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Prospective cohort study of patient demographics, viral agents, seasonality, and outcomes of influenza-like illness in Mexico in the late H1N1-pandemic and post-pandemic years (2010-2014)

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ABSTRACT

Objectives: Influenza-like illness (ILI) caused by respiratory viruses results in various respiratory clinical manifestations. The ILI002 prospective observational cohort study aimed to describe viral agents, seasonality, and outcomes of patients with ILI during four seasons in the influenza H1N1-pandemic and post-pandemic years (2010-2014).

Methods: Patients from six Mexican hospitals were enrolled from April 2010 to March 2014. Clinical data and nasopharyngeal swabs were obtained and tested for viral respiratory pathogens by real-time reverse-transcription polymerase chain reaction.

Results: Of the 5662 enrolled participants, 64.9% were adults and 35.1% were children. Among the 5629 participants with single-pathogen detection, rhinovirus (20.2%), influenza virus (11.2%), respiratory syncytial virus (RSV) (7.2%), and coronavirus (6.8%) were the most frequent pathogens. Co-infection occurred in 14.5% of cases; 49.3% of participants required hospitalization, particularly in RSV cases (42.9% adults, 89.6% children). The mortality rate was 2.8% higher among older adult participants and those with comorbidities. Influenza H1N1 had the highest mortality rate, yet almost half of the deceased had no pathogen. Rhinovirus persisted year-round, while influenza, coronavirus, and RSV peaked during cooler months.

Conclusions: Analyses showed that some viruses causing ILI may lead to severe disease and hospitalization irrespective of comorbidities. These findings may help in decision-making about public health policies on prevention measures, vaccination, treatment, and administration of health care.

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Introduction

Influenza-like illness (ILI) is characterized by various symptoms, caused by both upper and lower respiratory tract disease. It ranges from self-limited to severe, potentially life-threatening disease [1]. ILI may be caused by respiratory viruses including influenza virus types A and B, rhinovirus (human rhinovirus [HRV]/enterovirus), human parainfluenza viruses, respiratory syncytial virus (RSV) and human coronavirus [2]. Severity depends on factors such as underlying medical conditions and age. Risk factors for severe disease with influenza infection include age (<5 or >65 years), chronic lung or heart disease, history of smoking, immunocompromise, and obesity [3]. Children, the elderly, and people with impaired immune systems are also susceptible to severe disease caused by non-influenza respiratory viruses [4]. Viruses cause 27.5-39.2% of community-acquired pneumonia in immunocompetent patients [5]. Some respiratory viruses can cause widespread epidemics or even pandemics, with incidence and distribution influenced by factors such as seasons, geography, environmental parameters, and human behavior [6].

Given the public health importance of ILI during and after the H1N1 outbreak, the Mexican and US governments created the Mexican Emerging Infectious Diseases Clinical Research Network (LaRed). In this prospective cohort study of people seeking medical care for ILI during the late influenza H1N1 pandemic and post-pandemic years (2010-2014), we describe patient characteristics, viral agents identified, patient outcomes, and the seasonality of identified viral agents.

Materials and methods

Study design and settings

ILI002 was an observational, prospective, cohort study, conducted from April 2010 to April 2014 by LaRed, spanning five hospitals (two specialized for children, two for adults, and one for a general population) in Mexico City and one in San Luis Potosí (a general hospital for adults and children). The hospitals were in a subtropical climate.

Study population and definitions

Patients aged ≥1 month seeking medical care for ILI were followed for 28 days. ILI was defined by the presence of at least one respiratory symptom (shortness of breath, postnasal drip, and cough) and one of the following criteria: (1) fever (≥38°C) on examination, participant-reported fever, or self-reported feverishness (sweats, chills, feeling cold) in the past 24 hours; and (2) one or more non-respiratory symptoms (malaise, headache, myalgia, and chest pain). Inpatients spent ≥24 hours hospitalized, while outpatients received ambulatory treatment and spent <24 hours in the hospital.

Outcomes

The main outcomes' (hospitalization and death) associations with virus family, medical history, and ILI signs and symptoms at the time of presentation to the hospital were measured. Frequencies of identified respiratory viral agents by age group, their associations with medical history, and ILI signs and symptoms were investigated. Frequencies of respiratory viral agents were tracked to demonstrate seasonal trends.

Procedures

Patients with ILI from outpatient services, emergency departments, and hospitalization areas of the six participating hospitals were invited to participate in this study. Following informed consent/assent, demographics, medical history, and nasal swabs for polymerase chain reaction (PCR) detection of respiratory pathogens were obtained at enrollment.

Symptoms, concurrent treatment, impact on daily function, hospitalizations, and death were assessed at 14 and 28 days after enrollment. The signs and symptoms evaluated included respiratory indicators (such as rales/crepitations, wheezing, productive cough, dyspnea, and sore throat) and non-respiratory indicators (such as fever or self-reported feverishness, diarrhea, fatigue, headache, nausea, and red eyes). Follow-up was performed during ambulatory visits or at participant's hospitalization. Day-14 follow-up was conducted by in-person interview if hospitalized or by phone call otherwise. Day-28 follow-up was conducted by in-person interview, regardless of hospitalization status. Information was gathered from medical records.

Molecular detection of respiratory pathogens

Nasopharyngeal swabs (FLOQSwabs®; Copan, Brescia, Italy; CE 0344) were collected and placed in viral transport media at 4°C and sent within 72 hours to the Molecular Biology Laboratory of the Infectious Diseases Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán for processing and storage at −70°C. Samples from San Luis Potosí were refrigerated, stored at −70°C at the Facultad de Medicina, Universidad Autónoma de San Luis Potosí, and later transported to the central laboratory. All samples were tested by quantitative real-time reverse-transcription PCR for influenza (identification and subtyping) following the US Centers for Disease Control and Prevention protocol and for a range of respiratory pathogens using the RespiFinder-19® (samples between April 2010 and May 2012) and RespiFinder-22® (formerly RespiFinder Plus, for samples between June 2012 and March 2014) from PathoFinder BV, Maastricht, the Netherlands. The RespiFinder-19® kit can detect and differentiate adenovirus, coronavirus NL63, OC43, 229E, human metapneumovirus, influenza A virus, influenza A virus subtype H5N1, influenza B virus, human parainfluenza virus types 1-4, RSV A and B, and HRV/enterovirus, as well as *Bordetella pertussis, Chlamydophila pneumoniae, Legionella pneumophila*, and *Mycoplasma pneumoniae*. The RespiFinder-22® kit removed the ability to detect influenza H5N1 but added the ability to detect coronavirus HKU1, influenza A virus subtype H1N1, and bocavirus. The detection range varies between 5 and 50 copies per reaction for most targets.

Statistical analysis

Demographics and medical history were summarized in children (aged 0-18 years), adults (aged 19-59 years), and older adults (aged >59 years). Descriptive statistics summarized continuous variables (median, minimum, and maximum) and categorical variables (counts and percentages). For children aged 0-18 years, body mass index (BMI) was categorized by comparison with the BMI distribution in a reference population of the same age, according to World Health Organization multicenter growth studies. Counts and percentages of participants with detected pathogens were reported overall and by age group. Participants with coinfections were grouped separately. Seasonality of virus types was summarized by counts and relative frequencies each month. Virus family type and participant characteristics were described; counts and frequencies of participants with specified medical history, signs, and symptoms were shown for frequently identified virus families in children and adults. Laboratory values, medications, medical history, and clinical signs and symptoms were compared between survivors and non-survivors. Unadjusted logistic regression models were used to calculate odds ratios, 95% confidence intervals, and *P*-values, with $P < 0.05$ considered statistically significant. Laboratory results were standardized and included in separate regression models to assess mortality odds based on a one standard deviation difference. Medical history, medications, and clinical signs/symptoms were binary categorical variables, allowing for the estimation of mortality odds relative to the reference group. The analytic data set was constructed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA). Statistical analyses were performed using R, version 4.1.3.

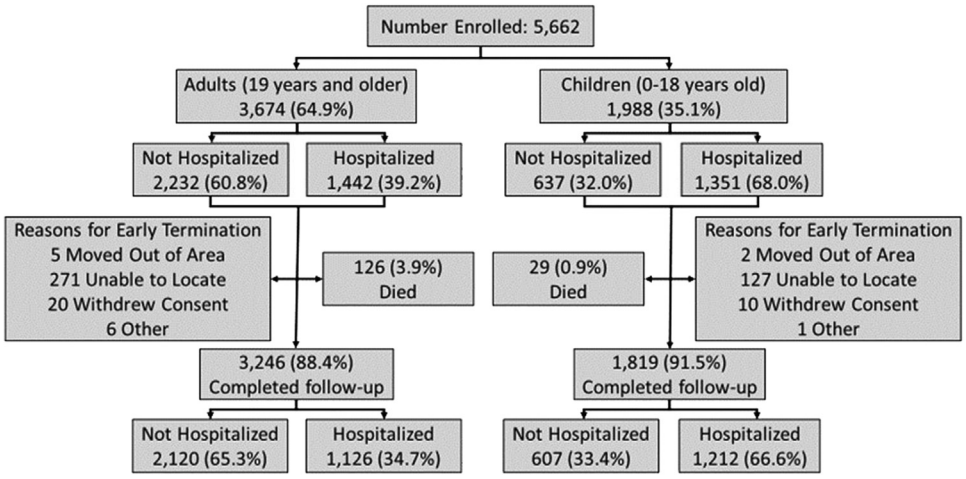

Figure 1. Flowchart of study participants seeking care for influenza-like illness at 6 hospitals in Mexico.

Ethical considerations

All study protocol procedures were performed in compliance with relevant laws and institutional guidelines and were evaluated and approved by the institutional review boards from each participant institution, namely the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (Date 26.01.2010; Ref 116), Instituto Nacional de Enfermedades Respiratorias (Date 16.03.2010; Ref C12-10), Hospital General Dr. Manuel Gea González (Date 23.06.210; Ref 36-50-2010), Instituto Nacional de Pediatría (Date 10.03.2010; Ref INP 014/2010), Hospital Infantil de México Federico Gómez (Date 06.12.2010; Ref HIM/2010/074), and Hospital Regional Dr. Ignacio Morones Prieto (Date 16.10.2012; Ref 88-12). All participants provided written informed consent. Parents or legal representatives provided consent for children, while assent was obtained for those aged >8 years. All procedures adhered to the World Medical Association's International Code of Medical Ethics (Declaration of Helsinki) for human experimentation and relevant laws and guidelines.

Results

Characteristics of the study population

A total of 5662 participants were enrolled between April 2010 and April 2014; 3674 (64.9%) were adults and 1988 (35.1%) were children. Among them, 428 (11.6%) adults and 169 (8.5%) children did not complete follow-up (Figure 1). Most adults (19-59 years of age) were female, and most were overweight, whereas most children were male, and most had normal BMI. The most frequent chronic medical conditions were asthma (9.6%) and cardiovascular disease (11.0%). The median number of days between symptom onset and enrollment was 1 day, and 37.7% of participants were inpatients at baseline (Table S1).

Viral agents

Among 5629 participants (99.4% of total) tested, the most frequent pathogen was HRV/enterovirus (30.0%) followed by influenza virus (18.7%). The proportions of participants with single infections of these viruses were 20.2% and 11.2%, respectively. Coronavirus and RSV infected approximately 7% of participants each, while adenovirus, bocavirus, metapneumovirus, and parainfluenza virus each were detected in less than 5% of participants. No pathogen was detected in 27.6% of participants, and 14.5% had coinfections (Table S2).

Seasonal distribution of viruses

Influenza, coronavirus, and RSV were more often found during cooler months in Mexico (November-April). HRV/enterovirus was found throughout the whole year, although during 2013, its distribution showed a larger proportion during warmer months (May-October) (Figure 2). For coronavirus, the most frequent types were OC43 (2010-2011 and 2012-2013), NL63 (2011-2012), and 229E (2013-2014). The most frequent influenza types/subtypes during the 2010-2011 and 2012-2013 periods were influenza A H3N2 and influenza B, while influenza A H1N1 was the most prevalent during the 2011-2012 and 2013-2014 periods. RSV A was the most frequent RSV subtype throughout the study period (Figure 3).

Medical history and symptoms

Among children, 40.3% had chronic medical conditions. The most common respiratory symptom was productive cough (73.6%), with the highest proportion occurring in children positive for RSV (78.9%). Fever was the most common non-respiratory symptom in children, with the highest proportions occurring in those infected with influenza virus (93.5%) and RSV (90.3%). Fatigue and headache were less frequent among children infected with coronavirus, HRV/enterovirus, and RSV (<25%) than among those infected with influenza virus (fatigue: 43.0%; headache: 38.2%).

Among adults, 40.2% had chronic medical conditions. The most common respiratory symptoms were sore throat (65.5%) and productive cough (56.4%), and the most common non-respiratory symptom was fatigue (69.8%). Out of all pathogens, RSV had the highest proportion of adults with chronic medical conditions (50.5%), productive cough (67.6%), and fatigue (75.2%), while HRV/enterovirus had the highest proportion of adults with sore throat (73.9%).

A substantial proportion of children (59.8%) and adults (48.1%) were taking antibiotics at enrollment, while lower proportions were taking antiviral medications (≤20%), except for adults with influenza (37.7%) (Table 1).

Outcomes

Hospitalization occurred in 2776 (49.3%) participants, 1343 (48.4%) children and 1433 (51.6%) adults. Among children with single-virus infections, the highest proportion of hospitalizations (89.6%) occurred among those with RSV, followed by those with metapneumovirus (78.9%). Among the children with coinfections, 69.6% required hospitalization. Among adults aged 19-59 years, the highest proportion of single-virus hospitalizations (48.1%) occurred in those positive for bo-

Table 1
Distribution of relevant medical history characteristics and symptoms of patients with single infection by any of the four most frequently observed pathogens, or with any other single- or multiple-pathogen infection.

	Children n (%)						Adults n (%)					
	Coronavirus	Influenza	HRV/enterovirus	RSV	Other	Total	Coronavirus	Influenza	HRV/enterovirus	RSV	Other	Total
n	76	186	348	298	1071	1979	308	446	790	105	2001	3650
Medications												
Any antiviral	8 (10.5%)	33 (17.7%)	26 (7.5%)	14 (4.7%)	96 (9.0%)	177 (8.9%)	54 (17.5%)	168 (37.7%)	114 (14.4%)	18 (17.1%)	396 (19.8%)	750 (20.5%)
Antibiotics[a]	31 (40.8%)	102 (54.8%)	180 (51.7%)	206 (69.1%)	663 (62.0%)	1182 (59.8%)	98 (31.8%)	232 (52.3%)	318 (40.3%)	50 (47.6%)	1057 (52.9%)	1755 (48.1%)
Inhaled steroids[b]	3 (3.9%)	16 (8.6%)	37 (10.6%)	36 (12.1%)	117 (10.9%)	209 (10.6%)	20 (6.5%)	55 (12.5%)	65 (8.2%)	19 (18.1%)	256 (12.8%)	415 (11.4%)
Systemic steroids[c]	14 (18.4%)	23 (12.4%)	61 (17.5%)	47 (15.8%)	171 (16.0%)	316 (16.0%)	44 (14.3%)	105 (23.8%)	177 (22.4%)	34 (32.4%)	499 (25.0%)	859 (23.6%)
Medical History												
Chronic medical condition	33 (43.4%)	69 (37.1%)	155 (44.5%)	104 (34.9%)	436 (40.7%)	797 (40.3%)	94 (30.5%)	154 (34.5%)	301 (38.1%)	53 (50.5%)	865 (43.2%)	1467 (40.2%)
Asthma	5 (6.6%)	13 (7.0%)	35 (10.1%)	12 (4.0%)	53 (4.9%)	118 (6.0%)	20 (6.5%)	51 (11.4%)	98 (12.4%)	15 (14.3%)	240 (12.0%)	424 (11.6%)
Cardiovascular disease	1 (1.3%)	2 (1.1%)	15 (4.3%)	6 (2.0%)	42 (3.9%)	66 (3.3%)	44 (14.3%)	56 (12.6%)	103 (13.0%)	22 (21.0%)	323 (16.1%)	548 (15.0%)
COPD	4 (5.3%)	2 (1.1%)	10 (2.9%)	13 (4.4%)	38 (3.5%)	67 (3.4%)	6 (1.9%)	9 (2.0%)	13 (1.6%)	6 (5.7%)	39 (1.9%)	73 (2.0%)
Diabetes	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	2 (0.1%)	10 (3.2%)	15 (3.4%)	21 (2.7%)	4 (3.8%)	88 (4.4%)	138 (3.8%)
Smoking: current/former smoker	1 (1.3%)	1 (0.5%)	9 (2.6%)	0 (0.0%)	12 (1.1%)	23 (1.2%)	116 (37.7%)	182 (40.8%)	302 (38.2%)	37 (35.2%)	806 (40.3%)	1443 (39.5%)
Respiratory Symptoms												
Rales/crepitations	30 (39.5%)	56 (30.1%)	172 (49.4%)	228 (76.5%)	649 (60.6%)	1135 (57.4%)	39 (12.7%)	117 (26.2%)	107 (13.5%)	19 (18.1%)	487 (24.3%)	769 (21.1%)
Wheezing	17 (22.4%)	33 (17.7%)	109 (31.3%)	112 (37.6%)	298 (27.8%)	569 (28.8%)	25 (8.1%)	68 (15.2%)	132 (16.7%)	21 (20.0%)	351 (17.5%)	597 (16.4%)
Productive cough	52 (68.4%)	127 (68.3%)	240 (69.0%)	235 (78.9%)	788 (73.6%)	1442 (72.9%)	124 (40.3%)	254 (57.0%)	442 (55.9%)	71 (67.6%)	1168 (58.4%)	2059 (56.4%)
Dyspnea	7 (9.2%)	17 (9.1%)	34 (9.8%)	24 (8.1%)	94 (8.8%)	176 (8.9%)	72 (23.4%)	174 (39.0%)	249 (31.5%)	50 (47.6%)	758 (37.9%)	1303 (35.7%)
Sore throat	22 (28.9%)	69 (37.1%)	79 (22.7%)	23 (7.7%)	212 (19.8%)	405 (20.5%)	208 (67.5%)	283 (63.5%)	584 (73.9%)	73 (69.5%)	1244 (62.2%)	2392 (65.5%)
Non-Respiratory Symptoms												
Fever	58 (76.3%)	174 (93.5%)	250 (71.8%)	269 (90.3%)	909 (84.9%)	1660 (83.9%)	144 (46.8%)	357 (80.0%)	380 (48.1%)	46 (43.8%)	1142 (57.1%)	2069 (56.7%)
Diarrhea	7 (9.2%)	18 (9.7%)	34 (9.8%)	38 (12.8%)	127 (11.9%)	224 (11.3%)	26 (8.4%)	59 (13.2%)	65 (8.2%)	12 (11.4%)	148 (7.4%)	310 (8.5%)
Fatigue	11 (14.5%)	80 (43.0%)	86 (24.7%)	69 (23.2%)	281 (26.2%)	527 (26.6%)	226 (73.4%)	333 (74.7%)	542 (68.6%)	79 (75.2%)	1366 (68.3%)	2546 (69.8%)
Headache	18 (23.7%)	71 (38.2%)	62 (17.8%)	15 (5.0%)	138 (12.9%)	304 (15.4%)	230 (74.7%)	340 (76.2%)	530 (67.1%)	63 (60.0%)	1357 (67.8%)	2520 (69.0%)
Nausea	16 (21.1%)	53 (28.5%)	68 (19.5%)	92 (30.9%)	226 (21.1%)	455 (23.0%)	62 (20.1%)	142 (31.8%)	160 (20.3%)	25 (23.8%)	451 (22.5%)	840 (23.0%)
Red eyes	10 (13.2%)	67 (36.0%)	64 (18.4%)	53 (17.8%)	217 (20.3%)	411 (20.8%)	132 (42.9%)	177 (39.7%)	246 (31.1%)	34 (32.4%)	546 (27.3%)	1135 (31.1%)
Hospitalized	38 (50.0%)	77 (41.4%)	220 (63.2%)	267 (89.6%)	741 (69.2%)	1343 (67.9%)	68 (22.1%)	177 (39.7%)	248 (31.4%)	45 (42.9%)	895 (44.7%)	1433 (39.3%)

COPD, chronic obstructive pulmonary disease; HRV, human rhinovirus; RSV, respiratory syncytial virus.

[a] Six participants infected by one of the specified pathogens were omitted because it is unknown whether their current medications include antibiotics.

[b] 11 participants infected by one of the specified pathogens were omitted because it is unknown whether their current medications include inhaled steroids.

[c] 10 participants infected by one of the specified pathogens were omitted because it is unknown whether their current medications include systemic steroids.

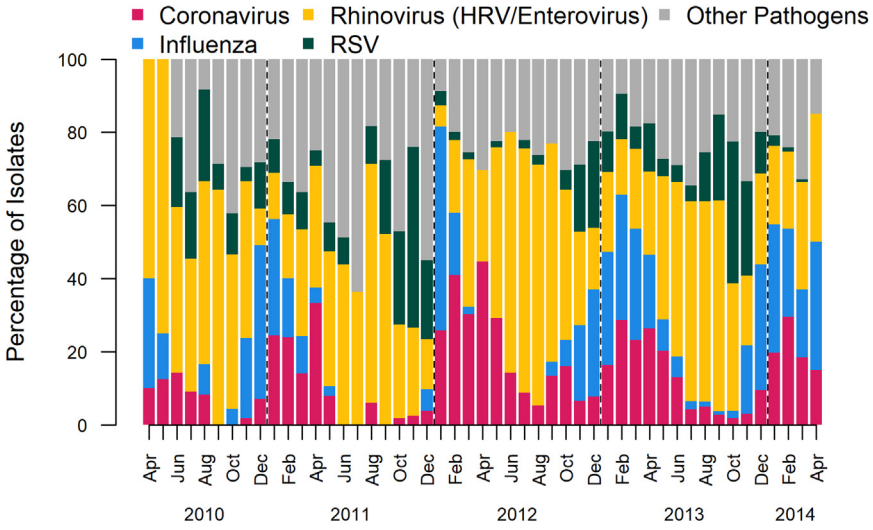

Figure 2. Monthly distribution of viral isolates for the most prevalent viruses (April 2010 to April 2014). RSV, respiratory syncytial virus.

cavirus, while 28.8% of co-infected participants required hospitalization. Among older adults (aged >59 years), 71.2% required hospitalization.

Among 5629 patients with pathogen results, 155 (2.8%) died. Older adults (aged >59 years) had the highest proportion of deaths (10.9%, N=61), and those infected with bocavirus, influenza, metapneumovirus, and RSV had mortality rates exceeding 10%. Adults (aged 19-59 years) had a proportion of deaths of 2.1% (N=65), and the largest number of deaths (N=9) occurred among those with the influenza A H1N1 subtype. Lastly, children had the lowest proportion of deaths (1.5%, N=29), with most deaths occurring among those positive for influenza. Of the participants who died, 45.2% had no pathogen identified, and 11.6% had coinfections (Table 2).

Elevated creatinine phosphokinase, creatinine, C-reactive protein, lactate dehydrogenase, neutrophil count, or white blood cell count, or lower hematocrit, hemoglobin, lymphocytes, or platelets were associated with higher mortality, as were prior use of systemic steroids or antiviral medications. Current or former smoking, cardiovascular disease, diabetes, or immunodeficiencies were associated with greater likelihood of death, whereas asthma was associated with lower mortality. Dyspnea, rales or crepitations, or fever were associated with higher odds of dying, while sore throat, wheezing, fatigue, headache, nausea, or red eyes were associated with lower mortality (Table 3).

Discussion

This study investigated the demographics, viral agents, outcomes, and seasonal variation in outcomes of patients with ILI, of whom almost half required hospitalization. Our data provide a standardized picture of ILI epidemiology, seasonality, and clinical presentation. HRV/enterovirus was the most common pathogen (17.6% children, 21.6% adults), followed by influenza virus, RSV, and coronavirus. Cinemre et al. [7] also reported HRV/enterovirus (23%), followed by influenza A or B virus (20.4%) and coronavirus (8.6%) as the most common causes in Turkey. In our cohort, influenza caused 11.2% of ILI cases and 30-50% of the cases during peak seasons, in accordance with previous reports [8].

HRV/enterovirus and coronavirus circulated all year, peaking in late spring (May, June) and early summer (June, July), while the RSV infection rate was lower in spring (March-June). Souty et al. [8] also found an HRV/enterovirus peak during spring and an RSV peak from late autumn to early winter. Influenza predominated during late autumn and winter (late September to late March). Different influenza subtypes' epidemiology throughout the years (A H3N2 and B in 2010 and 2012; A H1N1 in 2011 and 2013) is consistent with Tadesse et al. [9], who reported two peak seasons, during the last months of the year and from April to June. We observed only one peak of influenza during the last months of every year, and in 2013 the peak prolonged until early spring (March and April). Ye et al. [10] described that the seasonality of influenza may vary, especially after the A/H1N1 pandemic, finding peaks extending beyond the winter season. In China, influenza A/H3N2 had multiple peaks in some years. Similarly, our population experienced increased frequency of this subtype when winter peaks extended into spring. Symptoms differed by pathogen. Coronavirus infections displayed upper respiratory symptoms, while RSV infection showed lower respiratory symptoms. Rales and crepitations were common in RSV-infected children, while dyspnea was the most frequent symptom in adults. Influenza patients, particularly adults, experienced headache more often. Souty et al. [8] also associated cough, dyspnea, and absence of headache with RSV detection, while they associated headache with influenza. The most frequent signs and symptoms of HRV/enterovirus infection were fever and productive cough in children, and sore throat, fatigue, and headache in adults. This difference in the symptoms between children and adults has also been found in other studies [11]. Overall, participants with lower respiratory tract infection signs and symptoms (i.e., dyspnea, rales or crepitations) and elevated acute-phase reactants had increased mortality, while participants with upper respiratory tract symptoms or systemic symptoms (sore throat, fatigue, headache, nausea, or red eyes) showed lower risk.

It is noteworthy that 48.3% of the participants did not exhibit fever as part of their symptoms, as fever is commonly included in the definition of ILI in many studies [12]. Our findings suggest that a substantial proportion of respiratory infections do not necessarily manifest with fever, even those involving the need for hospitalization (22.5% of hospitalized patients did not have fever) (Table S3). Mandating fever as a prerequisite for ILI diagnosis would exclude a significant number of participants. Notably, the European Centre for Disease Prevention and Control definition aligns with this perspective, acknowledging that fever/feverishness need not be included as a mandatory criterion for ILI diagnosis [13].

In this hospital-based study, 49.3% of participants were hospitalized at baseline or during follow-up. Participants with RSV had the highest hospitalization rate (65.1%), in agreement with data that show RSV infection as a leading cause of hospitalizations in children worldwide [14], and as a common cause of hospitalization in older adults [15]. The link between RSV infection and hospitalization may decline in the future because of the introduction of a new vaccine in some countries, such as Mexico and the United States in 2023. This vaccine has been linked to reduced risk of lower respiratory tract disease in the < 1 and > 59 years population [16].

Older adults and those with health conditions such as cardiovascular disease, diabetes, or immunodeficiencies faced a higher risk of death.

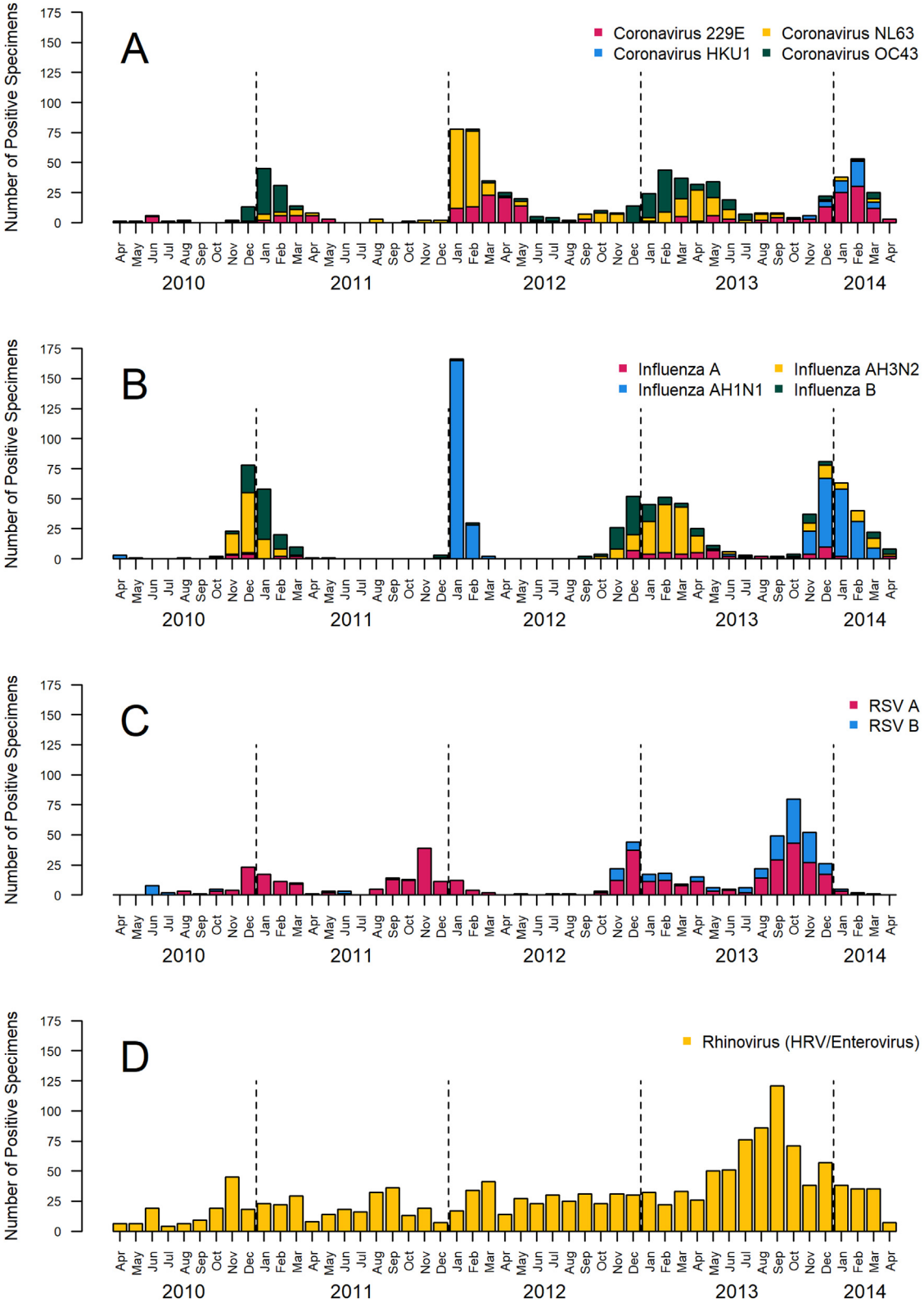

Figure 3. Distribution of viral isolates (April 2010 to April 2014). Monthly frequencies of observed virus subtypes are shown for coronavirus (a), influenza virus (b), respiratory syncytial virus (c), and rhinovirus (d). Co-infected individuals are counted multiple times, once for each virus subtype detected.
RSV, respiratory syncytial virus.

Table 2
Percentage of hospitalized or dead patients (N = 5629) with valid pathogen test, grouped by pathogen.

		Hospitalized n (%)				Death n (%)		
	Total	Age 0-18	Age 19-59	Age >59	Total	Age 0-18	Age 19-59	Age >59
Total	2776 (49.3)	1343 (67.9)	1035 (33.5)	398 (71.2)	155 (2.8)	29 (1.5)	65 (2.1)	61 (10.9)
Pathogen								
Adenovirus	62 (56.4)	36 (62.1)	21 (45.7)	5 (83.3)	2 (1.8)	1 (1.7)	1 (2.2)	0 (0.0)
Bocavirus	46 (65.7)	27 (73.0)	13 (48.1)	6 (100.0)	3 (4.3)	0 (0.0)	1 (3.7)	2 (33.3)
Bordetella pertussis	16 (76.2)	11 (100.0)	3 (42.9)	2 (66.7)	1 (4.8)	1 (9.1)	0 (0.0)	0 (0.0)
Chlamydophila pneumoniae	0 (0.0)	0 (0.0)	0 (0.0)	[a]	0 (0.0)	0 (0.0)	0 (0.0)	[a]
Coronavirus	106 (27.6)	38 (50.0)	48 (17.6)	20 (55.6)	8 (2.1)	1 (1.3)	5 (1.8)	2 (5.6)
Coronavirus 229E	33 (26.0)	10 (47.6)	19 (19.6)	4 (44.4)	3 (2.4)	1 (4.8)	2 (2.1)	0 (0.0)
Coronavirus HKU1	3 (13.6)	1 (50.0)	2 (10.0)	[a]	0 (0.0)	0 (0.0)	0 (0.0)	[a]
Coronavirus NL63	37 (32.5)	14 (53.8)	17 (21.8)	6 (60.0)	1 (0.9)	0 (0.0)	1 (1.3)	0 (0.0)
Coronavirus OC43	33 (27.3)	13 (48.1)	10 (13.0)	10 (58.8)	4 (3.3)	0 (0.0)	2 (2.6)	2 (11.8)
Influenza	254 (40.2)	77 (41.4)	147 (37.3)	30 (57.7)	20 (3.2)	5 (2.7)	9 (2.3)	6 (11.5)
Influenza A	16 (40.0)	5 (45.5)	9 (33.3)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Influenza A H1N1	125 (47.9)	38 (52.8)	79 (45.4)	8 (53.3)	16 (6.1)	4 (5.6)	9 (5.2)	3 (20.0)
Influenza A H3	74 (37.2)	18 (36.0)	42 (33.9)	14 (56.0)	3 (1.5)	1 (2.0)	0 (0.0)	2 (8.0)
Influenza B	39 (29.5)	16 (30.2)	17 (24.6)	6 (60.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (10.0)
Metapneumovirus	128 (64.6)	90 (78.9)	24 (35.3)	14 (87.5)	4 (2.0)	2 (1.8)	0 (0.0)	2 (12.5)
Mycoplasma pneumoniae	40 (71.4)	18 (81.8)	21 (63.6)	1 (100.0)	2 (3.6)	1 (4.5)	0 (0.0)	1 (100.0)
Parainfluenza virus (PIV)	127 (52.0)	83 (70.9)	29 (28.2)	15 (62.5)	1 (0.4)	1 (0.9)	0 (0.0)	0 (0.0)
PIV1	18 (48.6)	15 (75.0)	1 (7.7)	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PIV2	29 (54.7)	21 (70.0)	6 (31.6)	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PIV3	44 (51.2)	31 (73.8)	10 (25.6)	3 (60.0)	1 (1.2)	1 (2.4)	0 (0.0)	0 (0.0)
PIV4	36 (52.9)	16 (64.0)	12 (37.5)	8 (72.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinovirus (HRV/ enterovirus)	468 (41.1)	220 (63.2)	183 (26.6)	65 (64.4)	20 (1.8)	3 (0.9)	9 (1.3)	8 (7.9)
Respiratory syncytial virus (RSV)	312 (77.4)	267 (89.6)	26 (32.5)	19 (76.0)	6 (1.5)	3 (1.0)	0 (0.0)	3 (12.0)
RSVA	230 (77.4)	192 (88.9)	22 (36.1)	16 (80.0)	6 (2.0)	3 (1.4)	0 (0.0)	3 (15.0)
RSVB	82 (77.4)	75 (91.5)	4 (21.1)	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Co-infections	403 (49.3)	259 (69.6)	113 (28.4)	31 (66.0)	18 (2.2)	5 (1.3)	9 (2.3)	4 (8.5)
Negative Pathogen Cases	814 (52.4)	217 (64.0)	407 (41.9)	190 (78.5)	70 (4.5)	6 (1.8)	31 (3.2)	33 (13.6)

Percentages correspond to the proportion of participants who were hospitalized/dead among those who tested positive for the pathogen of interest within a particular age group.

[a] Neither *Chlamydophila pneumoniae* nor coronavirus HKU1 were detected in participants aged >59 years. *Legionella* infection was detected in no participant.

For the four frequent ILI causes, 30.5-50.5% of adult patients presented comorbidities, stressing the need for identifying severe disease risk factors. Asthma, chronic obstructive pulmonary disease, and immunocompromise have been associated with severe disease [17]. However, the fact that over half of the patients had no chronic condition highlights the importance of ILI as a cause of disease even in persons without comorbidity. Participants using systemic steroids before enrollment were more likely to have severe disease [18]. Other authors have also confirmed this relationship [19].

Among children having coronavirus infection (OC43, 229E, NL63, HKU1), 50% were hospitalized and 43.4% had chronic medical conditions that could have predisposed them to hospitalization. This hospitalization rate was lower than that reported by Heimdal et al. (60.7%) [20]. Only one child with coronavirus died, indicating that the observed coronavirus variants mainly cause mild disease in immunocompetent patients. In contrast, 40.2% of patients with influenza were hospitalized, with the rate varying across age groups and peaking in older adults [21]. Mortality rates were subtype-dependent, and influenza H1N1 caused the highest mortality rates among children and adults.

In this study, we used a multiplex PCR for detecting viral pathogens: 72.4% of participants had at least one pathogen identified, and 14.5% had co-infection. Hospitalization rates were high among children and older adults with coinfections (69.6% and 66.0%, respectively), and 2.2% of the participants with coinfections died. However, we did not find an association between the detection of two pathogens and higher hospitalization rates compared with single-pathogens infections [22]. Among all the participants, 27.6% did not have a pathogen detected. These findings may be due to bacterial infections (not included in the multiplex PCR assay used, RespiFinder-22®), new pathogens, or a need for better diagnostics to detect current pathogens.

Approximately 50% of participants with documented viral infections were prescribed antibiotics, demonstrating overuse. This rate is similar to that found by other ILI studies [23] and the Centers for Disease Control and Prevention in the United States, which estimates that up to 50% of prescribed antibiotics are unnecessary [24]. Despite molecular testing's potential to accurately diagnose disease [25], reports indicate continued antibiotic prescribing after viral confirmation, necessitating investigation into the role of viral diagnostics in preventing antibiotic overprescription and subsequent antimicrobial resistance [26].

The strengths of this study include prospectively enrolling and evaluating a large cohort, and offering insights into the epidemiological and clinical characteristics of adult and young patients with ILI in Mexico over several seasons. Limitations include exclusively enrolling hospital-seeking patients, potentially influencing hospitalization rates and disease severity. However, participant recruitment at triage allowed the recruitment of patients not requiring hospitalization, reducing potential bias. Another limitation common in observational studies are self-reported symptoms. However, this was complemented with evaluation of signs and laboratory tests. Thorax images (chest X-rays or computed tomography scans) could have further strengthened objective evaluation of respiratory symptoms, but the study lacked access to them. Nevertheless, we were able to analyze the associations between PCR-detected agents and symptoms of upper (sore throat, fatigue, headache, nausea, or red eyes) and lower (dyspnea, rales, crepitation) respiratory tract infection. Other limitations include not adjusting regression models for confounding variables, including age, sex, socioeconomic status, and comorbidities, which may introduce bias when assessing the association with death. Interpretation of these associations requires consideration of potential selection bias and the limited number of death outcomes.

Table 3
Unadjusted associations between mortality and clinical laboratory tests, medications, medical history, and symptoms.

		Patients who survived Median [Range] n = 5507	Patients who died Median [Range] n =155	Odds ratio Estimate (95% CI)	*P*-value
Laboratory Tests					
	Creatinine phosphokinase (U/L)	91.00 [1.00, 7784.00]	109.00 [10.00, 8450.00]	1.24 (1.16, 1.34)[a]	<0.001
	Creatinine (mg/dL)	0.66 [0.03, 38.96]	0.99 [0.10, 9.70]	1.23 (1.12, 1.36)	<0.001
	C-reactive protein (mg/l)	1.13 [0.00, 58.50]	12.10 [0.00, 35.96]	1.87 (1.68, 2.08)	<0.001
	Hematocrit (%)	41.90 [0.00, 92.40]	36.50 [13.20, 63.40]	0.54 (0.47, 0.63)	<0.001
	Hemoglobin (g/dL)	14.00 [4.10, 48.70]	12.20 [4.70, 20.10]	0.51 (0.44, 0.59)	<0.001
	Lactate dehydrogenase (U/L)	237.00 [17.00, 9549.00]	462.50 [31.00, 5175.00]	1.50 (1.35, 1.68)	<0.001
	Lymphocytes (%)	21.00 [0.00, 92.00]	8.00 [1.00, 62.00]	0.25 (0.18, 0.34)	<0.001
	Neutrophils (%)	67.00 [0.00, 99.00]	85.00 [10.00, 98.00]	2.98 (2.34, 3.80)	<0.001
	Platelets (10^9/L)	237.00 [0.00, 862.00]	184.00 [3.00, 551.00]	0.48 (0.39, 0.58)	<0.001
	White blood cell count (10^9/L)	8.30 [0.10, 57.40]	10.40 [0.30, 72.10]	1.36 (1.23, 1.52)	<0.001
		n (% of patients who survived)	**n (% of patients who died)**		
Medications					
	Any antiviral	874 (15.9%)	58 (37.4%)	3.17 (2.27, 4.42)	<0.001
	Inhaled steroids[b]	612 (11.1%)	16 (10.3%)	0.95 (0.56, 1.60)	0.838
	Systemic steroids[c]	1123 (20.4%)	57 (36.8%)	2.36 (1.69, 3.31)	<0.001
History					
	Current/former smoker[d]	1416 (25.7%)	60 (38.7%)	1.82 (1.31, 2.54)	<0.001
	Asthma	540 (9.8%)	4 (2.6%)	0.24 (0.09, 0.66)	0.005
	Cardiovascular disease	579 (10.5%)	41 (26.5%)	3.06 (2.12, 4.42)	<0.001
	COPD	135 (2.5%)	5 (3.2%)	1.33 (0.54, 3.29)	0.542
	Diabetes	130 (2.4%)	10 (6.5%)	2.85 (1.47, 5.54)	0.002
	Immunodeficiency	82 (1.5%)	6 (3.9%)	2.66 (1.14, 6.20)	0.023
	Renal disorder	57 (1.0%)	3 (1.9%)	1.89 (0.58, 6.09)	0.288
Respiratory Symptoms					
	Productive cough	3421 (62.1%)	95 (61.3%)	0.97 (0.70, 1.34)	0.834
	Dyspnea	1407 (25.5%)	82 (52.9%)	3.27 (2.37, 4.51)	<0.001
	Rales/crepitations	1791 (32.5%)	123 (79.4%)	7.98 (5.38, 11.81)	<0.001
	Sore throat	2778 (50.4%)	38 (24.5%)	0.32 (0.22, 0.46)	<0.001
	Wheezing	1152 (20.9%)	19 (12.3%)	0.53 (0.33, 0.86)	0.010
Non-Respiratory Symptoms					
	Diarrhea	521 (9.5%)	15 (9.7%)	1.03 (0.60, 1.76)	0.928
	Fatigue	3023 (54.9%)	70 (45.2%)	0.68 (0.49, 0.93)	0.017
	Fever	3632 (66.0%)	122 (78.7%)	1.91 (1.29, 2.81)	0.001
	Headache	2799 (50.8%)	40 (25.8%)	0.34 (0.23, 0.48)	<0.001
	Nausea	1282 (23.3%)	20 (12.9%)	0.49 (0.30, 0.78)	0.003
	Red eyes	1543 (28.0%)	10 (6.5%)	0.18 (0.09, 0.34)	<0.001

CI, confidence interval; COPD, chronic obstructive pulmonary disease.
[a] Estimates for laboratory tests show the odds ratios for a one standard deviation difference in each laboratory result.
[b] 11 participants were omitted because it is unknown whether their current medications include inhaled steroids.
[c] 10 participants were omitted because it is unknown whether their current medications include systemic steroids.
[d] The reference group for current or former smoker is non-smoker.

Our study generates relevant information on the characteristics and seasonality of the main viruses responsible for ILI in a Mexican population over 4 years. It may help promote future investigation of the epidemiology of these respiratory diseases that may lead to hospitalization in both patients with and without comorbidities. Our results support the fact that the circulating respiratory viruses impact the seasonal pattern, prevalence, and co-circulation of other viruses. The impact of different subtypes of influenza on each other [27], the interference of HRV/enterovirus with influenza A virus [28], and the interference between HRV/enterovirus and RSV [29] have been reported elsewhere. Our study emphasizes the importance of ongoing respiratory infection surveillance, especially post-SARS-CoV-2, because potential interactions and coinfections between SARS-CoV-2 and other viruses have been associated with increased morbidity and mortality [30].

Conclusion

The data set collected over 4 years provides valuable information about the prevalence of respiratory viruses and co-infection before the 2019 COVID-19 pandemic, which can help determine COVID-19–specific effects. This may influence future decision-making about public health policies regarding disease prevention (including vaccination), the administration of health resources, and areas for focus in future research.

Declarations of competing interest

Doctor Daniel E. Noyola reports a relationship with AbbVie Inc, Sanofi Pasteur, MSD, GSK, Pfizer, and AstraZeneca that includes speaking and lecture fees. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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Arturo Galindo-Fraga: Conceptualization, Funding acquisition, Writing – review & editing, Project administration. **Paola del Carmen Guerra-de-Blas:** Data curation, Writing – original draft. **Ana A. Ortiz-Hernández:** Investigation, Methodology. **Kevin Rubenstein:** Data curation, Formal analysis, Writing – original draft. **Ana M. Ortega-Villa:** Data curation, Formal analysis, Writing – original draft, Software. **Alejandra Ramírez-Venegas:** Investigation, Methodology, Validation. **Rafael Valdez-Vázquez:** Investigation, Methodology, Validation. **Sarbelio Moreno-Espinosa:** Conceptualization, Supervision, Writing – review & editing, Project administration. **Beatriz Llamosas-**

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Ethical approval

All the study protocol procedures were performed in compliance with relevant laws and institutional guidelines, and were evaluated and approved by the institutional review boards from each participating institution. These included the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (Date 26.01.2010; Ref 116), Instituto Nacional de Enfermedades Respiratorias (Date 16.03.2010; Ref C12-10), Hospital General Dr. Manuel Gea González (Date 23.06.210; Ref 36-50-2010), Instituto Nacional de Pediatría (Date 10.03.2010; Ref INP 014/2010), Hospital Infantil de México Federico Gómez (Date 06.12.2010; Ref HIM/2010/074), and Hospital Regional Dr. Ignacio Morones Prieto (Date 16.10.2012; Ref 88-12). All participants provided written informed consent. Parents or legal representatives provided consent for children, while assent was obtained for those aged >8 years. All procedures adhered to the World Medical Association's International Code of Medical Ethics (Declaration of Helsinki) for human experimentation and relevant laws/guidelines. The project is registered on ClinicalTrials.gov (NCT02378090).

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Data availability statement

The data presented in this study are publicly available at the following link: https://www.kaggle.com/datasets/arturogalindo/etiology-seasonality-outcomes-of-ili-in-mexico. In case the data are used, please cite the authors of this article and the third-party owner of the data set, the Mexican Emerging Infectious Diseases Clinical Research Network (LaRed).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2024.100394.

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