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The incidence, natural history and associated outcomes of influenza-like illness and clinical influenza in Italy

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Objectives. This study investigated the epidemiology, natural history and resource use associated with influenza in the general population setting in Italy.

Methods. For a 3-month winter epidemic period, 202 GPs reported daily the number of visits performed for influenza-like illness (ILI), clinical influenza and any other cause. In addition, the first 10 cases of clinical influenza requiring a doctor's visit in each month of the 3-month period and for a total of 30 cases per GP were recorded carefully and followed-up, for evaluation of clinical evolution, associated outcomes and resource use.

Results. Almost 200 000 visits were performed by 202 GPs, ILI and clinical influenza accounting for 13.8 and 8.3% of all-cause visits, respectively. A total of 6057 cases of clinical influenza were also recorded and evaluated for associated outcomes and resource use. Twenty percent of the patients were at risk because they were elderly (>65 years) or presented with concomitant chronic conditions. Almost all the patients received at least one prescription for symptomatic drugs and 36% received a prescription for antibiotics. Thirty-five percent of patients had at least one complication from influenza, primarily upper and lower respiratory tract bacterial infections. At-risk patients had a significantly higher complication rate (odds ratio = 2.89) and required more instrumental exams and hospitalizations compared with the general population, accounting for most of the direct costs associated with clinical influenza. Patients with clinical influenza had an average of 5 days absence from work or school.

Conclusions. Influenza is associated with significant morbidity in the general and at-risk population, a high degree of resource use in the at-risk population and substantial reduction or loss of productivity in the active working Italian population.

Keywords. General practice, health care, influenza.

Introduction

The social and economic impact of influenza has been documented extensively.[1] In the active working population, influenza epidemics are associated with substantial loss of productivity and with health care resource utilization even in a non-epidemic year in the USA.[2] Among elderly patients, or patients with concomitant chronic cardiac, respiratory, renal or metabolic diseases, annual influenza epidemics are associated with increased morbidity and hospitalization rates, and excess mortality.[3] During a typical epidemic year, it is estimated that 10 000–40 000 deaths caused by influenza and an average of 130 000–170 000 influenza-associated hospitalizations occur annually in the USA, respiratory infective complications being the leading cause of influenza-associated excess mortality and hospitalization.[4,5]

Few data are available about the epidemiology, natural history, resource utilization and outcomes associated with influenza in Italy, despite the fact that influenza is recognized as the third leading cause of mortality from infectious diseases in Italy, after AIDS and tuberculosis.[6] The only available study completed to date reports that during the epidemic year 1989/1990, influenza was associated with 32 excess hospitalizations and 22.4 excess

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deaths per 100 000 population compared with a non-epidemic year in the Italian province of Siena.[7] During epidemic years, influenza is associated with considerable expense, mostly attributable to indirect costs for reduced or lost productivity in the active working population. However, no recent data are available on the detailed resource use associated with influenza, the general practice excess workload and diagnostic and therapeutic paths of patients with a diagnosis of influenza during a typical epidemic year in Italy.

Methods

Design
A total of 202 GPs of the Italian College of General Practitioners (SIMG), equally distributed between one northern and one southern Italian region (Lombardy and Puglia, respectively), participated in the 606 study (606 is the acronym for Studio Epidemiologico sull' Incidenza e gli Outcomes della Sindrome influenzale e Influenza (SEI O SEI, i.e the Italian for the number 606). From December 15th 1998 to March 15th 1999, participating GPs recorded daily the number of visits performed (both at home and in the surgery) for clinical influenza, influenza-like illness (ILI) and any other cause. Each GP was supplied with data record forms for each enrolled patient. The record forms were kept in the doctor's bag for use both at the surgery and at patients' homes. At the end of each month of study, the record forms were filed for subsequent analysis.

Outcome measures
In addition, for each of the 3 months of the observation period, the first 10 cases of clinical influenza which occurred were registered and followed-up by each of the 202 GPs for demographic, clinical and outcome data collection. Data recorded included patient age, sex and work, details of concurrent diseases and of clinical influenza symptoms and diagnosis, date of the visit and date of onset of clinical influenza symptoms, vaccination, medications prescribed and taken, frequency and type of complications, work or school days lost, further visits required (both primary care and specialist visits), incidental first aid access or hospitalizations and diagnostic investigations required.

Clinical influenza and ILI
For the purpose of the study, clinical influenza was defined as a syndrome characterized by the concurrent presence of fever (body temperature >38°C for two consecutive days), at least one systemic symptom from among myalgia/arthralgia, malaise, headache, feverishness and asthenia, and at least one respiratory symptom from among cough, nasal congestion/rhinorrhea and sore throat. ILI was defined as any acute respiratory illness characterized by one or more, but not all, of these symptoms.

Results

During the observation period that included the winter 1998/1999 influenza epidemic period, a total of 197 437 visits were made by 202 GPs. The number of patients per physician ranged from 550 to 1824, with an average of 1367, consistent with the national average, for a cumulative observed population of 276 000.

Table 1 reports the distribution over time of both ILI and clinical influenza frequencies. As expected, ILI frequency remained stable during the observation period, while clinical influenza frequency peaked during the second half of February to decrease steadily thereafter according to a typical epidemic trend. ILI and clinical influenza accounted for 13.8 and 8.3%, respectively of all-cause visits. All in all, ILI and clinical influenza accounted for 22.1% of all-cause visits of the winter epidemic period.

A total of 6192 cases (an average of 31 per GP) of clinical influenza were recorded; each data record form had 62 items to be completed. A quality control procedure was adopted so that record forms with >5% of missing data were excluded. A total of 135 cases were excluded from the analysis, because either data were missing or patients were younger than 10 years (Figure 1). These patients are in fact usually seen by family paediatricians and their inclusion could have led to a biased interpretation of the distribution by age of clinical influenza attack rate distribution by age. In all, 6057 cases were evaluated for clinical presentation and evolution, associated outcomes and resource use.

Demographics
Figure 1 also reports demographics of the patients included in the analysis. Average age was 40 years. As expected, clinical influenza peaks in the younger decades of age and steadily decreases with age, probably because of the progressively growing immune memory of the older population for influenza viral strains already circulated in the past. The comparatively low incidence

TABLE 1 *Frequency of influenza-like illness (ILI) and clinical influenza (I)*

Period	Visits (*n*)	ILI (%)	I (%)	ILI + I (%)
15–31 December 1998	23.901	15.3	5.6	20.9
1–15 January 1999	30.781	15.4	6.9	22.3
16–31 January 1999	35.461	13.6	7.6	21.2
1–14 February1999	35.142	14.1	10.1	24.2
15–28 February 1999	33.915	13.8	11.9	25.7
1–15 March 1999	38.237	11.6	6.7	18.3
15 December 1998–15 March 1999	197.437	13.8	8.3	22.1

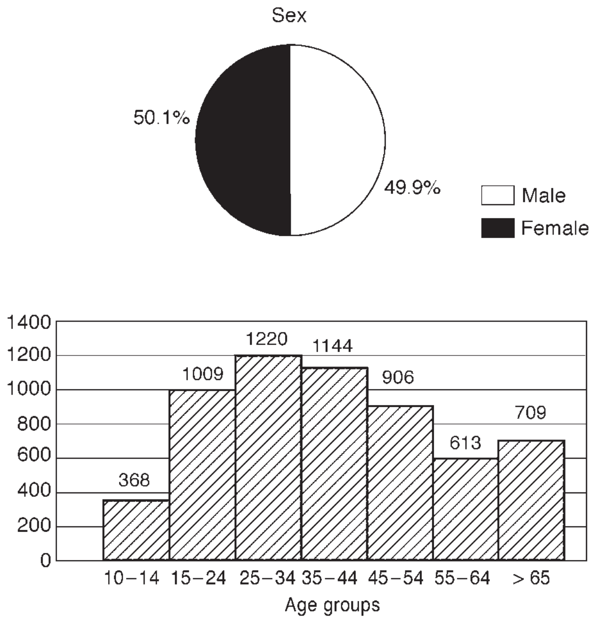

FIGURE 1 *Cases of clinical influenza recorded and socio-demographic characteristics*

TABLE 2 *Symptomatological pattern, drugs and complications of clinical influenza recorded*

	n	%
Cases of clinical influenza evaluated	6057	100.0
Fever >38°C for at least 2 days	5779	95.4
Systemic symptoms[a]		
Headache	4254	70.2
Malaise	4238	70.0
Asthenia	3570	58.9
Feverishness	2142	35.4
Respiratory symptoms[a]		
Cough	4958	81.9
Sore throat	3579	62.8
Cold/rhinorrhea	3157	52.1
Time from symptom occurrence		
no more than 2 days	4108	69.5
3–5 days	1502	25.4
6–8 days	191	3.2
>8 days	108	1.9
NR	148	
Vaccination	356	5.9
Drug administration	5826	97.3
Drug administered		
Paracetamol	4605	76.0
Antitussive	2656	43.4
Antibiotics	2156	35.6
ASA/NSAIDs	1967	32.5
Natural compounds	153	2.6
NR	69	
Occurrence of complications	2125	35.1
Complications[a]		
Upper respiratory tract infections	893	14.7
Bronchitis	892	14.7
Sinusitis	194	3.2
Otitis	94	1.6
Pneumonia	82	1.4
Other	102	1.7

[a] Percentage of all evaluated patients.

in the 10–14 year age group is not reliable as most of the patients aged under 14 years usually are referred to paediatricians and not family physicians.

Most of the patients (21.6%) were workers, clerks (20%), students (15.8%) or housewives (15.5%); others included independent professionals (4.1%), traders (3.0%) and the unemployed (2.8%); other categories were represented by the remaining 17.2%.

At-risk patients

Twelve percent of the patients were elderly, over 64 years, an age conventionally considered a risk factor for influenza complications. In addition, 16.5% of patients (including a significant proportion of the elderly) had at least one concomitant chronic condition; in descending order, respiratory disorders such as asthma or chronic obstructive pulmonary disease (COPD) (7.3%), heart disease (6.0%) and diabetes (3.2%). In total, 1190 patients (20%) had at least one risk factor and were considered to be at-risk patients for influenza complications.

Clinical influenza symptoms

Table 2 reports the prevalence of influenza symptoms in the studied population of patients with clinical influenza. High fever was one of the selection criteria and was present in virtually the whole population. The most prevalent systemic symptoms were, as expected, headache (70.2%) and myalgia/arthralgia (70%), followed by anorexia (59%) and feverishness (35.4%). The most prevalent respiratory symptoms were cough (82%) and sore throat (62.8%). Nasal symptoms were present in 52% of the reported cases.

Time to consultation

In the majority of cases, consultation with the doctor occurred within 2 days from symptom onset (70%); 25.4% of patients consulted later (3–5 days) after symptom onset.

Vaccination

Only 5.9 and 34% of the overall population and the at-risk population, respectively, received pre-season vaccination against influenza, despite the fact that anti-influenza vaccination is widely recommended as the main preventive measure against influenza complications in the group of subjects at increased risk of complications. Out of 356 patients vaccinated, 67% were elderly (>65 years) and 71.6% had at least one concurrent chronic disease, mainly cardiac (38.2%) or respiratory (32.9%).

Medications

Table 2 reports the type of medication prescribed by the doctor to patients or self-prescribed by patients with a diagnosis of clinical influenza. Virtually all patients (97.3%) took at least one medicine for the treatment of clinical influenza or influenza symptoms. In most cases, patients took paracetamol (76%) to control fever; 43.4% of the patients took cough mixtures or sedatives; and 32.5% aspirin or non-steroid anti-inflammatory drugs. It is of note that almost 36% of the patients with a diagnosis of clinical influenza had at least one prescription for antibiotics.

Risk for complications

Table 3 shows the results of a chi-square test comparison looking at the risk for complications between patients exposed and non-exposed to several recognized risk factors. All at-risk patients (the elderly, patients with COPD/asthma or heart disease) were exposed to a statistically significant increase in complication rate compared with the not at-risk population. The second part of Table 3 shows the increased risk for complications of patients with different risk factors calculated according to a logistic regression model. Elderly patients had a statistically significant, albeit clinically modest, increased risk [70%; odds ratio (OR) 1.7], while patients with concomitant chronic diseases had both a statistically and clinically relevant increased risk (300%; OR 2.89) for influenza-related complications.

TABLE 3 *Occurrence of complications: comparison between those exposed and not exposed to risk factors*

Risk factor	Yes	No	*P*
Age >65 years	709	5260	
with complications	57.8%	32.3%	<0.001
COPD/asthma	440	5076	
with complications	68.4%	32.1%	<0.001
Cardiopathy	366	5150	
with complications	61.7%	33.1%	<0.001
At least one pathology/ concurrent condition	911	4605	
with complications	60.7%	29.9%	<0.001
At least one of the preceding	1190	4855	
with complications	56.8%	29.8%	<0.001

	Odds ratio	95% CI	*P*
Age >65 years	1.702	1.405–2.062	<0.001
Concurrent conditions	2.889	2.444–3.414	<0.001

P-values were from the chi-square test and the odds ratio was from a logistic regression model.

Antibiotics/complications

Almost 36% of the patients with the clinical diagnosis of influenza received at least one prescription of antibiotics throughout the study. Despite the fact that the viral origin of influenza is well known and that antibiotic therapy is not of use to treat influenza, these may had been given either preventatively to avoid bacterial complication in the at-risk group of patients or to treat established suspect infections.

The rational use of prescription antibiotics in that group of patients with clinical influenza may be supported by the fact that a similar proportion (35.1%) of patients had at least one influenza-related complication. Most of the antibiotic prescriptions were in fact made by the GPs when a complication was suspected, either because the patient's condition did not improve after 3–4 days of conventional therapy or the patient presented with a productive cough or other clinical symptoms of probable complication. In Italy, however, antibiotics are available only by GP prescription. Virtually all the complications were of a bacterial nature, mainly upper (19.5%) and lower respiratory tract infections (14.7%) (Table 2).

Visits/examinations/hospitalizations

Each GP reported where requested visits were made. Sixty-six percent of the patients with a diagnosis of clinical influenza were visited at home, and 34% in the surgery, influenza therefore being a significant source of GPs' excess workload during the epidemic period. A total of 622 subsequent control visits were made by GPs. Five percent of the patients with a diagnosis of clinical influenza had at least one complication requiring specialist visits or instrumental examinations, most of them being thorax X-ray for suspected lower respiratory tract infections (Table 4). Twenty-six hospitalizations were recorded (0.4%), again most of them (20/26) occurring in at-risk patients, mostly with concurrent respiratory conditions such as asthma or COPD. Pneumonia and bronchitis were the most commonly reported causes of hospitalization.

Loss of productivity

Most of the subjects (65.9–69.2%) lost between 3 and 5 days of either school or work because of the influenza. On average, workers and employees lost 4.9 days, self-employed people 4.3 days and students 4.7 days. The average number of lost days is very similar between different groups, albeit that, as expected, the self-employed tended to return to work earlier (Table 5).

Discussion

During the surveyed period, almost 197 500 visits were performed by 202 GPs for 10 104 cumulative days of observation. On average, each family physician performed 137 visits for ILI and 82 visits for clinical influenza over a cumulative 51 days of survey. The attitude of Italian

TABLE 4 *Resource use: visits/examinations/hospitalizations*

	n	%
Place of the GP visit		
Patient's home	3819	65.7
Surgery	1969	33.9
Both	28	0.5
NR	241	
Occurrence of specialist visits, examinations and hospitalizations	252	4.2
Pneumologist	6	
ENT	3	
Neurologist	2	
Cardiologist	1	
Not specified	10	
X-ray thorax	164	
X-ray paranasal sinuses	9	
X-ray skull	2	
X-ray not specified	6	
Haematology	13	
ECG	5	
Arterial blood gas analysis	2	
Throat swab	1	
Audiometry	1	
Visit to emergency unit	1	
Hospitalization	26	

NR = not reported.

TABLE 5 *Absence from work and school*

	Employees (n = 2501)	Self-employed (n = 426)	Students (n = 952)
None	0	0	0
1–2	147	48	54
3–5	1560	254	570
6–7	468	48	158
>7	193	23	42
NR	133	53	128
Mean (SD)	4.9 (1.6)	4.3 (1.7)	4.7 (1.5)
Range	1–8	1–8	1–8
Median	5	4	5
Q1–Q3	4–6	3–5	4–5

NR = not reported; Q1–Q3 = upper and lower quartiles.

patients is to consult their GP because of influenza. The rate of consultation is estimated at ~60%, most visits being home visits (65.7%) and occurring within 48 hours from symptom onset (69.5%).

Considering the very high attack rate of influenza in the general population and the estimated ~10 million patients being affected by a syndrome consistent with the definition of clinical influenza during the 1998/1999 epidemic season in Italy,[8] the impact of influenza on the daily activities of Italian GPs can be easily appreciated. In Italy, there are ~55 000 GPs. According to our findings, each GP performed an average of 82.3 visits during the survey period; more than 4.5 million visits are therefore estimated to have been performed, mostly at the patient's home, during the 1998/1999 influenza epidemic.

In addition, the influenza epidemic also accounts for a substantial loss of productivity in the affected population. On average, each clinical influenza case accounted for 4.78 days of work or school days lost. The 1998/99 epidemic is estimated to have caused the loss of ~48 million working or school days in Italy.

In terms of direct costs, antibiotic prescription largely accounts for most of the resource use associated with the influenza epidemics. Thirty-six percent of patients with a diagnosis of clinical influenza had at least one prescription of antibiotics. Interestingly, this also coincides with the proportion of patients who had at least one influenza-associated complication (35.1%), which in virtually all cases were of bacterial origin (basically upper respiratory tract infections and bronchitis). These data would therefore support the evidence that antibiotics were prescribed appropriately during this study, only when deemed necessary to treat influenza-related suspected bacterial infections. This apparently is in contrast to earlier reports of indiscriminate antibiotic prescription and misuse for the treatment of upper respiratory tract infections of viral origin in the ambulatory care setting.[9]

As expected, at-risk patients were exposed to an increased risk of experiencing influenza-related complications of any origin, the risk ranging from a 70% increase in elderly patients with no concomitant chronic conditions compared with the general population (OR = 1.7) to almost a 3-fold increase in patients with concurrent respiratory diseases (OR = 2.889).

Apart from fever, which was a selection criterion, the most prevalent and distinctive symptoms of clinical influenza included cough (82%), headache (70.2%) and malaise (70%). These data also confirm previous observations[10] that clinical diagnosis based on the concurrent presence of high fever and cough when influenza virus is known to circulate in the community is a good predictor of influenza virus infection.[11]

In conclusion, yearly influenza epidemics in Italy are associated with a substantial loss of productivity in the general population and increased pharmaceutical expenditure related to the excess prescription of antibiotics to treat influenza-related bacterial complications in both the general and at-risk populations. Influenza remains an important component of family physicians' workload, particularly because of the high incidence in the peak period and high prevalence of home visits.

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