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# Age Differences in Comorbidities, Presenting Symptoms, and Outcomes of Influenza Illness Requiring Hospitalization: A Worldwide Perspective From the Global Influenza Hospital Surveillance Network

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**Background.** The Global Influenza Hospital Surveillance Network (GIHSN) was established in 2012 to conduct coordinated worldwide influenza surveillance. In this study, we describe underlying comorbidities, symptoms, and outcomes in patients hospitalized with influenza.

**Methods.** Between November 2018 and October 2019, GIHSN included 19 sites in 18 countries using a standardized surveillance protocol. Influenza infection was laboratory-confirmed with reverse-transcription polymerase chain reaction. A multivariate logistic regression model was utilized to analyze the extent to which various risk factors predict severe outcomes.

**Results.** Of 16 022 enrolled patients, 21.9% had laboratory-confirmed influenza; 49.2% of influenza cases were A/H1N1pdm09. Fever and cough were the most common symptoms, although they decreased with age ( $P < .001$ ). Shortness of breath was uncommon among those <50 years but increased with age ( $P < .001$ ). Middle and older age and history of underlying diabetes or chronic obstructive pulmonary disease were associated with increased odds of death and intensive care unit (ICU) admission, and male sex and influenza vaccination were associated with lower odds. The ICU admissions and mortality occurred across the age spectrum.

**Conclusions.** Both virus and host factors contributed to influenza burden. We identified age differences in comorbidities, presenting symptoms, and adverse clinical outcomes among those hospitalized with influenza and benefit from influenza vaccination in protecting against adverse clinical outcomes. The GIHSN provides an ongoing platform for global understanding of hospitalized influenza illness.

**Keywords.** age; epidemiology; hospitalization; influenza; mortality.

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Influenza is an important global cause of morbidity and mortality. Each year, across the globe, there are an estimated 1 billion cases of influenza, 3–5 million of which are severe cases and 290 000–650 000 lead to influenza-related deaths [1, 2]. Nevertheless, the annual impact of influenza may vary depending on the virus, host, and contextual factors, including the virulence of circulating strains, degree of match achieved between vaccine and circulating strains, vaccine coverage, and pre-existing population immunity [3]. Prevention and control of seasonal influenza is a global priority because influenza represents a substantial burden on people's health worldwide.

Although globalization has increased the viral spread between countries and regions, it also offers opportunities for collaborative efforts to combat influenza's far-reaching health and social effects. In addition to the vital work of individual jurisdictions in understanding their influenza epidemiology, it is essential to consider a global perspective. Seasonality differs geographically, with the Northern and Southern Hemispheres generally experiencing a winter influenza season, whereas intertropical zones may experience prolonged or even year-round transmission [4]. It is notable that some countries such as China, Brazil, and India have subregional variations in influenza circulation, mixing areas with northern and southern hemisphere circulation patterns [5].

The Global Influenza Hospital Surveillance Network (GIHSN) was established in 2012 to provide a coordinated influenza surveillance platform. Since its inception, the GIHSN has expanded to provide an evolving picture of the experience and burden of severe influenza leading to acute care hospitalization worldwide and has aimed to become a platform to assess the effectiveness of influenza vaccines. In this study, we present results from the 2018/2019 influenza season, focusing on age differences in underlying comorbidities, presenting symptoms, and adverse clinical outcomes.

## METHODS

The GIHSN's coordinated active influenza surveillance has grown steadily since its establishment [3, 6–9]. During the 2018/2019 influenza season, 19 international sites representing 18 countries participated in GIHSN. These included 11 Northern Hemisphere sites in 10 countries (Canada, China, France, Lebanon, Mexico, Romania, Serbia, Spain, Romania, Russia-Moscow, and Russia-St. Petersburg), 4 intertropical sites (Columbia, India, Ivory Coast, and Kenya) and 4 Southern Hemisphere sites (Argentina, Brazil, Peru, and South Africa).

### Enrollment

Enrollment was based on an active surveillance protocol with case definitions and data collection standardized across all participating sites. Patients were recruited according to 2 protocols: one for those <5 years of age and one for ages  $\geq 5$  years.

Inclusion criteria for patients aged  $\geq 5$  years were based on the modified European Centre for Diseases Control (ECDC) definition of influenza-like illness (ILI), requiring (1) acute illness (onset within 7 days from hospital admission), (2) at least 1 systemic symptom of fever or feverishness, headache, myalgia, or malaise, and (3) at least 1 of 3 respiratory symptoms: cough, sore throat, or shortness of breath [10]. Patients aged <5 years were included if an illness met the above definition, although specific symptoms were not recorded. Due to differences in local public health surveillance priorities, patient volumes, and capacity (funding and human resource) for enrollment, the protocol was necessarily subject to some local adaptations at each site. For example, sites could enroll all patients or systematically target enrollment to patients presenting on certain days of the week. Local priorities included a focus on the assessment of vaccine effectiveness; enrollment focused on including all positive patients and a matched subset of negative controls. As such, the percentage positivity in each site does not necessarily reflect circulating case positivity in the cities and regions represented. However, coordinating the case definition and clinical data collection protocol across sites allows for robust comparison of clinical characteristics or influenza cases across participating sites.

### Laboratory Testing

Laboratory-confirmed influenza (LCI) virus infection was defined by the GIHSN protocol [3]. For influenza virus detection, posterior nasopharyngeal swab samples were collected from patients (and, in some cases, an additional nasal sample for those aged <14 years and a pharyngeal swab for those aged  $\geq 14$  years). Influenza virus infection was confirmed using reverse-transcription polymerase chain reaction (RT-PCR) testing and was further subtyped at local laboratories or sent to regional reference laboratories according to local protocols. A subset of sites performed multiplex testing for a panel of other respiratory viruses.

### Measures

Demographic and clinical data were retrieved from the GIHSN database, which contains data for laboratory-confirmed cases of influenza from all sites throughout the season. Demographic data collected for this study included sex and age; the latter was further divided into age categories (<5 years, 5–17 years, 18–49 years, 50–64 years, 65–79 years, and  $\geq 80$  years) to gain a better understanding of the age structure of the population. Each case's minimum data consisted of symptoms, symptom onset date, laboratory test result date, number and type of comorbidities, smoking status, influenza vaccination status, and disease outcome. Comorbidities were determined from a predefined list, including human immunodeficiency virus (HIV), cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), asthma, neuromuscular

**Table 1. Characteristics of Patients Enrolled in the GIHSN Study by Site in the 2018/2019 Influenza Season**

Recruiting Site	Laboratory Confirmed Influenza N (%Within Site)	Influenza Negative N (%Within Site)	Age (Years) Median [IQR]	Influenza Vaccine Uptake N (%Within Site) <sup>a</sup>
Overall	3512 (21.9)	12 510 (78.1)	9.0 [1.1–61.0]	2094 (13.1)
Northern Hemisphere				
France—Lyon	43 (40.2)	64 (59.8)	71.0 [57.5–84.0]	48 (44.9)
Spain—Valencia	297 (9.8)	2748 (90.2)	73.0 [49.0–84.0]	1220 (40.1)
Romania	416 (44.5)	518 (55.5)	13.0 [2.5–53.0]	100 (16.8)
Serbia	336 (44.7)	415 (55.3)	60.0 [39.0–69.0]	21 (2.8)
Russia-Moscow	174 (21.2)	648 (78.8)	24.0 [2.3–52.0]	29 (3.5)
Russia-St. Petersburg	1096 (36.0)	1945 (64.0)	4.3 [1.6–22.0]	127 (4.1)
Canada	252 (53.8)	216 (46.2)	67.0 [52.0–79.0]	203 (43.4)
Mexico	163 (27.4)	432 (72.6)	4.5 [1.2–49.0]	100 (16.8)
China-Shanghai	164 (14.2)	992 (85.8)	0.8 [0.2–2.7]	6 (0.5)
Lebanon	124 (24.7)	379 (75.3)	37.0 [6.0–66.0]	46 (9.1)
Intertropical Region				
India	230 (23.5)	748 (76.5)	58.0 [38.0–70.0]	15 (1.5)
Ivory Coast	32 (7.8)	377 (92.2)	2.0 [0.7–28.0]	17 (4.1)
Kenya	22 (4.3)	484 (95.7)	1.2 [0.5–3.0]	0 (0)
Colombia	15 (12.2)	108 (87.8)	1.3 [0.4–28.0]	27 (22)
Southern Hemisphere				
South Africa	90 (5.6)	1504 (94.4)	0.7 [0.1–2.9]	0 (0)
Brazil	23 (6.2)	346 (93.8)	1.5 [0.4–5.0]	149 (40.4)
Argentina	18 (4.3)	404 (95.7)	1.0 [0.4–2.0]	11 (2.6)
Peru	17 (8.5)	182 (91.5)	3.2 [0.7–15.5]	27 (13.6)

Abbreviations: GIHSN, Global Influenza Hospital Surveillance Network; IQR, interquartile range.

NOTE: Influenza vaccine uptake by site is illustrated graphically in [Supplementary Figure 1](#).

<sup>a</sup>To calculate the influenza vaccine uptake, the entire enrolled hospitalized sample within the site was used as the denominator.

disease, immunodeficiency/transplant, liver/kidney disease, neoplasm, diabetes, obesity, rheumatologic/autoimmune disease, and active tuberculosis (TB). Mortality was determined at both 30 days and after the entire period of clinical follow-up. Time to death was calculated starting with the time of hospital admission.

### Statistical Analysis

We used descriptive statistics focusing on comparisons across age groups. Kruskal-Wallis's test compared continuous variables between groups and Pearson's  $\chi^2$  test categorical variables. The Mann-Kendall test was used to evaluate trends in the association between age groups and categorical proportions, whereas the Cochran-Mantel-Haenszel test was conducted to calculate mortality proportions per age group within each stratum of vaccination status.

We used Kaplan-Meier analysis to estimate the probability of survival and log-rank testing for between-group comparison. We also used a multivariate logistic regression to model the composite outcome of admission to intensive care unit (ICU) or death as a function of age groups, adjusted for comorbidities and vaccination status for the current influenza season. The regression results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). A sensitivity analysis was conducted using mixed effects in the regression models to account for variability between sites, and this is presented in the [Supplementary Materials](#).

Statistical significance was set at a 2-sided  $P < .05$ . We used R version 4.2.3 (The R Foundation for Statistical Computing, Vienna, Austria) in R-Studio 2023.03.0 + 386 "Cherry Blossom" Release (RStudio Inc., Boston, MA, USA) to conduct all analyses.

### Ethics and Patient Consent

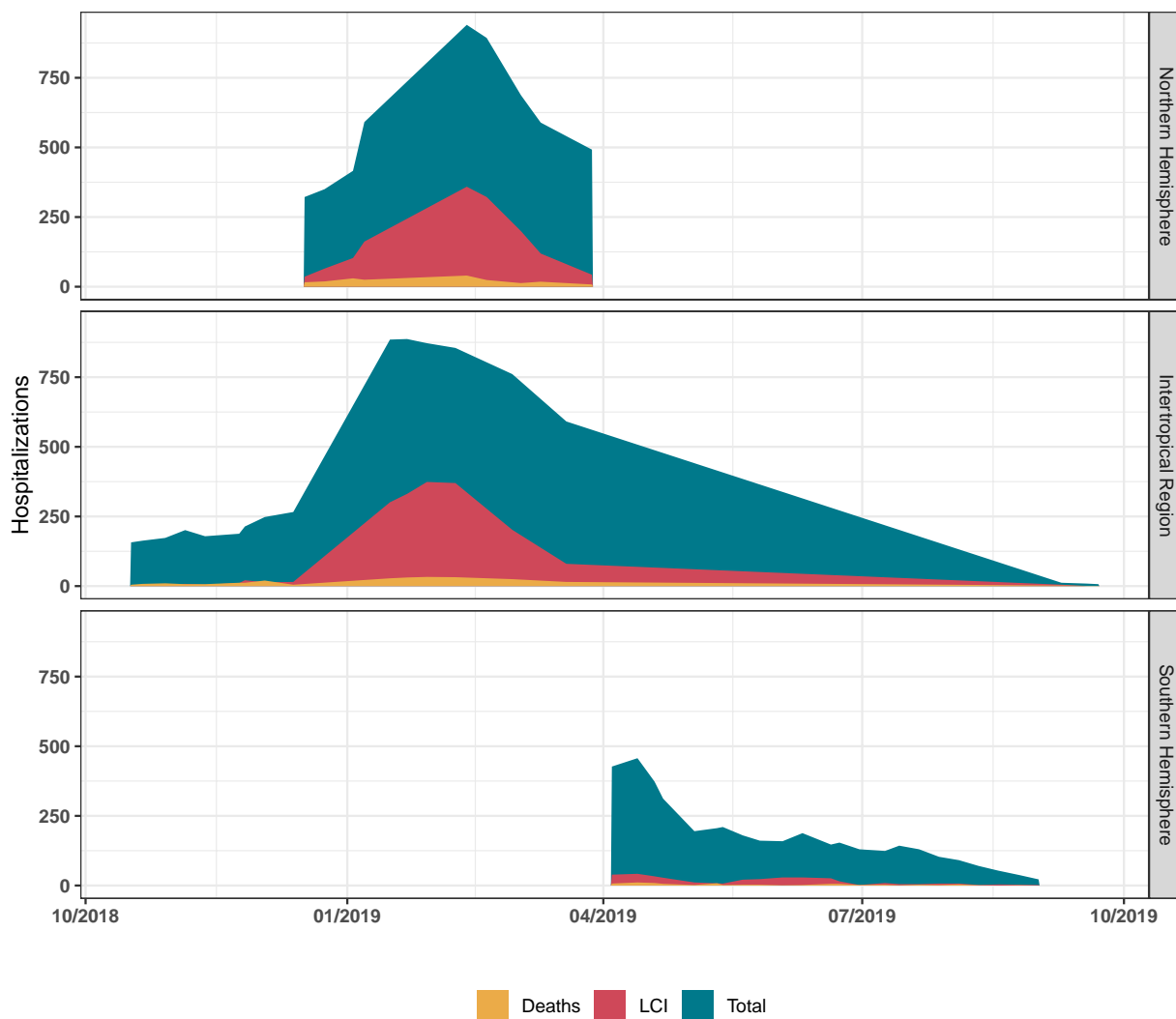
The GIHSN protocol was reviewed and approved by the respective Research Ethics Boards of all participating sites, and patient consent was acquired in adherence to local regulations after the approval.

## RESULTS

We enrolled 16 022 patients, 3512 (21.9%) of whom had LCI. [Table 1](#) presents the enrollment by recruitment site, including the breakdown of patients by influenza test outcome and age distribution. [Figure 1](#) shows the overall number of hospital admissions, LCI, and deaths according to the epidemiological week from October 2018 to October 2019. Influenza vaccine uptake by site is illustrated graphically in [Supplementary Figure 1](#).

### Characteristics of Patients With Laboratory-Confirmed Influenza Virus Infection

[Table 2](#) shows the characteristics of LCI cases stratified by age. Among patients with LCI, presenting symptoms were not collected for children <5 years, whereas the symptoms varied by age for those 5 years and older. Fever and cough were the



**Figure 1.** Hospital admissions, laboratory-confirmed influenza virus infection, and deaths grouped by epidemiological weeks from October 2018 to October 2019.

most common presenting symptoms, although the prevalence decreased with age; for example, 98.9% of those aged 5–17 years reported fever and 95.0% reported cough, falling to 80.7% with fever and 85.5% with cough in those aged  $\geq 80$  years ( $P$  for temporal trend = .027). A majority of adults aged  $\geq 50$  years presented with shortness of breath: 58.1% aged 50–64 years, 61.7% aged 65–79 years, and 75.3% aged  $\geq 80$  years ( $P$  for temporal trend = .027). Shortness of breath was uncommon among those aged  $< 50$  years but increased with age.

Patient comorbidities varied by site and by age group (Table 2). Among adults, CVDs (22%), diabetes (10.7%), COPD (9.9%), and obesity (6.1%) were the most common comorbidities. Most children  $< 5$  years had no underlying conditions, whereas more than half of older adults had cardiovascular illnesses. Some sites in lower-income settings had a relatively high burden of underlying infectious diseases

(eg, HIV infection and active TB), whereas others in higher-income settings had more chronic noninfectious diseases.

#### 2018/2019 Influenza Season Circulating Strains

Influenza A/H1N1pdm09 was the most frequently detected strain, at 49.2% of all influenza-positive tests (presumably more, including the un-subtyped Influenza A strains). It is notable that all 4 strains (A/H1N1pdm09, A/H3N2, B/Yamagata-like, and B/Victoria-like) cocirculated from a global perspective. Influenza A strain distribution varied by age (Table 3), with more A/H1N1pdm09 in younger age groups ( $P$  for trend = .024) and more A/H3N2 in older age groups. Influenza B was detected predominantly in the youngest (both B lineages with Victoria slightly predominating compared with Yamagata) and oldest (B Yamagata only) age groups. It is notable that enrollment profiles should be kept in mind in interpreting these trends,

**Table 2. Characteristics of Laboratory-Confirmed Influenza Cases, Stratified by Age Group**

Feature, N (%)	<5 Years	5–17 Years	18–49 Years	50–64 Years	65–79 Years	80+ Years	<i>P</i> for Temporal Trend
N	1149 (32.7)	359 (10.2)	769 (21.9)	456 (13.0)	504 (14.4)	275 (7.8)	...
Male sex	516 (44.9)	153 (42.6)	477 (62.0)	233 (51.1)	236 (46.8)	156 (56.7)	.452
<b>Smoking Habit</b>							
Current smoker (parent smoking status for children)	348 (30.3)	101 (28.1)	186 (24.2)	149 (32.7)	105 (20.8)	20 (7.3)	.132
Never smoker	635 (55.3)	212 (59.1)	499 (64.9)	180 (39.5)	201 (39.9)	160 (58.2)	1.000
Past smoker	121 (10.5)	40 (11.1)	84 (10.9)	127 (27.9)	198 (39.3)	95 (34.5)	1.000
Not available	45 (3.9)	6 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	...
Influenza Vaccination in the Current Season	39 (3.4)	18 (5.0)	33 (4.3)	37 (8.1)	99 (19.6)	97 (35.3)	.024
Not available	31 (2.7)	5 (1.4)	23 (3.0)	31 (6.8)	37 (7.3)	26 (9.5)	...
<b>Presenting Symptoms</b>							
Fever	0 (0.0)	355 (98.9)	743 (96.6)	431 (94.5)	455 (90.3)	222 (80.7)	.027
Not available	1149 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	...
Cough	0 (0.0)	341 (95.0)	695 (90.4)	425 (93.2)	441 (87.5)	235 (85.5)	0.086
Not available	1149 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	...
Shortness of breath	0 (0.0)	75 (20.9)	267 (34.7)	265 (58.1)	311 (61.7)	207 (75.3)	0.027
Not available	1149 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	...
Malaise	0 (0.0)	282 (78.6)	574 (74.6)	327 (71.7)	323 (64.1)	186 (67.6)	0.086
Not available	1149 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	...
Headache	0 (0.0)	158 (44.0)	470 (61.1)	222 (48.7)	213 (42.3)	75 (27.3)	.220
Not available	1149 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	...
Myalgias	0 (0.0)	120 (33.4)	384 (49.9)	236 (51.8)	230 (45.6)	111 (40.4)	1.000
Not available	1149 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	...
Sore throat	0 (0.0)	175 (48.7)	372 (48.4)	184 (40.4)	167 (33.1)	65 (23.6)	.027
Not available	1149 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	...
<b>Chronic Comorbidities</b>							
Any chronic comorbidities	124 (10.8)	58 (16.2)	283 (36.8)	352 (77.2)	460 (91.3)	261 (94.9)	.008
Not available	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)	...
Cardiovascular disease/high blood pressure	17 (1.5)	6 (1.7)	55 (7.2)	185 (40.6)	318 (63.1)	190 (69.1)	.024
Not Available	183 (15.9)	15 (4.2)	4 (0.5)	6 (1.3)	9 (1.8)	4 (1.5)	...
Chronic obstructive pulmonary disease	13 (1.1)	5 (1.4)	21 (2.7)	81 (17.8)	149 (29.6)	78 (28.4)	0.024
Not available	35 (3.0)	4 (1.1)	4 (0.5)	6 (1.3)	9 (1.8)	4 (1.5)	...
Asthma	9 (0.8)	17 (4.7)	42 (5.5)	28 (6.1)	35 (6.9)	26 (9.5)	.008
Not available	183 (15.9)	15 (4.2)	4 (0.5)	6 (1.3)	9 (1.8)	4 (1.5)	...
Diabetes mellitus	1 (0.1)	0 (0.0)	44 (5.7)	103 (22.6)	153 (30.4)	74 (26.9)	.060
Not available	35 (3.0)	4 (1.1)	4 (0.5)	6 (1.3)	9 (1.8)	4 (1.5)	...
Immunodeficiency (except HIV)/organ transplant	7 (0.6)	2 (0.6)	27 (3.5)	17 (3.7)	19 (3.8)	6 (2.2)	.259
Not available	35 (3.0)	4 (1.1)	4 (0.5)	6 (1.3)	9 (1.8)	4 (1.5)	...
Renal impairment	1 (0.1)	0 (0.0)	19 (2.5)	37 (8.1)	53 (10.5)	44 (16.0)	.024
Not available	35 (3.0)	4 (1.1)	4 (0.5)	6 (1.3)	9 (1.8)	4 (1.5)	...
Rheumatologic disease/autoimmune disease	0 (0.0)	1 (0.3)	18 (2.3)	18 (3.9)	27 (5.4)	24 (8.7)	.008
Not available	35 (3.0)	4 (1.1)	4 (0.5)	6 (1.3)	9 (1.8)	4 (1.5)	...
Neurological or neuromuscular disease	9 (0.8)	8 (2.2)	14 (1.8)	20 (4.4)	37 (7.3)	39 (14.2)	.024
Not available	35 (3.0)	4 (1.1)	4 (0.5)	6 (1.3)	9 (1.8)	4 (1.5)	...
Cirrhosis/liver disease	2 (0.2)	2 (0.6)	14 (1.8)	20 (4.4)	19 (3.8)	6 (2.2)	.132
Not available	35 (3.0)	4 (1.1)	4 (0.5)	6 (1.3)	9 (1.8)	4 (1.5)	...
Neoplasm	1 (0.1)	8 (2.2)	24 (3.1)	42 (9.2)	66 (13.1)	29 (10.5)	.024
Not available	35 (3.0)	4 (1.1)	4 (0.5)	6 (1.3)	9 (1.8)	4 (1.5)	...
Obesity	0 (0.0)	0 (0.0)	52 (6.8)	48 (10.5)	66 (13.1)	49 (17.8)	.012
Not available	35 (3.0)	4 (1.1)	33 (4.3)	29 (6.4)	30 (6.0)	25 (9.1)	...
Active tuberculosis	0 (0.0)	0 (0.0)	2 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)	1.000
Not available	36 (3.1)	6 (1.7)	18 (2.3)	44 (9.6)	104 (20.6)	101 (36.7)	...
HIV infection	19 (1.7)	0 (0.0)	13 (1.7)	3 (0.7)	2 (0.4)	0 (0.0)	.338
Not available	36 (3.1)	6 (1.7)	18 (2.3)	44 (9.6)	104 (20.6)	101 (36.7)	...
Antivirals	339 (29.5)	92 (25.6)	210 (27.3)	127 (27.9)	157 (31.2)	94 (34.2)	.132

Abbreviations: HIV, human immunodeficiency virus.

**Table 3. Influenza (Strain and Subtype) and Multiplex Results by age Group**

Virus Strain and Subtypes	<5 Years	5–17 Years	18–49 Years	50–64 Years	65–79 Years	80+ Years	<i>P</i> for Temporal Trend
N (%)	1149 (32.7)	359 (10.2)	769 (21.9)	456 (13.0)	504 (14.4)	275 (7.8)	...
Influenza A/H1N1pdm09	663 (57.7)	198 (55.2)	337 (43.8)	242 (53.1)	216 (42.9)	73 (26.5)	.024
Influenza A/H3N2	407 (35.4)	121 (33.7)	327 (42.5)	138 (30.3)	189 (37.5)	153 (55.6)	.452
Influenza A untyped	85 (7.4)	17 (4.7)	78 (10.1)	73 (16.0)	86 (17.1)	38 (13.8)	.132
Influenza B Yamagata	14 (1.2)	8 (2.2)	17 (2.2)	11 (2.4)	11 (2.2)	13 (4.7)	.259
Influenza B Victoria	21 (1.8)	6 (1.7)	11 (1.4)	0 (0.0)	4 (0.8)	0 (0.0)	.035
Influenza B untyped	28 (2.4)	12 (3.3)	6 (0.8)	0 (0.0)	4 (0.8)	0 (0.0)	.180
Multiplex virus-virus codetections <sup>a</sup>							
Human seasonal coronavirus type not specified	8 (0.7)	2 (0.6)	3 (0.4)	1 (0.2)	4 (0.8)	0 (0.0)	.259
Not available	119 (10.4)	7 (1.9)	67 (8.7)	34 (7.5)	28 (5.6)	11 (4.0)	...
Metapneumovirus	13 (1.1)	1 (0.3)	3 (0.4)	3 (0.7)	0 (0.0)	0 (0.0)	.180
Not available	110 (9.6)	14 (3.9)	62 (8.1)	28 (6.1)	22 (4.4)	11 (4.0)	...
RSV	45 (3.9)	2 (0.6)	2 (0.3)	3 (0.7)	5 (1.0)	3 (1.1)	.707
Not available	94 (8.2)	12 (3.3)	61 (7.9)	28 (6.1)	22 (4.4)	11 (4.0)	...
Adenovirus	6 (0.5)	2 (0.6)	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	.085
Not available	174 (15.1)	12 (3.3)	67 (8.7)	34 (7.5)	28 (5.6)	11 (4.0)	...
Bocavirus	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	.241
Not available	174 (15.1)	12 (3.3)	67 (8.7)	34 (7.5)	28 (5.6)	11 (4.0)	...
Parainfluenza type not specified	5 (0.4)	2 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	.314
Not available	175 (15.2)	12 (3.3)	67 (8.7)	34 (7.5)	28 (5.6)	11 (4.0)	...
Rhinovirus	6 (0.5)	5 (1.4)	4 (0.5)	4 (0.9)	5 (1.0)	1 (0.4)	.707
Not available	190 (16.5)	14 (3.9)	67 (8.7)	34 (7.5)	28 (5.6)	11 (4.0)	...

Abbreviations: RSV, respiratory syncytial virus.

<sup>a</sup>Not all recruiting sites have run multiplex tests. For standardization purposes, the totality of laboratory-confirmed influenza cases was considered the denominator to estimate the proportions per age group.

**Table 4. Outcomes of Laboratory-Confirmed Influenza Cases by Age Group**

Outcomes Within Each Category	Overall	<5 Years	5–17 Years	18–49 Years	50–64 Years	65–79 Years	80+ Years	<i>P</i>
N	3512 (100%)	1149 (32.7)	359 (10.2)	769 (21.9)	456 (13.0)	504 (14.4)	275 (7.8)	-
Length of stay (days), median [IQR]	6 [4–8]	5 [3–7]	6 [4–7]	5 [3–8]	7 [4–11]	7 [4–11]	7 [4–11]	<.001
ICU admission, n (%)	267 (7.6)	48 (4.2)	18 (5.0)	52 (6.8)	63 (13.8)	65 (12.9)	21 (7.6)	<.001
Mechanical ventilation, n (%)	151 (4.3)	8 (0.7)	2 (0.6)	29 (3.8)	39 (8.6)	55 (10.9)	18 (6.5)	<.001
30-day mortality, n (%)	125 (3.5)	4 (0.3)	0 (0.0)	29 (3.8)	37 (8.1)	38 (7.5)	17 (6.1)	<.001
Mortality, n (%)	128 (3.6)	4 (0.3)	0 (0.0)	30 (3.9)	37 (8.1)	39 (7.7)	18 (6.5)	<.001

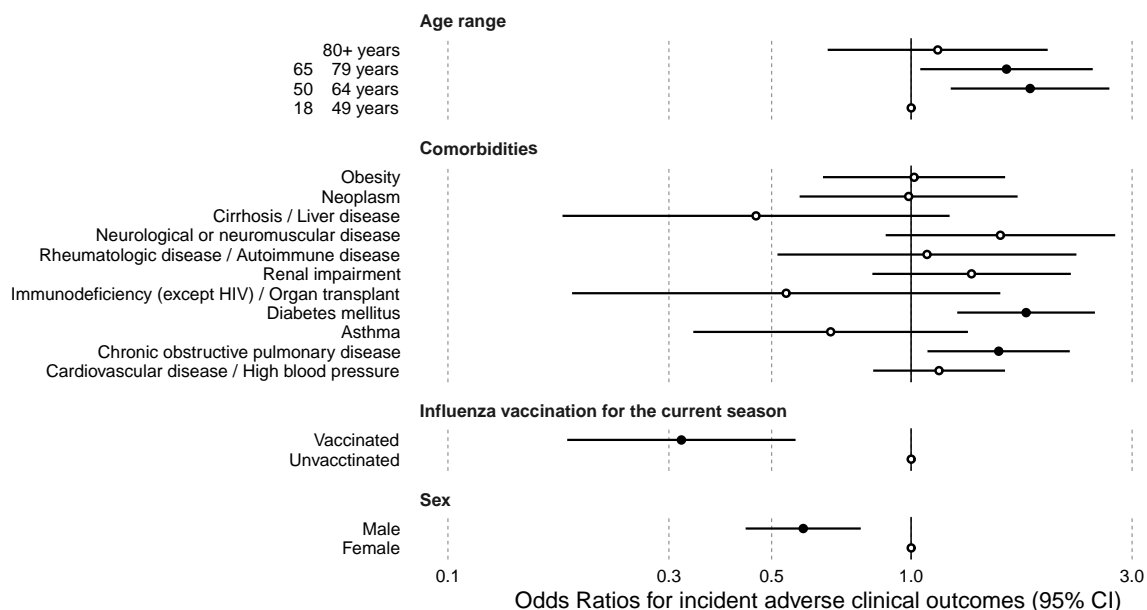
Abbreviations: ICU, intensive care unit; IQR, interquartile range.

NOTES: Differences in the length of stay (days) distribution across age groups were tested using the Kruskal-Wallis rank-sum test. We used Pearson's  $\chi^2$  test for the remaining categorical variables. Mortality was reported at both 30 days and for the entire period of clinical follow up, which ranged from 1 to 274 days.

because some countries enrolled only children and others enrolled only adults, such that age differences in influenza strain/type reflect both differential susceptibility of some age groups to specific strains and also differential geographical circulation patterns. Among patients enrolled at sites where RT-PCR testing was done to detect additional viruses, respiratory syncytial virus was the most tested and detected noninfluenza virus, followed by rhinovirus, metapneumovirus, and seasonal coronavirus. These patterns of viral infection underlying illness differed by age group, with the younger patients being generally more likely to have noninfluenza viruses (Table 3). However, it is worth noting that age distribution and viral types were likely influenced by the characteristics of recruitment sites and their laboratory testing facilities.

#### Clinical Adverse Outcomes

Clinical adverse outcomes were generally worst for the youngest children (<5 years) and in adults at older ages. Hospital lengths of hospital stay tended to increase with age. Rates of mechanical ventilation and ICU admission were relatively high in children <5, and for adults these were associated with increasing age in all but the oldest age group: ICU admission peaked in adults aged 50–64 and mechanical ventilation was highest in those age 65–79, and both decreased in adults aged 80+. Mortality was 3.6% for children <5 and was highest in adults aged 50–64 (8.1%), with a slight decrease for the oldest age groups to 7.7% for those 65–79% and 6.5% for those 80+ (Table 4). The global mortality rate and 30-day mortality rate were similar, with only a negligible difference.



**Figure 2.** Forest plot illustrating the odds ratios (circles) and associated 95% confidence intervals ([CI] horizontal bars) from the logistic model for the composite severe outcome of death or intensive care unit admission of laboratory-confirmed influenza cases in the 2018/2019 season. Hollow circles indicate where the confidence interval crosses the null, representing the point estimates for which the covariables have no significant effect. HIV, human immunodeficiency virus.

Specifically, 3 deaths occurred after 30 days of the initial assessment, and 4 deaths occurred for those under 17. To account for the follow-up period and its effect on the denominator of those at risk of the outcome, we used a time-to-event analysis strategy that censored the deaths after the 30-day mark. The overall survival rate of patients assessed within 30 days was 71.5%, with a 95% CI of 64.5%–79.2%. We found that the median time-to-death was 7 days, with the first quartile set at 4 days and the third set at 12 days, with no significant difference between age groups. Our results revealed a statistically significant difference in survival probability between males and females, with males having higher survival rates (log-rank test,  $P = .007$ ).

Patients not admitted to an ICU had higher survival rates than those admitted to an ICU (log-rank test,  $P < .001$ ). These results, along with survival curves stratified by age, sex and presence of chronic conditions, are illustrated in [Supplementary Figure 2](#). Mortality peaked at age 50–64 (8.1%) and then decreased slightly at older ages. The Cochran-Mantel-Haenszel test, adjusted for strata (vaccination status), was used to compare the percentage of death in the age range stratum and showed what appears to be the effect of the vaccine in attenuating mortality, as higher vaccine uptake was noted at older ages (data not shown,  $P < .001$ ). The distribution of vaccination status among surviving versus deceased patients is shown in [Supplementary Figure 3](#).

Analysis of influenza strain data from our study revealed statistically significant associations with the probability of survival (log-rank test,  $P = .009$ ) ([Supplementary Figure 4A](#)).

Influenza A infection had a higher estimated 30-day survival probability than influenza B infection (log-rank test,  $P = .034$ ) ([Supplementary Figure 4B](#)). Further stratification of influenza A revealed that those infected with influenza A/H1N1pdm09 had a higher estimated 30-day survival probability than those infected with influenza A/H3N2 (log-rank test,  $P = .006$ ) ([Supplementary Figure 4C](#)).

After filtering a sample to include only those with LCI, we evaluated the variables independently associated with ICU admission or death outcomes. Our modeling results revealed that middle-aged adults (50–64 years) had higher mortality, with a 1.80 OR (95% CI, 1.21–2.68), whereas the elderly (65–79 years) had 1.60 OR (95% CI, 1.04–2.46), of ICU admission or death. Patients with COPD and diabetes had 1.54 (95% CI, 1.07–2.19) and 1.77 (95% CI, 1.25–2.48) OR of the worst outcomes, respectively. It is notable that male gender and vaccination for the current influenza season were associated with lower OR of ICU admission or death, with the OR of 0.58 (95% CI, .43–.77) and 0.31 (95% CI, .17–.54), respectively ([Figure 2](#)). The [Supplementary Materials](#) include a sensitivity analysis using mixed effects in the regression models to account for variability between sites ([Supplementary Figure 5](#)), illustrating that the results remained consistent except that age and COPD were no longer statistically significant.

## DISCUSSION

During the 2018/2019 influenza season, 3512 (21.9%) patients of all ages who were admitted to the hospital and enrolled at



GIHSN sites had laboratory-confirmed influenza. There was cocirculation of influenza A/H1N1pdm09, A/H3N2, B Yamagata-like, and B Victoria-like, with variability noted between countries and regions. Symptoms varied significantly with age, with younger patients more likely to present with fever and cough and older adults presenting with shortness of breath. Severe outcomes were experienced across the age continuum. Middle and older age (particularly age 50–64 and 65–79) and underlying diabetes or COPD were independently associated with the composite outcome of death or ICU admission, whereas male sex and influenza vaccination were associated with lower odds of these severe outcomes. Very few children and young adults had comorbidities, which were much more frequent in older age groups.

Cardiovascular illness, diabetes, respiratory conditions, neoplasm, and kidney disease were the most common comorbidities, although comorbidity profiles differed across age groups and sites. It is notable that only a minority of younger patients had any underlying illnesses at all (<1% for ages 0–5 years, < 1.5% for those aged 5–17 years, and <5% for those aged 18–49 years). These findings underscore that influenza virus infection can cause severe illness requiring hospitalization, even among children, adolescents, and previously healthy individuals. The low rate of comorbidities in this international sample contrasts with a study from Canada, which reported that approximately one third of children aged 0–59 months admitted to hospital with influenza had complex underlying comorbidities [11], suggesting that contextual factors such as socioeconomic status and clinical care pathways may play an essential role in profiles of underlying illness. A meta-analysis has identified underlying comorbidity as a critical risk factor for influenza hospitalization among children, listing neurological conditions, prematurity, sickle cell, immunosuppression, diabetes, and age <2 years as higher risk conditions [12]. Children with more than 1 of these factors were at the highest risk.

It is notable that, using an international surveillance network, our study is unique in providing an international comparison of these comorbidities underlying influenza hospital admissions. Our finding that comorbidities increased with age, and was exceptionally high among older adults, is consistent with findings in the literature [13–16]. Not surprisingly, the profile of underlying comorbidities also varied widely between sites, according to local epidemiology of infectious and noninfectious illnesses. This is consistent with other international reports [17]. Among comorbidities, COPD and diabetes were independently associated with increased odds of the most severe outcomes. Similar results were also reported regarding the positive association between these comorbidities and adverse clinical outcomes in patients hospitalized with influenza. Researchers recently showed that older adults with diabetes have higher rates of severe influenza-associated outcomes than those without [18].

On the other hand, others found no association between diabetes and adverse clinical outcomes in hospitalized patients with influenza during Catalonia's 2017–2018 influenza season [19]. However, the authors showed that COPD was associated with mortality in the age group 15 to 49 years, similar to the results found in New Zealand [20]. Although the effect of influenza vaccination among diabetic patients remains inconclusive, a recent study found that influenza vaccination in diabetic patients reduced the risk of hospitalization for influenza by approximately half [21]. Future studies should analyze the effectiveness of influenza vaccination on adverse clinical outcomes in diabetic patients, considering other factors mentioned here.

Fever and cough were the most common presenting symptoms, at over 90%. This finding is not surprising given that the enrollment protocol was based on the ECDC case definition of ILI, in which fever and cough are prominent [10]. We observed age differences in presenting symptoms, with older adults less likely to present with typical ILI symptoms and more likely to experience shortness of breath. This is consistent with prior reports in the literature that the sensitivity of ILI case definitions varies with age and is lower among older adults [22, 23] and has led to suggestions that criteria be modified in older adults and residents of long-term care facilities [22, 24, 25].

Influenza A/H1N1pdm09 (49.2%) was the dominant influenza strain detected in the GIHSN during the 2018/2019 influenza season. However, it is notable that there were substantial differences between sites in the strain distribution pattern, and, from a global perspective, there was cocirculation of A/H1N1pdm09, A/H3N2, B Victoria, and B Yamagata, creating a mixed season overall. This finding is consistent with other reports from the same season, in which both A/H1N1pdm09 and A/H3N2 and, to a minor degree, influenza B were reported [26–28]. Overall, the seasonal influenza vaccine was reported to be well matched to circulating A/H1N1 strains, but the majority of circulating A/H3N2 strains were mismatched [29]. This variability also emphasizes the need for more research to understand why influenza epidemiology can vary widely, even between neighboring countries. The differences in strain circulation are consistent with previous experience in the GIHSN [3]. There were also age differences in the strain prevalence; for example, consistent with prior reports, B Yamagata was more often detected in older adults, whereas B Victoria and B Yamagata were more frequently detected in hospitalized children. This is consistent with prior reports that B Victoria may preponderantly affect younger children, whereas older adults may be more affected by B Yamagata [30–32]. We also found that influenza A > influenza B in their strength of association with mortality (Supplementary Figure 4). This finding is consistent with other reports showing that clinical outcomes of patients with influenza A may be more severe than those with influenza B, regardless of gender, age, and underlying health conditions [33, 34].

Although vaccination rates varied widely between sites, likely reflecting international differences in influenza vaccination policy, programs, and availability [35], we found that influenza vaccination in the current season was associated with statistically significantly lower odds of experiencing the most severe outcomes (ICU admission and mortality). Our analyses also showed that vaccination was associated with the plateau (and indeed slight attenuation) of mortality in the oldest age groups, in whom vaccination uptake was highest. The magnitude of this association is consistent with prior reports that influenza vaccine effectiveness tends to be highest against the most severe outcomes [13]. Care-seeking and access patterns, which vary across sites and resource settings, represent other factors that may have contributed to our finding of differential mortality between age groups; the importance of this variability between sites is highlighted by our sensitivity analyses in which these were accounted for using mixed-effects models.

The RT-PCR testing for additional respiratory viruses was performed in some sites and demonstrates that many other viral illnesses cocirculate during influenza season and can present similarly to influenza with illness severe enough to require acute care hospitalization. This is consistent with prior literature reports [36, 37], although awareness in the public and medical communities remains better for pediatric than older age groups. Future analyses may indicate the role of coinfection between influenza and other respiratory viruses as a determining disease severity factor.

We found that women had higher odds of death or ICU admission. The causes of this association are unclear, although some prior studies have reported differences in influenza mortality between sexes. Although we adjusted our analyses for comorbidity and age, it is also possible that this difference may relate to discrepancies in frailty, which tends to be higher for women than for men [38]. We also found that the likelihood of severe outcomes (particularly in-hospital death and ICU admission) tended to increase with age among adults, although with some reduction at the oldest age groups as discussed above. This increase in adverse outcomes with age is consistent with findings in the existing literature [16, 39]. However, age alone may not explain this finding. A growing body of evidence suggests that individuals vary widely in their health status and vulnerability to adverse outcomes related to influenza, even within defined age groups; this variability can be measured using the concept of frailty [40, 41], particularly at older ages. Starting from the 2019/2020 influenza season, the Clinical Frailty Scale is included in the GIHSN data collection and will be a feature of future season reports and analyses [42].

Our study is not without limitations. Symptoms were not documented for children under age 5, and functional status was documented only for the age group  $\geq 65$ . Enrollment was based on ILI criteria, which likely resulted in disproportionate underenrollment of older adults with influenza, who tend to present atypically,

even without fever. We could not grade the severity of individual comorbidities, and although we relied on hospital medical records rather than patient self-report, the possibility of undiagnosed comorbidity remains. Unmeasured confounding may remain, including in the estimate of vaccine effectiveness. Despite the standardized protocol, there are differences between-country data collection approaches, because individual sites coordinate with internal regional and national surveillance structures. Because individual sites are based at specific hospitals or institutions, some countries over- or underrepresented specific patient groups. For example, some sites enrolled only adults, whereas others in pediatric institutions enrolled only children. Some sites are in specialized infectious disease, respiratory illness, or maternity hospitals, whereas others are in general facilities. Nevertheless, these differences also contribute to the richness of the network in providing a snapshot of the experience of hospitalized influenza illness and care around the world.

## CONCLUSIONS

The GIHSN contributes to the global understanding of hospitalized influenza illness in diverse international settings and all age groups. Future seasons will include more nuanced consideration of the impact of frailty and add data on whole-genome sequencing in the context of ongoing data collection on clinical presentation and outcomes.

## Supplementary Data

**Supplementary materials** are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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