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

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- Summary: We demonstrate how to use baseline and prospective data from global clinical research networks to rapidly assess the severity of an emerging influenza pandemic.

ABSTRACT 250 words (max 250)

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 INSIGHT, a global clinical influenza research network, to make more accurate case fatality ratio (CFR) estimates early in a future pandemic. Such assessments are now an integral part of the WHO pandemic definition and an essential part of pandemic response.

Methods. We estimated the case fatality ratio 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 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}.

Conclusion. Data from a clinical research network yielded accurate pandemic severity estimates, including increased severity among younger people. Going forward, already-operating research networks with global presence would substantially aid rapid assessment of clinical severity, both in absolute terms and relative to recent influenza seasons.

INTRODUCTION

In 2009, uncertainty about the emerging virus' clinical severity hindered the early global response. Although the rapid spread of pH1N1 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]. But 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 catastrophic 1918 pandemic, and a June 2009 assessment put it in the 1957 pandemic range (Table 1)[3,4, 5].

An evaluation of the 2009 pandemic response ordered by the WHO Director General [6] found that a systematic way to assess both transmissibility and clinical severity—also known as its "seriousness" [7]—is needed in the early phase of a future pandemic to assess the level of threat accurately and mobilize resources appropriately. CFR is one important measure of clinical severity; others include the risk of admission to the 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 [8]. The US-CDC has proposed a scheme for comparing pandemic and seasonal influenza graphically, plotting attack rates against clinical severity [9].

In 2009, UK Public Health England spearheaded what has become a standard first-line approach to assessing the clinical severity of a pandemic, the "First Few Hundred" (FF100) [10]. 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 about symptoms, risk factors and risk of progression to severe illness or death [11–17]. These data can in turn be combined with other data on population attack rates to forecast national or global hospitalization and mortality estimates using a pyramid modeling strategy [18,19].

FF100 studies, however, typically 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 [20]. 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 studying 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 US National Institutes of Health. Since 2009, INSIGHT has undertaken two cohort studies—one outpatient (FLU002) and one inpatient (FLU003)—specifically to address gaps in clinical research on the emerging influenza pandemic, including factors linked to disease progression and severe outcomes [21]. INSIGHT annually enrolled hundreds of patients with suspected or confirmed influenza, with intake sites in 12 countries around the world. 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 papers on influenza have been published using INSIGHT data, including protocol descriptions and preliminary data [21], an exploration of biomarkers of influenza case severity [22], patient outcomes after pH1N1 infection [23] and phylogeography of the pH1N1 virus [24].

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/subtypes and non-influenza 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 sero-epidemiology data—final estimates that would only be available several years after the next pandemic emerges [1,2,12]. Finally, 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 NIAID-funded INSIGHT network initially focused solely on pH1N1, but later expanded to include all influenza types/subtypes and emerging respiratory pathogens such as MERS and SARS. Sites, located in five of six world regions (Figure 1), consecutively enroll adult patients $\geq$18 years of age with suspected influenza. FLU002 recruits patients presenting 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 requiring hospitalization. At enrollment, patient medical histories and demographic information are recorded, and blood and oropharyngeal swabs 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 two seasons, October 2009 through September 2011, and the post-pandemic influenza period as October 2012 through September 2015 (last three complete INSIGHT seasons, skipping the 2011-12 season as a transition). Patients who were lost to follow-up were treated as missing and removed from the analysis.

We identified nine relevant case series in the literature reporting data on adults >18 years. After excluding studies with less than 100 patients or which were of a specialty population (such as high-risk patients), we chose two outpatient studies, one set in the US [25] and one in the United Kingdom [10], and two inpatient studies [14,16], both set in the US, for comparison with FLU002 and FLU003 pH1N1 laboratory-confirmed patients during the pandemic period (Table 2).

We calculated the medically attended case fatality ratio (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.

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

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 adults aged ≥18 years with ILI sought care for their illness [26] and a UK serology study that found that 25% of influenza-infected adults aged 25-64 years were symptomatic [27]. Assuming that the non-medically attended and asymptomatic influenza cases would not progress to severe illness, we have:

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

where “infection” is defined as a person who responded immunologically.

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

Data analysis was done in SAS version 9.4 and Excel. The FLU 002 and FLU 003 protocols were approved by the institutional review boards (IRB) or institutional ethics committees (IEC) at the University of Minnesota and at each of the participating clinical sites; ClinicalTrials.gov identifiers NCT01056354 and NCT010561. All patients (or their proxies) gave signed informed consent prior to enrollment.

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RESULTS

Descriptive comparison of INSIGHT patient findings to other FF100 studies.

During the pandemic period (October 2009 through September 2011) a total of 559 ILI and 384 hospitalized patients tested influenza pH1N1 positive. Of these, 99.6% of pH1N1-infected FLU002 outpatients were 18-64 years, compared to only 88% of the FLU003 inpatients. During the post-pandemic period (October 2012 through September 2015) a total of 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 period, after the network expanded to sites in all five 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 [23] 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. 5.0% 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%), for all adults as well as for those aged 18-64 years. The CFR_{MA} for patients ≥65 years of age could not be established with confidence due to the small number

of older outpatients in the study. As a non-historic control we have the all-ages CFR_{MA} of influenza-test-negative patients was 0.1% during the pandemic period, albeit with wide confidence intervals. 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 adults 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 ≥65 years positive for any influenza virus in the post-pandemic period, versus 0.04%, for younger adults positive for any influenza virus. For the post-pandemic period (any sub-type), we also estimated the conditional probabilities and the CFR_{MA} by region (Table 4).

Converting CFR_{MA} to CFR_{AR}. 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 indicating that ~25% of all cases are asymptomatic [26], and from survey data indicating that ~25% of adult ILI cases sought medical attention [27], and found the CFR_{AR} to be 0.03% (0.01% to 0.04%)(see table 5), or 16-fold lower than the medically attended CFR.

DISCUSSION

When an influenza pandemic emerges, rapid and accurate estimates of clinical severity has recently been added by WHO as an element needed to characterize the threat level and to guide the global response. Our analysis of data from INSIGHT, a global network with both out- and inpatients that allowed "leveraged" computation of CFR based on multiplying conditional probabilities of disease progression, demonstrates how pre-established global research networks can immediately begin rigorous studies to estimate the case fatality ratio, a key parameter of clinical severity of an emerging pandemic.

The assessments of clinical severity in the 2009 pandemic became less dire as time passed [5]. The earliest estimate of CFR, an FF100-like case series of hospitalized patients in Mexico, was a disturbing 2% of all influenza-positive patients. But as studies of the first (summer) wave in the US, 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 towards sicker patients in the earliest FF100-type case series studies[5]. But another reason 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 indicating that the probability of symptomatic people seeking medical treatment was 25% [26] and that the probability of infected individuals being asymptomatic was also 25% [27], our CFR_{MA} value was equivalent to a CFR_{AR} of .025%. That is in reasonable agreement with the final global WHO CFR_{AR} estimate of 0.02% [1,2,28].

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. We found that all-ages pH1N1 CFR_{MA} was about 5-fold lower than in the pandemic period, and approaching values for both H3N2 and B, as well as for influenza-negative patients.

Age greatly influences both seasonal and pandemic clinical severity estimates. In all four influenza pandemics since 1900, mortality has been higher than normal in younger people and lower than normal in seniors, sometimes dramatically so [28]. In the post-pandemic period (2012-2015) we found that the CFR_{MA} of pH1N1 for adults 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 immunity. Moreover, in the post-pandemic period people aged ≥65 years with any influenza virus had a CFR_{MA} approximately 10-fold higher than people <65. These results corroborate a previous meta-analysis of FF100 studies, which concluded that age is an important confounder of CFR estimates for pH1N1 pandemic influenza [5]. 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.

Ironically, 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 was ~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. And if that is not enough, 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 [29].

The best way around those measurement problems 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 single 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 that were recruited under different circumstances at different sites, often in different countries. It is therefore possible the two cohorts differed in age composition, health status or other important respects that could bias the result. But 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 outpatient and inpatient pH1N1 patients 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 "negative control group" of influenza-negative patients did not have a significant drop in CFR_{MA} between the pandemic and post-pandemic period. We conclude that the measured decrease in pH1N1 clinical severity was real and not due to ascertainment or other bias.

Going from Research Mode to Emergency Footing

Our retrospective analysis of 2009 pandemic clinical severity indicates that it is possible to use a research network 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 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 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 helping to assess clinical severity, global research networks such as INSIGHT could play other key roles in pandemic response: comorbidity patterns, risk factors, hospital and ICU utilization, mortality risk of hospitalized patients. Moreover, protocols enrolling children could be used to understand the pathogen in this key age group. And 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.

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Conflict of Interest
Drs. Simonsen and Taylor report earning consulting fees from Sage Analytica, LLC, during the conduct of the study; Dr. Lynfield reports she co-editor on a book on Infectious Disease Surveillance published by Wiley Blackwell, with royalties are donated to the Minnesota Department of Health.

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Figure legends

Figure 1. A map of INSIGHT influenza protocol patient intake sites. Blue markers indicate FLU002 outpatient sites and red markers indicate FLU003 inpatient sites.

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 INSIGHT outpatient (FLU002) and inpatient (FLU003) data. Modeling was also done for 18-64 and 65+ age groups separately due to known differences in attack rates and pre-existing immunity.

Report	Date of publication	Setting	Estimated Case Fatality Ratio (CFR)	Severity
WHO report [4]	May '09	Early outbreaks Mexico	2%	1918-like
Fraser et al. Science [3]	June '09	First wave Mexico	0.4%	1957-like
Castro-Jimenez, et al. Eursurveillance [30]	July '09	First wave Colombia	3.8%	1918-like
Baker et al. Eurosurveillance [31]	July '09	New Zealand first complete season	0.1%	1968-like
Presanis et al. PLoS Medicine [18]	Sept. '09	1st wave in two US cities	0.04%	1968-like
van Kerkhove et al. Flu & Other Respi Viruses [32]	Jan. '13	Global estimate for first season, CONCISE Network	0.02%	seasonal

Table 1. Evolution of the estimated Case Fatality Ratio (CFR) over time; see also Wong et al. [3].

INPATIENT STUDIES (Ward and ICU combined)					OUTPATIENT STUDIES		
Study	***Country***	**USA**		**Global**	**USA**	**UK**	**Global**
	First Author	**Jain**	**Louie**	**INSIGHT 003**	**Dawood**	**McLean**	**INSIGHT 002**
	(N) adults (unless noted)	150	744	282	642 (L)	392 (M)	559
	Adult median age (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%	-
	GI symptoms	26%	34%	-	25%	28%	-
	Myalgia	51%	41%	-	-	80%	-
	Headache	45%	22%	-	-	84%	-
	Shortness of breath	73%	66%	-	-	44%	-
Comorbid-ities	At least one 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%
	HIV only	-	15%	4%	-	-	8%
	Cardiovascular disease	20%	19%	14%	0.4%	1.0%	0.4%
	COPD	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 (I)	Hospitalized	100%	100%	100%	9%	6%	5%
	Died	9%	15%	9%	0.5%	0%	0.2%
	ICU	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%	-	-	-

Table 2. Findings on clinical symptoms, demographics and underlying illness from INSIGHT H1N1 influenza inpatient (FLU003) and outpatient (FLU002) protocols for the pandemic period October 2009 through September 2011 and select studies that either presented or allowed extraction of similar findings for adults ≥18 years of age.

			N(outpatient)	N(inpatient)	P(H|ILI)	P(D|H)	CFR/% (95% CI)
Pandemic (2009-11)	**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)

Table 3. Estimated CFR among medically attended cases from INSIGHT data for the pandemic and post-pandemic periods, computed as the product of the risk of FLU002 ILI outpatients getting hospitalized and the FLU003 hospitalized patients having died at day 60
*CFR not calculated when fewer than 100 outpatients or inpatients contained in any stratum

Region	Positive for any influenza (N)		Probabilities		
	FLU002	FLU003	P(H|ILI)	P(D|H)	CFR_{MA} (95% CI)
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)
N. America	183	233	0.044	0.034	0.15%(0.01; 0.29)
S. America	1164	92	0.004	0.152	*
All regions	2651	827	0.014	0.052	0.07% (0.04; 0.11)

Table 4. Numbers of patients that test positive for influenza, probabilities of progression to hospitalization and death, and CFR_{MA}, by INSIGHT geographic region in the post-pandemic period.

*CFR not calculated when fewer than 100 outpatients or inpatients contained in any stratum

Source	Measure		Estimate	Lower bound	Upper bound
This study	Case Fatality Ratio based on persons with medically attended ILI	CFR_{MA}	0.4%	0.2%	0.6%
Brooks-Pollock et al BMC Inf Dis 2011. UK survey of health care seeking behavior; adults	Probability of seeking medical care given ILI	$P(ILI_{MA} \mid ILI)$	0.25	0.25	0.25
Hayward et al, Lancet Resp Med 2015. Serology study	Probability of having ILI symptoms given H1N1pdm infection (based on antibody titers)	$P(ILI \mid Inf)$	0.25	0.25	0.25
Multiplying the three figures	**Case Fatality Ratio based on persons with influenza infection**	**CFR_{AR}**	**0.03%**	**0.01%**	**0.04%**

Table 5. Conversion of CFR_{MA} to CFR_{AR} estimates using two UK studies, one a survey of health seeking behavior among adult ILI patients, and the other a serology study.