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Epidemiology and Burden of Influenza in Children 0–14 Years Over Ten Consecutive Seasons in Italy

Elisa Barbieri, PhD, PharmD, Gloria Porcu, MSc,†‡ Daniele Donà, PhD, MD,* Sara Cavagnis, MD,§ Luigi Cantarutti, MD,§ Antonio Scamarcia, MD,§ Ian McGovern, MPH,¶ Mendel Haag, PhD, PharmD,‖ Carlo Giaquinto, MD,*§ and Anna Cantarutti, PhD†‡*

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Background: In Europe, influenza vaccination coverage in the pediatric population is low. This study describes the influenza incidence and associated healthcare utilization in the pediatric population in Italy.

Methods: Deidentified data from electronic medical records for children 0–14 years old seen by >150 family pediatricians in the Pedianet network in Italy were evaluated for 10 influenza seasons spanning 2010–2020. Incidence of influenza (cases per 1000 person-months), related sequelae and associated healthcare resource use were determined using diagnostic, prescription and medical examination data.

Results: Over 10 seasons, an average of 8892 influenza cases (range, 4700–12,419; total 88,921) were diagnosed in a cohort of 1,432,384 children 0–14 years of age. Influenza vaccination coverage was 3.6% among children with an influenza diagnosis and 6.8% among children without. Influenza-related healthcare resource utilization included 1.58 family pediatrician visits per influenza episode and 220 ED and 111 hospital admissions, with the highest resource usage among children 1–4 years and lowest among children <6 months old. The most common influenza complications were acute otitis media (2.9% of influenza cases) and pneumonia (0.5%). Antibiotics were prescribed in 38.7% of influenza cases; no antiviral agents were prescribed. One intensive care unit admission and 2 cases requiring ventilatory support were documented. No influenza-related deaths were reported.

Conclusion: Pediatric influenza vaccination was low despite the burden and healthcare use related to seasonal influenza in the pediatric population during a 10-year period in Italy.

Key Words: influenza, children, influenza epidemiology, pediatric burden

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From the *Division of Pediatric Infectious Diseases, Department for Women's and Children's Health, University of Padua, Padua, Italy; †Unit of Biostatistics, Epidemiology and Public Health; ‡National Centre for Healthcare Research and Pharmacoepidemiology, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy; §Società Servizi Telematici (SoSeTe), Pedianet Project, Padova, Italy; ¶Seqirus USA Inc., Cambridge, Massachusetts; and ‖Seqirus Netherlands BV, Amsterdam, The Netherlands.

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Address for correspondence: Gloria Porcu, MSc, Unit of Biostatistics, Epidemiology and Public Health, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Via Bicocca degli Arcimboldi, 8 (Building U7), 20126 Milano, Italy. E-mail: gloria.porcu@unimib.it.

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Each year, seasonal influenza causes up to a billion infections worldwide, up to 5 million severe cases, and approximately half a million deaths.[1] Approximately 10% of seasonal influenza infections occur in children younger than 5 years, with an associated 870,000 hospitalizations globally.[2] Although the rates of pediatric morbidity and mortality are low compared to older adults, children younger than 2 years, who have immature immune systems, are at high risk of influenza infections.[3] Moreover, prolonged viral shedding in children increases the risk of transmission to vulnerable family members.[4,5] The burden of pediatric influenza imposes significant costs to individuals and society, including direct medical expenditures and indirect costs due to lost productivity from parents who must care for sick children and who may also contract influenza from these children.[6,7]

Vaccinating children and adolescents protects not only the children themselves but also interrupts community transmission of influenza.[8,9] However, vaccine coverage for children has been historically low in Europe.[10,11] Prior to the coronavirus disease 2019 pandemic, vaccination rates in Italy were <5% for children ≤8 years of age, and although coverage increased significantly after free influenza vaccines for this age group were authorized, >80% of Italian children were not vaccinated against influenza in 2020–2021.[11]

To assess the burden of influenza among a pediatric population in Italy, we conducted a retrospective, observational study of influenza diagnoses and influenza-related healthcare utilization among Italian children ≤14 years of age.

MATERIALS AND METHODS

Study Design

This study was a noninterventional, retrospective cohort study that evaluated influenza burden and healthcare utilization in children 0–14 years old between August 1, 2010 and January 31, 2020 in Italy. This study was designed, implemented and reported in accordance with Good Pharmacoepidemiological Practice, applicable local regulations and the ethical principles laid down in the Declaration of Helsinki. This study used an anonymized database for which informed written consent was requested from the children's parents or legal guardians for data collection. Centralized, anonymized data were analyzed by data custodians; therefore, approval by an institutional review board was not necessary.

Data Source and Linkages

Data were from anonymized electronic medical records from the Pedianet network in Italy. This network includes >150 family pediatricians (FP) and has an established record of providing data for epidemiologic research.[12] The database included demographic, clinical and prescription information. A full linkage to hospital records providing information on intensive care unit and ventilation support was available only for the Veneto region for the period between January 1, 2017 and January 31, 2020. Data on all

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other ED and hospital admissions, procedures and discharge dates were obtained from FP records.

Study Population

The study included all children enrolled in Pedianet from birth through age 14 years during the study period. Age group categories [0 to <6 months, 6–12 months, 12–59 months (1–4 years), 60–119 months (5–9 years), 120–179 months (10–14 years)] were determined based on the child's age on October 1 of each year. If a child was born during the season, the child was included in the season from the time of registration in the Pedianet database. Exclusion criteria included missing data on age or sex, fewer than 2 visits registered by the FP (except for infants <1 year of age), and <12 months of follow-up prior to the influenza season (except for infants <1 year of age) to document chronic comorbid conditions considered risk factors for influenza or its complications. These included cardiovascular, gastroenterologic, hematologic, metabolic, neurologic, renal and respiratory diseases as well as immunosuppressive disorders or therapies and diseases associated with aspirin therapy.

Observation Periods

Each influenza season was defined as a fixed period from October 1 to April 30, except the 2019–2020 influenza season, which was truncated at January 31, 2020, due to the start of the coronavirus disease 2019 pandemic. The baseline period used to define chronic comorbid conditions comprised the 12 months (October 1–September 30) preceding each influenza season. A 30-day observation period from the influenza index date (ie, date of influenza diagnosis) was used for the analysis of influenza-related healthcare resource utilization, treatment and complications. The latest date for this observation period was up to and including March 1, 2020. Outcomes related to in-hospital events were evaluated from January 1, 2017 to January 31, 2020.

Outcome Ascertainment

The primary outcome for the study was influenza episode, identified through outpatient or inpatient records of FP visits, ED visits and hospital admissions during each influenza season. Influenza episodes and complications were identified using International Classification of Diseases 9th Edition, Clinical Modification (ICD-9-CM) codes (Table, Supplemental Digital Contents 1 and 2, http://links.lww.com/INF/F233) and a free text string developed by an expert clinical data manager (in Italian, *nflue*). Hospital admission due to influenza was analyzed based on any first event of hospitalization for a given subject in a season.

The study was descriptive in nature. All analyses were conducted by season. Characteristics were described overall and separately for those experiencing (cases) and not experiencing (control) influenza in each season. All descriptive and regression analyses were conducted for the overall population (age 0–14 years) and separately by age groups (0 to <6 months, 6–12 months, 12–59 months, 60–119 months, 120–179 months) and by risk groups. Subjects with more than 1 type of risk factor could contribute data to multiple risk groups. In addition, a stratified analysis was conducted based on the number of risk factors (0, 1 or ≥2).

For each season, the cumulative incidence rate and respective 95% confidence interval (CI) were calculated by dividing the number of new first incident cases during the seasonal follow-up period by the source population's follow-up period and expressed as person-months. Only the first events were counted per subject. Incidence was estimated based on person-month to reduce underestimation in infants born during the influenza season. If a subject died or was transferred out of the dataset, the associated person-time was right-truncated.

Multivariate logistic regression was fitted for investigating the association between gender, age group and risk groups and in a separate model by the number of risk factors and the odds of experiencing the first diagnosis of influenza.

RESULTS

Study Population and Influenza Cases

Over the 10 influenza seasons between 2010 and 2020, 1,496,931 children 0–14 years old were enrolled in the study. After exclusions based on lack of information on age or sex or less than 12 months of follow-up, the final cohort included a total of 1,432,384 children who experienced a total of 88,921 episodes of influenza, that is, an average of 8892 influenza cases per season (range, 4700 in 2019–2020 to 12,419 in 2010–2011). The prevalence of influenza (number of cases/number of children) ranged from 3.4% in 2013–2014 to 8.6% in 2010–2011 (Table 1).

Across all influenza seasons, the average age of the study population was ~6 years, and 52% of the population were male (Table, Supplemental Digital Content 3, http://links.lww.com/INF/F233). Approximately 40% of cases across the 10 seasons were

TABLE 1. Study Population Disposition and Numbers of Documented Influenza Cases

	Children 0–14 Years Old (N)				Influenza Cases (N)			
		Exclusions				Exclusions		
Influenza Season	Enrolled	Sex Not Recorded	<12 Months Follow-up*	Final Cohort	ILIs	Test Negative	<30 Days Follow-up	Final Cases, n (%)
2010–2011	148,882	−2	−5199	143,681	13,031	−25	−587	12,419 (8.6)
2011–2012	151,640	−3†	−5153	146,484	8501	−25	−358	8118 (5.5)
2012–2013	153,391	−1	−4925	148,465	12,624	−29	−538	12,057 (8.1)
2013–2014	154,389	−1	−5031	149,357	5314	−12	−172	5130 (3.4)
2014–2015	154,619	−1	−5320	149,298	10,445	−54	−424	9967 (6.7)
2015–2016	153,063	−1	−6029	147,033	11,133	−22	−394	10,717 (7.3)
2016–2017	155,328	−1	−11,230	144,097	7138	−5	−225	6908 (4.8)
2017–2018	149,641	−1	−10,809	138,831	11,266	−17	−525	10,724 (7.7)
2018–2019	142,526	−1	−5830	136,695	8537	−6	−350	8181 (6.0)
2019–2020	133,452	0	−5009	128,443	4847	−10	−137	4700 (3.7)

*For children >12 months of age.
†Includes 1 child excluded due to no recorded birth date and 2 excluded for lack of information on sex.
ILI indicates influenza-like illness.

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documented in the Veneto region, which may be due to a higher proportion of FP enrollment in Pedianet. Baseline characteristics were compared between children who had an influenza episode (influenza cases) and those who did not (controls). More children with an influenza episode (74.1%; range, 67.8%–83.5%) than controls (57.5%; range, 52.3%–72.1%) visited their FP in the previous 12 months. Use of prescription medication during the previous 12 months was higher among influenza cases (74% vs. 55% of controls). Rates of prior hospitalizations were similar between the influenza cases (0.52%) and controls (0.41%). Low-income exemptions, which were reported for the 2014–2015 through the 2019–2020 season, applied to approximately 7% (range, 1.4%–12.5%) of cases and controls (Table, Supplemental Digital Content 3, http://links.lww.com/INF/F233).

Most children were healthy without previous comorbidities. During the 201–-2011, 2012–2013, 2014–2015 and 2015–2016 seasons, significantly more children with influenza had experienced a previous respiratory condition versus control group children, whereas there were no significant differences in prior respiratory illnesses in the other seasons. Rates were ≤1% in all comparison groups across all 10 seasons (Table, Supplemental Digital Content 3, http://links.lww.com/INF/F233). In each season, influenza vaccine coverage was lower among children who had an influenza episode (3.6%; range, 2.1%–5.1%) compared to children who did not (6.8%; range, 5.4%–8.9%).

Incidence of Influenza Infections

Overall, the incidence of influenza ranged from 5.1 to 13.0 episodes per 1000 person-months. In age subgroups, the highest rates were observed among children 1–4 years of age and the lowest among infants 6 months or younger (Fig. 1). The rates were similar between male and female subjects (Figure, Supplemental Digital Content 4, http://links.lww.com/INF/F233). Over most seasons, the incidence of influenza was 1.2 to 2.5 times higher among children with ≥2 risk factors than children with no risk factors, although CIs overlapped (Figure, Supplemental Digital Content 5, http://links.lww.com/INF/F233).

A total of 446 rapid influenza tests and 62 polymerase chain reaction (PCR) tests were performed. Of these, 63 rapid tests (15.5%) and 1 PCR (1.6%) were positive.

When the risk of influenza infection was evaluated across age groups and seasons, children 6–12 months and 1–4 years of age had the highest risk of influenza infection over the 10-year period compared with children <6 months of age, who had the lowest influenza incidence and served as the reference group (Fig. 2). In general, the risk was higher in the 2010–2011 season for all age classes.

When the risk of influenza was examined according to influenza risk factors, no significant associations between risk factors and influenza infection were found due to small numbers of at-risk children, which led to wide CIs and/or an inability to define odds ratios (Figure, Supplemental Digital Content 6, http://links.lww.com/INF/F233).

Influenza-Associated Medical Visits and Hospitalizations

As shown in Table 2, over the 10 seasons studied, there were 1.58 FP visits per episode of influenza. The frequency of FP visits decreased with increasing age, from 2.08 among infants <6 months to 1.4 visits among children 10–14 years old ($P < 0.001$). Children with ≥2 risk factors visited a FP an average of 2.07 times per episode compared with 1.57 visits per episode for children with no risk factors ($P < 0.001$). Children with respiratory and neurologic conditions had significantly higher frequencies of visits per episode than children with no risk factors (Table 2).

Over the 10 seasons, a total of 220 ED visits and 111 hospitalizations were identified from FP records in association with the 88,921 influenza cases. The average hospital stay was approximately 4.7 days, with no significant differences between age groups. In the 62 cases in which time to hospitalization was documented, an average of 7.8 days passed between FP visit and hospital admission overall, although in the 6–12 month and 10–14 years age groups, the average time-to-hospitalization was 3.4 days.

In the Veneto region between 2017 and 2020, 127 ED visits and 15 hospitalizations of 12,146 influenza episodes were reported. The highest rate of Veneto ED visits (0.4 per influenza episode) was documented among infants 6–12 months old. Of the 15 hospitalizations, 1 hospitalized child was admitted to the intensive care unit, and 2 additional children required external noninvasive ventilation support. No other intensive care interventions were reported.

The rate of influenza-associated hospitalizations and the prevalence of risk factors in the study population were too low to estimate associations between influenza risk factors and influenza hospitalization. No deaths due to influenza or its complications were reported.

Influenza-Associated Medical Care

Overall, in 45% of influenza episodes, the child received medical treatment. Significantly more medications were prescribed to male children, younger children, those with ≥2 risk factors, and those with cardiovascular, respiratory, neurologic and metabolic conditions as well as diseases associated with aspirin therapy (Table 2). Antibiotics were prescribed to 38.7% of children overall and were more commonly prescribed to younger than older children (0 to <6 months, 49.2%; 6–12 months, 49.1%; 1–4 years, 44.0%; 5–9 years, 34.3% and 10–14 years, 32.4%; $P < 0.001$ for age group differences). Nebulized corticosteroids were prescribed in 12.3% of cases overall and were also more frequently given to younger than older children (0 to <6 months, 16.7%; 6–12 months, 15.4%; 1–4 years, 12.6%; 5–9 years, 12.0% and 10–14 years, 11.5%; $P < 0.001$ for age group differences). No children were prescribed antivirals.

In the Veneto region, oxygen saturation measurement was performed in 30% of the 127 ED cases reported, and blood exams were performed in 15% of these cases. PCR exams and chest radiographs were performed in <0.01% of cases.

Influenza Complications of Interest

Complications occurring within 30 days of follow-up after the influenza index date were evaluated in 84,745 influenza episodes. The most common complications were acute otitis media (AOM), pneumonia and acute sinusitis (Table 3). AOM and pneumonia mainly affected children 1–4 years of age with no previous risk factors. Acute sinusitis was more prevalent in children 5–9 years old.

Febrile convulsions were evaluated in 55,228 influenza episodes occurring in children 6 months to 6 years of age with no previous neurologic conditions; 30 cases were reported (0.54 per 1000 influenza cases), 28 of which occurred in the 1–4 years age group (Table 3). Asthma, dehydration and myositis were uncommon (<0.3 per 1000 influenza cases) and neurologic and cardiovascular exacerbations and the need for ventilation were rare (≤0.02 per 1000 influenza cases). No cases of myocarditis or deaths were reported (Table 3).

DISCUSSION

In this retrospective, observational study of influenza in 1,496,931 children ≤14 years of age, we found a total of 88,921 influenza cases over 10 seasons between 2010 and 2020 in Italy, with the highest incidence reported in children 1–4 years old and

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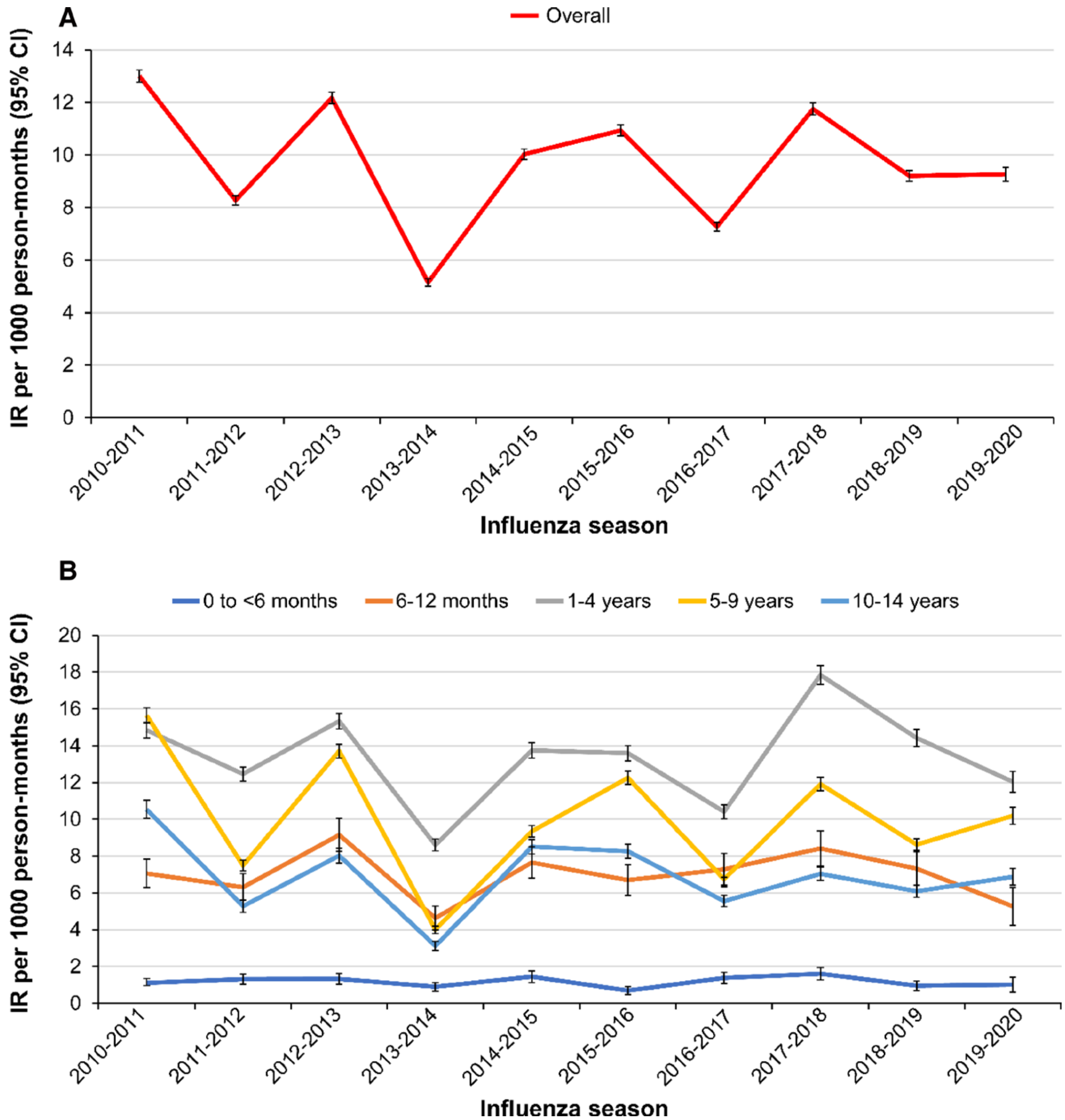

FIGURE 1. Incidence rates (IR) of influenza episodes in children 0–14 years old during Northern Hemisphere influenza seasons between 2010 and 2020 (data source: Pedianet, Italy). Error bars represent 95% confidence intervals (CI). A: Overall population. B: Age subgroups.

the lowest among children <6 months of age. Over this 10-year period, 3.6% children diagnosed with influenza and 6.8% of those without influenza had been vaccinated against influenza. The most common influenza complications were AOM and pneumonia, reported for 2.9% and 0.5% of influenza cases, respectively. Notably, 38.7% of children diagnosed with influenza received antibiotic therapy, while none received antiviral therapy.

Previous studies of pediatric burden in Italy found rates of influenza-associated AOM of 10.8% to 13.9% and pneumonia rates of 0.4% to 8.1%, compared to 2.9% and 0.5% found in our study.[7,13,14] Our study found few cases of severe influenza or complications in this pediatric population, which is consistent with other reports.[7,13,14] Nevertheless, each influenza case was associated with ≥1 FP visit, suggesting a high burden in terms of both direct medical costs and indirect costs such as lost work time for parents.

A strength of our study was the use of the Pedianet database, which allowed us to study a very large population-based cohort and included data on sociodemographic characteristics, clinical

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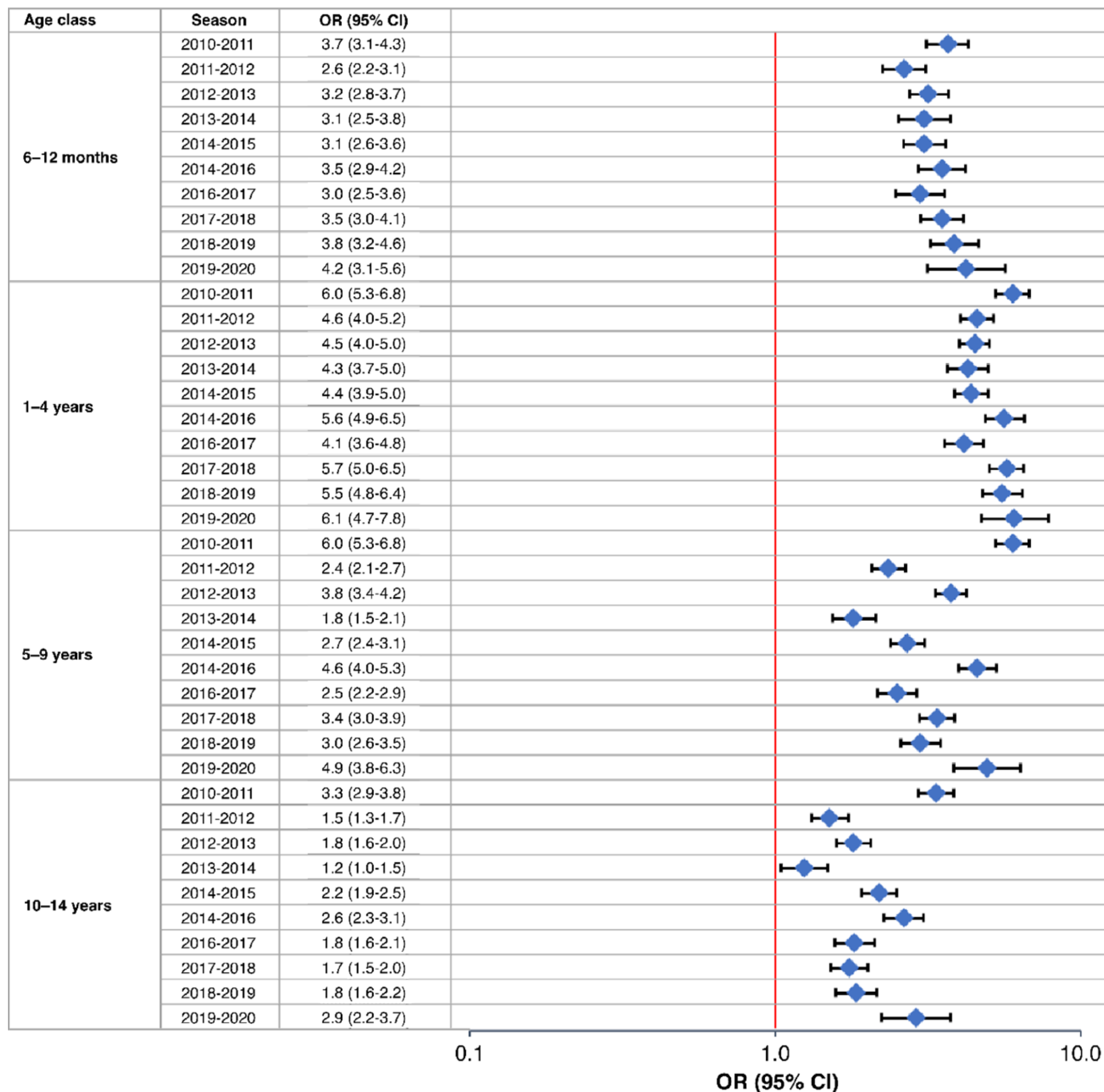

FIGURE 2. Odds ratios (OR) of influenza infection by age category compared with the 0 to <6-month age group (OR = 1, red line) in each Northern Hemisphere influenza season between 2010 and 2020 (data source: Pedianet, Italy). Diamond, OR point estimate; whiskers, 95% confidence interval (CI).

information and medicine utilization, to evaluate the burden of influenza and related complications. Moreover, we applied an algorithm on the clinical note-free text based on European Centre for Disease Prevention and Control (ECDC) influenza-like illness (ILI) definition to reduce misclassification.

The main limitation of this study was the lack of laboratory confirmation of the influenza cases. Influenza cases were determined based on physician diagnoses of influenza following clinical evaluation of signs and symptoms, which is a subjective assessment. Relatively few of the study patients were tested for influenza and among those that were tested only 16% of the antigen tests and 1.6% of the PCR tests performed were positive. Because influenza testing was not routinely performed, the ILI symptoms patients experienced could also have been caused by other respiratory viruses such as respiratory syncytial virus, adenovirus, rhinovirus and others. We partially addressed this limitation in case selection by applying an algorithm based on ECDC ILI criteria to the dataset and by excluding patients that tested negative for influenza. Another study found that ECDC ILI definition had only moderate sensitivity (57%) and specificity (49%) among children 5–14 years old.[15] Although there is a possibility for misclassification based on clinical diagnoses, the highest incidence observed in this study (8.6%) was actually still well below attack rates for lab-confirmed influenza observed in the placebo arms of some pediatric

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TABLE 2. FP Visits and Prescription Medication Usage Among Children 0–14 Years Old Over 10 Northern Hemisphere Influenza Seasons 2010–2020 (Data Source: Pedianet, Italy)

	FP Visits		Prescription Medications	
	Mean (SD)	*P* value	Mean (SD)	*P* value
Overall (n = 88,921)	1.58 (0.93)		0.79 (1.14)	
Sex				
Female (n = 42,682)	1.57 (0.92)	0.155	0.78 (1.12)	**<0.001**
Male (n = 46,239)	1.57 (0.92)		0.81 (1.16)	
Age category				
0 to <6 months (n = 659)	2.08 (1.21)	**<0.001**	0.96 (1.18)	**<0.001**
6–12 months (n = 2657)	1.93 (1.19)		0.93 (1.14)	
1–4 years (n = 38,330)	1.68 (1.00)		0.88 (1.18)	
5–9 years (n = 34,010)	1.49 (0.83)		0.72 (1.11)	
10–14 years (n = 13,265)	1.40 (0.76)		0.67 (1.06)	
Number of risk factors				
None (n = 87,222)	1.57 (0.92)	**<0.001**	0.79 (1.13)	**<0.001**
1 (n = 1644)	1.77 (1.10)		1.09 (1.48)	
≥2 (n = 55)	2.07 (1.33)		1.18 (1.40)	
Risk factors				
Cardiovascular	1.76 (1.20)	0.818	0.86 (1.31)	**0.006**
Respiratory	1.70 (1.08)	**0.009**	1.35 (1.69)	**<0.001**
Immunosuppressive disorders or therapies	1.85 (1.12)	0.568	1.03 (1.40)	0.670
Neurological	1.91 (1.18)	**0.004**	0.94 (1.23)	**0.011**
Renal	1.71 (0.99)	0.788	1.06 (0.97)	0.920
Diseases associated with aspirin therapy	1.75 (1.00)	0.877	0.68 (1.01)	**0.038**
Gastroenterological	1.64 (1.34)	0.648	0.79 (0.80)	0.433
Hematologic	1.00 (NA)	0.485	0.00 (NA)	0.460
Metabolic	1.94 (1.02)	0.086	0.73 (1.10)	**0.005**

FP indicates family pediatricians; NA, not applicable; SD, standard deviation.
Statistically significant differences between age or risk factor groups are highlighted with bold *P* values.

TABLE 3. Influenza Complications of Interest Reported Within 30 Days of Follow-up After Influenza Index Date

		Age Group Distribution*				
Complication, n (%)	Overall (n = 84,745)	0 to <6 Months	6–12 Months	1–4 Years	5–9 Years	10–14 Years
Acute otitis media	2527 (2.982)	23 (0.91)	123 (4.87)	1595 (63.12)	68 (2.69)	118 (4.67)
Pneumonia	412 (0.486)	2 (0.49)	17 (4.13)	243 (58.98)	109 (26.46)	41 (9.95)
Acute sinusitis	334 (0.394)	0	4 (1.20)	97 (29.04)	141 (42.22)	92 (27.54)
Febrile convulsion†	30 (0.054)	0	1 (3.33)	28 (93.33)	1 (3.33)	0
Asthma	24 (0.028)	0	0	10 (41.67)	10 (41.67)	4 (16.67)
Dehydration	22 (0.026)	0	1 (4.55)	14 (63.64)	6 (27.27)	1 (4.55)
Myositis	18 (0.021)	0	0	4 (22.22)	13 (72.22)	1 (5.56)
Neurological exacerbation	2 (0.002)	0	0	0	1 (50.00)	1 (50.00)
Need for ventilation	2 (0.002)	0	1 (50.00)	1 (50.00)	0	0
Cardiovascular exacerbation	1 (0.001)	0	1 (100.00)	0	0	0
Myocarditis	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

*Denominator = number of cases of each complication.
†Evaluated based on 55,228 influenza episodes occurring within 30 days of follow-up after the influenza index date in children 6 months to 6 years of age.

influenza vaccine efficacy clinical trials (eg, 16.2%), suggesting the rates observed in this study could actually be an underestimation of the true burden of influenza.[16] The lower sensitivity/specificity of influenza diagnoses (relative to use of laboratory testing) may have reduced the accuracy of our assessment of seasonal variation in the influenza epidemiology and the associated complications and healthcare resource use as the relative contribution of other respiratory viruses may vary from season to season.

Another limitation of this study design lies in its retrospective nature. It should not be excluded that at least a few influenza cases were seen in an ED without being reported to the FPs whose records provided the bulk of data for this study. However, such visits may be expected to have been identified because a follow-up examination by the FP is almost always recommended after ED discharge, especially for younger children. Moreover, according to the sub-analysis using the Veneto region data, where there is a direct linkage with ED and hospitalization databases, the number of cases that were seen only in the ED and not followed by a FP was 0.3% of overall cases, while hospitalizations accounted 0.09% of overall cases. Finally, the analysis of healthcare resource utilization was based on prescriptions and not on pharmacy dispensations; thus, it was not possible to assess the real-use of the healthcare resources.

In conclusion, our findings from this 10-year study in Italy demonstrate that influenza among children 0–14 years old represents a significant burden for sick patients and their families as well as for society, in terms of healthcare resource use. Vaccination of children may limit the spread of influenza to parents and, especially, grandparents who may be at high risk of influenza complications.[17–20] Vaccination rates in this study population were low, but another recent study found that vaccination rates in Italy

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more than doubled (reaching 19% for children 2–4 years of age) during the 2020–2021 season, when Italian authorities authorized extended free seasonal influenza vaccination to healthy children 6 months to 6 years old.[11] There are multiple factors that can impact influenza vaccine coverage, including providing free vaccines, perception of vaccine effectiveness or the severity of influenza, and recommendations from healthcare workers.[21] The most recent systematic assessment of influenza vaccine coverage, recommendations and reimbursement in the European Union/European Economic Area (EU/EEA), was conducted in 2018 and found that only 6 of 30 EU/EEA member states recommended vaccination for children and only 3 paid for both the vaccine and its administration.[22] Influenza vaccine coverage data is not widely available for Europe, but 2018 data from the World Health Organization shows that many European countries have similar coverage rates as observed in this study (below 10%).[10] The recent experience in Italy demonstrates that policy changes to recommend and provide free influenza vaccines to children have the ability to substantially increase vaccine coverage. Increased vaccination is the most effective method of reducing the burden of influenza, and children are 1 of the most vulnerable groups for influenza and a key group to target for vaccination as recommended by the World Health Organization.[23] These findings help reinforce high burden of influenza and the need for vaccination among children, not just in Italy, but globally.

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