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Background: Influenza is a major cause of respiratory illness resulting in 3–5 million severe cases and 291,243-645,832 deaths annually. Substantial health and financial burden may be averted by annual influenza vaccine application, especially for high risk groups.

Methods: We used an active facility-based surveillance platform for acute respiratory diseases in three hospitals in Guatemala, Central America, to estimate the incidence of laboratory-confirmed hospitalized influenza cases and identify risk factors associated with severe disease (defined as admission to the intensive care unit (ICU) or death). We enrolled patients presenting with signs and symptoms of acute respiratory infection (ARI) and obtained naso- and oropharyngeal samples for real-time reverse transcriptase polymerase chain reaction (RT-PCR). We used multivariable logistic regression to identify risk factors for ICU admission or death, adjusted for age and sex.

Results: From May 2008 to July 2012, among 6326 hospitalized ARI cases, 446 (7%) were positive for influenza: of those, 362 (81%) had influenza A and 84 (18%) had influenza B. Fifty nine percent of patients were aged ≤ 5 years, and 10% were aged ≥ 65 years. The median length of hospitalization was 5 days (interquartile range: 5). Eighty of 446 (18%) were admitted to the ICU and 28 (6%) died. Among the 28 deaths, 7% were aged ≤ 6 months, 39% 7–60 months, 21% 5–50 years, and 32% ≥ 50 years. Children aged ≤ 6 months comprised 19% of cases and 22% of ICU admissions. Women of child-bearing age comprised 6% of cases (2 admitted to ICU; 1 death). In multivariable analyses, Santa Rosa site (adjusted odds ratio [aOR] = 10, 95% confidence interval [CI] = 2–50), indigenous ethnicity (aOR = 4, 95% CI = 2–13, and radiologically-confirmed pneumonia (aOR = 5, 95% CI = 3–11) were independently associated with severe disease. Adjusted for hospital utilization rate, annual incidence of hospitalized laboratory-confirmed influenza was 24/100,000 overall, 93/100,000 for children aged < 5 years and 50/100,000 for those ≥ 65 years.

Conclusions: Influenza is a major contributor of hospitalization and death due to respiratory diseases in Guatemala. Further application of proven influenza prevention and treatment strategies is warranted.

Keywords: Influenza, Guatemala, Respiratory disease

Influenza is a major cause of respiratory illness resulting in 3–5 million severe cases and 291,243

[10]. In Guatemala, Lindblade, et al, described the clinical presentations of pandemic A(H1N1)pdm09 and seasonal influenza A (H1N1 and H3N2) from 2008 to

recording the same radiologic endpoints as are used for pediatric CXRs [26]. All digital images were reviewed independently by two radiologists and were classified as having consolidation or obscuring pleural effusion as an end-point, other consolidation/infiltrate, no consolidation/infiltrate/effusion or uninterpretable. In cases of discordant interpretations between the first two readers, a third interpretation was recorded and the final classification was determined by the majority. Consolidation was considered suggestive of a bacterial etiology [25].

Surveillance case definitions [27]

If a patient was five years or older, the case definition for acute respiratory infection (ARI) was:

> At least one of the following: documented fever (≥38°C) in the past 7 days; temperature <35.5°C with chills; or abnormal white blood cell count (>11,000/mm^3 or <3,000/mm^3) or abnormal white blood cell differential AND
> At least one of the following: tachypnea, cough, sputum production, hemoptysis, chest pain, dyspnea, shortness of breath, sore throat, or abnormal lung exam.

If a patient was less than five years old, the Integrated Management of Childhood Illness (IMCI) guideline criteria [28] for management of pneumonia-like illness was applied in 2011:

1. Age <2 months with tachypnea or chest in-drawing, OR
2. Age <2 months with cough or difficulty breathing and at least one of the following: cyanosis, stridor at rest, hypoxia (O_2 saturation <90%), head nodding, or general danger signs such as not drinking or breastfeeding, vomiting all intake, convulsions, lethargy or fainting, no movement or only when stimulated, OR
3. Age 2 to 59 months with cough or difficulty breathing and at least one of the following: tachypnea, chest in-drawing, cyanosis, head nodding, stridor at rest, hypoxia (O_2 saturation <90%) or general danger signs such as not drinking or breastfeeding, vomiting all intake, convulsions, lethargy or fainting.

Laboratory methods

Nasopharyngeal swab specimens were collected from each patient using a polyester swab that was placed in viral transport media, stored at 4-8 °C for ~ 24 h, then frozen at -20 °C and sent for laboratory analysis at Centro de Estudios en Salud (CES)-UVG where they were tested using real-time reverse transcriptase polymerase chain

Children aged < 6 months of age comprised 85 (19%) of hospitalized patients attributed to influenza and 19 of 80 (24%) of patients who required ICU admission. Two (2%) of 85 children aged < 6 months died or 7% of the 28 deaths. Other decedents included 11 (6%) of 176 children aged 7–60 months, 6 (6%) of 105 person aged 5–50 years, and 9 (11%) of 80 patients aged > 50 years. Among all hospitalized patients, 26 (6%) were women of reproductive age (15–49 years old); two were admitted to the ICU, and one died.

Comparing patients admitted to the ICU or decedents with other patients, bivariate analyses suggest site, ethnicity, pneumonia, household size, and the seeking of care before hospitalization were associated with severe disease. Age and sex, did not seem to predict severe disease in this population (Table 4). Antiviral therapy information was available for only 268 patients, but among these, 97% received antiviral therapy. In multivariate analyses adjusted for age and sex, three characteristics remained independent risk factor for poor outcome: site, ethnicity, and pneumonia characterized by consolidation and/or large effusion. Compared with patients in Guatemala City IGSS hospital, patients in Quetzaltengo had five times and Santa Rosa had nine times the odds of experiencing a severe disease. The odds of having severe disease were four times (95% CI = 2–13) higher in

1 Demographic characteristics of hospitalized laboratory-confirmed influenza cases of the Vigilancia Integrada Comunitaria (VICo) Respiratory Surveillance System, 2008–2012

Characteristics	Guatemala City[a] n = 60	Quetzaltenango (Xela) n = 224	Santa Rosa (Cuilapa) n = 162	Total n = 446	p-value
Age (years)					
Median	1.2	5.9	2.1	2.4	< 0.01[b]
Mean	4.5	24.3	15.3	18.3	
Range	0.06–83.3	0.04–89.8	0.03–80.9	0.02–83.6	
Age Group					
0–2	38 (63)	86 (38)	81 (50)	205 (46)	< 0.01[c]
> 2–5	18 (30)	25 (11)	13 (8)	56 (13)	
> 5–15	0	13 (6)	21 (13)	34 (8)	
> 15–50	2 (3)	44 (20)	25 (15)	71 (16)	
> 50–65	1 (2)	26 (12)	9 (6)	36 (8)	
> 65	1 (2)	30 (13)	13 (8)	44 (10)	
Sex					
Male	30 (50)	132 (59)	92 (57)	254 (57)	0.46[c]
Ethnicity					
Indigenous	5 (8)	146 (69)	6 (4)	157 (36)	< 0.01[c]
Ladino	55 (92)	65 (31)	155 (96)	275 (64)	
Monthly Income					
≤ Q1,000[e]	5 (8)	109 (64)	121 (75)	235 (53)	< 0.01[c]
> Q1,000	54 (90)	62 (28)	40 (25)	156 (35)	
Missing	1 (2)	53 (24)	1 (0.6)	55 (12)	
Parent's education[f] for children under five (n = 261)					
None	5 (9)	23 (22)	26 (28)	54 (21)	< 0.01[c]
Primary	41 (73)	67 (63)	67 (72)	175 (69)	
Secondary	10 (18)	16 (15)	0 (0)	26 (10)	
Adult patient's education (n = 185)					
None	1 (25)	24 (21)	20 (29)	45 (24)	0.03[d]
Primary	3 (75)	51 (45)	21 (31)	75 (41)	
Secondary	0 (0)	15 (13)	3 (4)	18 (10)	
Missing	0 (0)	23 (20)	24 (35)	47 (25)	

We estimated the cumulative incidence rate for hospitalized influenza at the two sites of the surveillance system. Overall, children < 5 years are at highest risk of hospitalization in both sites and for all years followed by those over 65 years. In general, the A(H1N1)pmd09 strain affected young persons more than those older than 50 years, a pattern seen world-wide. Younger age groups and older adults should be the targeted for vaccination [33]. A prospective study in Nicaragua documented high incidence of influenza, especially in infants 6–11 months, a vaccine eligible age [12]. In particular, better strategies to protect the youngest children (aged < 6 months) are needed as vaccination is not currently recommended for this age group. Immunization of pregnant women provides protection for women and their infants [34].

The present study clearly indicate children aged less than 5 years and persons 65 years and older have the highest incidence rates of influenza hospitalization. A strength of the present study is that cases were sought actively by study nurses and influenza virus was detected by sensitive PCR. Comparing incidence rates obtained in the present study with those estimated by attributing acute respiratory syndrome discharge diagnoses to the

proportion of monthly influenza positive tests by indirect fluorescent antibody [9], crude rates in children aged less than five years are similar (Table 5). However, a major difference is observed in the incidence among persons aged 65 years and older. We observed incidence rates in 2009–2012 of 22–65/100,000 compared with 2–10/100,000 modeled using multipliers and influenza laborat.074r4rma-

guardians in the three sites, or might reflect differences in epidemiology, or different specialties at the hospitals. For example, the Cuilapa National Hospital in Santa Rosa is a regional referral center for neonates and children. The three sites have very different environmental, socio-economic and ethnic profiles that might require different approaches in prevention and managing influenza. For instance, at the Cuilapa hospital, patients

4 Risk factors for severe disease among hospitalized patients enrolled in VICo respiratory syndrome surveillance, 2008–2012 (N = 446)

C (36.1 °F). Likewise, the common practice of cooking on open fires inside buildings and use of open fires for warmth among Mayans might increase the risk of respiratory infections [44]. The increased odds of severe disease among indigenous people in the rural highlands might be due to less access to the appropriate care, delayed treatment, nutritional, cultural, environmental, or other factors.

The IGSS Zona 9 hospital in Guatemala City, financed through workers and employer's contributions, may have better-equipped health care facilities that are more easily accessed compared with the other two sites. The vaccine

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