Knobel Freud, Rosa M Blazquez Garrido, Jose Maria Gatell, Jose Sanz Moreno, Jose Ramon Pano-Pardo, Jesus Sanz Sanz, Vincent Soriano. Thailand: Ploenchan Chetchotisakd, Kiat Ruxrungtham, Gompol Suwanpimolkul. United Kingdom: Brian J. Angus, David R. Chadwick, David Dockrell, Clifford L.S. Leen, Melanie Newport, Ed Wilkins. United States: Harry Anderson III, Jason V. Baker, David L. Cohn, Jack A. DeHovitz, Wafaa El-Sadr, Matthew S. Freiberg, Fred M. Gordin, Roy Gulick, David Gurka, Sally Hodder, Norman Markowitz, Richard M. Novak, Armando Paez, NamrataPatil, Annette Reboli, Michael Sands, Robert Schooley, Gary L. Simon, Zelalem Temesgen, Joseph Timpone, Daniel Z. Uslan, Barbara Heeter Wade.