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Clinical manifestations and socio-economic impact of influenza among healthy children in the community

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Summary *Objectives:* To evaluate the total burden of influenza among healthy children in the community in order to analyse the cost of influenza in paediatric age.
Methods: This prospective study involved a total community population of 21,986 children, 6988 of whom experienced an influenza-like illness (ILI) between 1 November 2008 and 30 April 2009. An electronic chart was completed, a nasopharyngeal swab was obtained, and information was recorded concerning the clinical outcomes and household impact of the ILI episodes. Influenza A and B viruses were detected in all the swabs by means of polymerase chain reaction, and costs of the disease were calculated.
Results: Influenza viruses were detected in 2143 cases (30.7%), an incidence of 96.4 per 1000 children. Influenza A and B viruses were found in respectively 1751 (81.7%) and 392 cases (18.3%). The mean cost of influenza was no less than €130, 32% higher than the cost of influenza-negative ILIs ($p < 0.001$). The influenza A cases were significantly more expensive than the influenza B cases ($p < 0.001$), and influenza in children aged <2 and 2–5 years was significantly more expensive than in children aged >5 years ($p < 0.05$). The differences were mainly related to the indirect costs of the parents' lost working days.

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Conclusions: The findings of this study confirm that influenza among healthy children is important because of its frequency and its indirect consequences on the households of infected children, and support the use of influenza vaccination in healthy children aged between 6 months and 5 years.

Introduction

Health authorities throughout the world consider influenza a potentially severe illness in children who are at risk of influenza-related complications because they have a chronic underlying disease, to whom they strongly recommend the annual administration of influenza vaccine.[1,2] On the contrary, the use of influenza vaccine in healthy children is widely debated, and only a minority of industrialised countries include universal influenza vaccination in their paediatric immunisation programmes.[1,3,4]

Those who object to the universal paediatric use of influenza vaccine think that the results of most of the studies carried out so far do not allow any firm conclusions to be drawn concerning the real importance of influenza in healthy children, and do not show that implementing a universal vaccination programme would be cost effective.[5] To support their doubts, the opponents of universal vaccination underline the fact that most of the studies specifically planned to measure the total burden of influenza have only involved patients suffering from a severe disease enrolled in Emergency Rooms or paediatric wards,[6–14] and may therefore overestimate the clinical importance of influenza and lead to conclusions that are quite different from those that would be obtained by analysing influenza in the community (where most cases are diagnosed). Furthermore, some studies have only considered influenza-like illness (ILI) and not laboratory-confirmed influenza,[6–8] thus introducing a significant confounding factor, particularly given the frequent co-circulation of different respiratory viruses during the influenza period.

Prospective and well-conducted community studies are needed to solve these problems and decide whether universal paediatric influenza vaccination should be recommended. Only a small number of such studies have so far been carried out,[15,16] and they have not answered all of the questions related to the real burden of influenza in healthy children. The aim of this study was to provide further information that would help to evaluate the cost of paediatric influenza and clarify the potential cost effectiveness of influenza vaccination.

Patients and methods

Study design

This prospective study of children with ILI was carried out in the community in Italy between 1 November 2008 and 30 April 2009. Italy is one of the few countries with a specific primary care system devoted to children aged less than 14 years; every child is registered at birth and receives free medical care from one of 6000 primary care pediatricians (PCPs) working for the National Health Service in the community. The study involved Pedianet, a network of PCPs mainly based in Northern Italy who usually participate in epidemiological and clinical research projects concerning the care of children in the community.[17,18] All of Pedianet's PCPs are experienced users of the same electronic patient record software; the data contained in their records are generated from routine patient encounters, and include diagnoses, symptoms, prescriptions, certificates, medical examinations, referrals, and hospitalisations. Fifty of the 185 PCPs belonging to Pedianet (27.0%) were randomly selected to participate in the study. The study protocol was approved by the Institutional Review Board of the Italian Local Health Centre to which each PCP belonged. Written informed consent of a parent or legal guardian was required for enrolment, and the older children were asked to give their assent.

Study population

The study enrolled all children aged less than 14 years without any severe chronic underlying medical condition who were examined by the participating PCPs because of signs and/or symptoms of ILI. As by the Italian Ministry of Health (http://www.ministerosalute.it),[19,20] ILI is an acute respiratory disease: of sudden onset, with fever (a temperature of $>38\ ^{\circ}C$) accompanied by at least one general symptom (headache, generalised malaise, a feverish sensation (sweating and chills) or asthenia) and at least one respiratory symptom (cough, pharyngodynia or nasal congestion).[19,20] The respiratory symptoms had to have lasted at least three days to be considered in the analysis, and only one new-onset illness could be included in any two-week period. The exclusion criteria included concomitant chronic diseases leading to an increased risk of influenza-related complications.[1]

Patient enrolment and evaluation

Upon enrolment, each PCP systematically recorded the patients' demographic characteristics and medical history using a specifically modified version of the standardised electronic questionnaires usually used to record the data regarding their patients. The data included gender and age, any previous administration of influenza vaccine, a detailed description of the signs and symptoms of the acute episode of respiratory tract infection and any other associated clinical manifestation, the prescribed laboratory and/or radiological examinations, and the prescribed drug therapy. After a complete physical examination, the children were classified into disease groups on the basis of well-established criteria.[21] Any associated non-respiratory diagnosis was also recorded. In the presence of signs and symptoms of more than one disease (including non-respiratory illnesses), the children were classified in the most severe disease group. In the case of a request for laboratory test or radiological examinations, the diagnosis was considered definite when the results became

available. Acute otitis media was diagnosed by means of pneumatic otoscopy, and a diagnosis of pneumonia was always confirmed by means of chest radiography.

In the presence of ILI, a nasopharyngeal sample was collected using a prenasal flocked swab, and stored in UTM-RT tubes (Kit Cat. No. 360c, Copan Italia, Brescia, Italy). Viral RNA was extracted from both swabs by means of a Nuclisens EasyMAG automated extraction system (Biomeriéux, Craponne, France), using phocine distemper virus (PDV) as the extraction control as previously described.[22,23] A total of 20 μL of eluate was reverse transcribed using a Taqman Reverse Transcription Reagents kit (Applied Biosystems, Foster City, CA, USA) in a reaction mixture containing 4.5 mM of $MgCl_2$, 0.5 mM of each dNTP, 2.5 μM of random hexamers, 20 U of RNase inhibitor, 62.5 U of reverse transcriptase, and 0.1 mg/mL of BSA. All of the reactions for real-time polymerase chain reaction (PCR) were set up as singleplex PCRs in a total volume of 25 μL using the Taqman Universal Master mix (Applied Biosystems), 200—800 nM of primers, 100 nM of TaqMan probe, and 10 μL of cDNA template, and the products were amplified using the ABI 7900HT Fast Real-Time PCR System (Applied Biosystems) and standard cycling parameters. The following primer-probe sets were used: influenza A, sense AAGACCAATCCTGTCACCTCTGA, antisense CAAAGCGTCTACGCTGCAGTCC, probe fam-TTTGTGTTCACGCTCACCGTGCC-bhq1; influenza B, sense GAGACACAATTGCCTACCTGCTT, antisense TTCTTTCCCACCGAACCAAC, probe tet- AGAAGATGGAGAAGGCAAAGCAGAACTAGC-eclipse; PDV, sense CGGGTGCCTTTTACAAGAAC, antisense TTCTTTCCTCAACCTCGTCC, probe vic-ATGCAAGGGCCAATTCTTCCAAGTT-bhq1. The influenza A and B RNAs were relatively quantified; the criterion for a positive reaction was a cycle threshold (CT) of <40 cycles.

The medical history of each child was re-assessed by the PCPs by means of telephone interviews 5—7 days after enrolment, and then every two days until the resolution of the illness. In the case of persistent fever and/or signs and symptoms of disease, or at the parents' request, a further medical examination was programmed. Any Emergency Room visits, hospitalisation or further medical examinations were also recorded. All of the follow-up data were entered in the children's electronic charts, and information regarding ILI and related morbidity among households was also obtained at the time of the first follow-up contact. The parents or legal guardians were asked to answer a list of questions regarding the involvement of other family members (ILI in household contacts, number of working days lost by parents in caring for their ill children, and their own respiratory diseases). These data were also recorded in the children's personal charts.

Economic evaluation

The costs of influenza-positive and influenza-negative episodes were analysed from the individual and societal perspectives.

The direct medical costs included the total cost of medical examinations, drug prescriptions and hospitalisations during the study period. The list price of the prescription's indicated active principle (Italian Directory of Medicines and Manufactures, 2009) was used to assess the cost of drug therapies in both the influenza-positive and the influenza-negative cases. The cost of a full course of oral (suspension) aminopenicillin or first- or second-generation cephalosporin was estimated to be €8.50, whereas the cost of antipyretics was €0.6 per treatment day. The cost of medical examinations was based on the "1997 National Tariff Nomenclator", but the data were updated to 2008 values on the basis of the official inflation rates, and so the resulting unit cost was €26.64 per examination. The cost of hospitalisation was evaluated on the basis of the DRG tariff of the Veneto Region for the diagnosis.[24]

The indirect costs included the caregivers' absences from work, which were assessed on the basis of the net productivity loss tables per capita (Banca Italia 2002) divided by 220 working days (i.e. the mean annual number of working days in Italy); the data were subsequently updated to 2008 using the official inflation rates. The mothers' and fathers' lost working days were therefore estimated to be respectively €66.00 and €85.50.

Statistical analysis

The data were analysed using SAS for Windows software, v. 9.1 (SAS Institute, Cary, NC, USA), and comparisons were made between the influenza-positive and the influenza-negative cases, between the age groups of the influenza-positive cases (<2 years *vs* 2—5 years *vs* >5 years), and between the viral types (influenza A *vs* influenza B). The continuous variables are given as mean values ± standard deviation (SD) or median values with ranges, and the categorical variables as absolute numbers and percentages. The continuous data were analysed using a two-sided Student's *t* test if their distribution was normal (based on the Shapiro—Wilk statistic) or a two-sided Wilcoxon's rank-sum test otherwise. The categorical data were analysed using contingency tables and the chi-squared or Fisher's test, as appropriate.

Results

The selected 50 PCPs were continuously following 26,102 children. Because eight of them refused to participate because of personal problems, the analysis was therefore made using the data provided by 42 PCPs (84.0%) that, at the beginning of the study, were continuously following 21,986 children aged <14 years. During the study period, a first episode of ILI was diagnosed in 6988 cases (31.8%). Laboratory evaluations of the nasopharyngeal samples collected during each visit for ILI showed that influenza viruses were associated with the disease in 2143 cases (30.7%), an incidence of 96.4 per 1000 children. Influenza A and B viruses were found in respectively 1751 (81.7%) and 392 cases (18.3). Influenza A viruses were found since the beginning of the study with a peak period between the 4th and 6th week of 2009. The last positive sample was identified in the 11th week of 2009. Influenza B-positive nasopharyngeal swabs were collected during the whole study period without a significant peak period.

Table 1 shows the demographic data, clinical presentations and clinical outcomes of the children with ILI, by influenza diagnosis and age. The influenza-negative and influenza-positive children were comparable in terms of gender and age, whereas influenza vaccination (which was rarely used) was

Table 1 Demographic data, clinical presentations and clinical outcomes among the study patients, by aetiology and age.

	Influenza-negative cases (n = 4845)	Influenza-positive cases (n = 2143)	Influenza-positive <2yrs (n = 343)	Influenza-positive 2–5 yrs (n = 1071)	Influenza-positive >5 yrs (n = 729)
Demographic data					
Males, No. (%)	2540 (52.4)	1093 (51.0)	182 (53.1)	536 (50.0)	375 (51.4)
Age, mean ± SD (yrs)	3.1 ± 2.0	3.8 ± 2.0	1.3 ± 0.4	3.6 ± 0.8	8.1 ± 2.7
Previous influenza vaccination, No. (%)	40 (8.3)*	85 (4.0)	10 (2.9)	43 (4.0)	32 (4.4)
Clinical presentation					
Presence of fever[a], No. (%)	4648 (95.9)	2141 (99.9)	341 (99.4)	1071(100.0)	729 (100.0)
High-grade fever[b], No. (%)	1885 (38.9)*	1249 (58.3)	179 (52.2)"	674 (62.9)	396 (54.3)"
Respiratory tract infection, No. (%)	4226 (87.2)	1843 (86.0)	264 (77.0)"°	932 (87.0)	647 (88.8)
Upper respiratory tract infection, No. (%)	3650 (75.3)	1650 (77.0)	237 (69.0)"°	816 (76.2)	597 (81.8)
Common cold, No. (%)	107 (2.2)*	353 (16.5)	66 (19.2)	173 (16.2)	114 (15.6)
Pharyngitis, No. (%)	2810 (58.0)^	1066 (49.7)	116 (33.8)"°	527 (49.2)°	423 (58.0)
Acute otitis media, No. (%)	733 (15.1)^	231 (10.8)	55 (16.0)"°	116 (10.8)	60 (8.2)
Lower respiratory tract Infection, No. (%)	576 (11.9)	193 (9.0)	27 (7.8)	116 (10.8)	50 (6.9)
Acute bronchitis, No. (%)	409 (8.4)	169 (7.9)	25 (7.3)	96 (9.0)	48 (6.6)
Wheezing, No. (%)	91 (1.9)	15 (0.7)	1 (0.3)	14 (1.3)	0 (0.0)
Pneumonia, No. (%)	76 (1.6)	9 (0.4)	1 (0.3)	6 (0.6)	2 (0.3)
Gastrointestinal tract Infection, No. (%)	619 (12.8)	300 (14.0)	79 (23.0)"°	139 (13.0)	82 (11.2)
Clinical outcomes					
Emergency Room attendance, No. (%)	101 (2.1)	55 (2.6)	10 (2.9)	33 (3.1)	12 (1.6)
Hospitalisation, No. (%)	39 (0.8)	16 (0.7)	5 (1.5)	8 (0.7)	3 (0.4)
Duration of fever, mean days ± SD	3.38 ± 1.74^	3.99 ± 1.99	4.01 ± 1.88	3.96 ± 1.64	3.64 ± 2.10
Duration of symptoms, mean days ± SD	5.39 ± 3.09^	6.22 ± 2.63	6.85 ± 2.97	6.40 ± 2.82	5.93 ± 2.31
Antibiotic prescriptions, No. (%)	2519 (52.0)*	922 (43.0)	130 (37.9)"	507 (47.3)	285 (39.0)"
Antipyretic prescriptions, No. (%)	4513 (93.1)	2130 (99.3)	340 (99.1)	1065 (99.4)	725 (99.5)
Duration of antipyretics, mean days ± SD	2.9 ± 2.34^	3.9 ± 3.5	4.4 ± 3.2	3.9 ± 3.6	3.6 ± 4.1
Further examinations, No. (%)	726 (15.0)*	514 (23.9)	89 (25.9)	250 (23.3)	175 (24.0)

*$p < 0.001$ and ^$p < 0.05$ *vs* influenza-negative cases; "$p < 0.05$ *vs* 2–5 years and °$p < 0.05$ *vs* >5years; no other significant differences.

[a] An an axillary temperature of ≥37.6 °C or a rectal temperature of ≥38 °C.

[b] An axillary temperature of ≥39 °C or a rectal temperature of ≥39.5 °C. SD: standard deviation.

Table 2 Influenza-like illness and related morbidity among households in the 7 days following a child's diagnosis, by aetiology and age.

	Influenza-negative cases ($n = 4845$)	Influenza-positive cases ($n = 2143$)	Influenza-positive <2yrs ($n = 343$)	Influenza-positive 2–5 yrs ($n = 1071$)	Influenza-positive >5 yrs ($n = 729$)
Similar disease within household, No. (%)	1211 (25.0)*	922 (43.0)	130 (37.9)"	555 (51.8)	237 (32.5)"
Mothers who remained absent from work, No. (%)	579 (12.0)*	349 (16.3)	49 (14.3)	185 (17.3)	115 (15.8)
Working days lost by mothers, mean days ± SD	3.39 ± 2.26^	4.46 ± 2.11	4.95 ± 2.61°	4.88 ± 2.03°	1.91 ± 2.34
Fathers who remained absent from work, No. (%)	96 (2.0)^	130 (6.1)	19 (5.5)°	74 (6.9)°	18 (2.5)
Working days lost by fathers, mean days ± SD	1.96 ± 2.04*	4.31 ± 2.73	5.61 ± 2.64°	4.99 ± 2.88°	1.98 ± 2.06

*$p < 0.001$ and ^$p < 0.05$ *vs* influenza-negative cases; "$p < 0.05$ *vs* 2–5 years and °$p < 0.05$ *vs* >5years; no other significant differences.

significantly less frequent among the influenza-positive patients ($p < 0.001$). Fever was documented in almost all cases in both groups, but the children with influenza more frequently had high-grade fever ($p < 0.001$). The incidence of upper respiratory tract infections (URTIs), lower respiratory tract infections (LRTIs) and gastrointestinal manifestations was quite similar in both groups, with URTIs being significantly more frequent than the other diagnoses ($p < 0.001$). Among the URTIs, common colds were more frequent among the influenza-positive children ($p < 0.001$), whereas pharyngitis and acute otitis media (AOM) were more frequent among the influenza-negative patients ($p < 0.05$). There was a similarly marginal need for local hospital Emergency Room attendance or hospitalisation in both groups. However, the influenza-positive children had a longer duration of fever ($p < 0.05$) and symptoms ($p < 0.05$), and required further examinations ($p < 0.001$). On the contrary, antibiotic prescriptions were significantly less frequent in the influenza-positive children ($p < 0.001$).

Among the influenza-positive children, those aged <2 or >5 years experienced high-grade fever significantly less frequently than those aged 2–5 years ($p < 0.05$). Moreover, the younger children had a significantly lower incidence of URTIs ($p < 0.05$) and pharyngitis ($p < 0.05$), and a significantly higher incidence of AOM ($p < 0.05$) and gastrointestinal symptoms ($p < 0.05$). There were no differences between the age groups in the other studied variables with the exception of antibiotic prescriptions, which were made significantly more frequently in the case of children aged 2–5 years ($p < 0.05$).

Table 2 summarises the household ILI data and the consequent number of parental lost working days, by influenza diagnosis and children's age. The households of the children with influenza experienced more ILIs than those of the influenza-negative patients ($p < 0.001$). This was more common among the households of children aged 2–5 years than among those aged <2 or >5 years ($p < 0.05$). Both the mothers and fathers of the influenza-positive children lost more working days than those of the influenza-negative children ($p < 0.001$), and this was significantly more evident among the parents of children aged <2 or 2–5 years.

Table 3 shows the demographic data, clinical presentations, clinical outcomes and household ILIs among the influenza-positive children, by viral type. In comparison with those infected by influenza B, the children with influenza A viruses were significantly younger ($p < 0.001$), less frequently received influenza vaccination ($p < 0.05$), and more frequently had high-grade fever ($p < 0.001$), a longer duration of fever ($p < 0.05$) and other symptoms ($p < 0.05$), and required more further examinations ($p < 0.05$). There were no between-group differences in any of the other demographic and clinical variables. Both the mothers and fathers of the children with influenza A experienced more ILIs than those of the influenza B patients ($p < 0.001$), and lost more working days ($p < 0.05$).

Table 4 compares the cost of influenza and influenza-negative ILIs. Overall, influenza was 32% more expensive ($p < 0.001$), mainly because of the higher indirect costs related to parental lost working days ($p < 0.05$).

Table 5 shows the cost of influenza by viral type and children's age. The influenza A cases were significantly more expensive than the influenza B cases ($p < 0.001$), and influenza in children aged <2 and 2–5 years was significantly more expensive than in children aged >5 years ($p < 0.05$). Once again, the differences were mainly related to the indirect costs of parental lost working days.

Discussion

Our findings seem to answer some questions concerning the real impact of influenza among healthy children in the community, and offer new information for deciding whether to implement the universal vaccination of healthy children. First of all, as it enrolled only otherwise healthy children in the community, the study was not affected by confounding factors such as an increased risk of complications due to underlying disease or the selection of more severe cases. Furthermore, it involved a large number of children of different ages and only analysed laboratory-confirmed cases. Finally, it collected data regarding the medical and socio-economic involvement of the family of each child with influenza.

Starting from these premises, the data show that influenza is a very common disease among otherwise healthy children, mainly causes mild illness (but clinically more important than all of the other ILIs as a whole), and the households of influenza-positive children are more greatly

Table 3 Demographic data, clinical presentations, clinical outcomes and impact on households of influenza-positive patients, by viral type.

	Influenza A-positive cases ($n = 1751$)	Influenza B-positive cases ($n = 392$)
Demographic data		
Males, No. (%)	879 (50.2)	214 (54.6)
Age, mean ± SD (yrs)	2.39 ± 2.76*	3.88 ± 1.62
Previous influenza vaccination, No. (%)	52 (3.0)^	33 (8.4)
Clinical presentation		
Presence of fever[a], No. (%)	1751 (100.0)	390 (99.5)
High-grade fever[b], No. (%)	1055 (60.3)*	194 (49.5)
Respiratory tract infection, No. (%)	1499 (85.6)	344 (87.8)
Upper respiratory tract Infection, No. (%)	1344 (76.8)	306 (78.1)
Common cold, No. (%)	293 (16.7)	60 (15.3)
Pharyngitis, No. (%)	856 (48.9)	210 (53.6)
Acute otitis media, No. (%)	195 (11.1)	36 (9.2)
Lower respiratory tract Infection, No. (%)	155 (8.8)	38 (9.7)
Acute bronchitis, No. (%)	135 (7.7)	34 (8.7)
Wheezing, No. (%)	12 (0.7)	3 (0.8)
Pneumonia, No. (%)	8 (0.5)	1 (0.3)
Gastrointestinal tract infection, No. (%)	252 (14.4)	48 (12.2)
Clinical outcome		
Emergency Room attendance, No. (%)	49 (2.8)	6 (1.5)
Hospitalisation, No. (%)	14 (0.8)	2 (0.5)
Duration of fever, mean days ± SD	4.22 ± 1.52^	3.25 ± 2.19
Duration of symptoms, mean days ± SD	6.52 ± 2.67^	5.16 ± 2.61
Antibiotic prescriptions, No. (%)	766 (43.7)	156 (39.7)
Antipyretic prescriptions, No. (%)	1749 (99.9)	381 (97.2)
Duration of antipyretics, mean days ± SD	4.1 ± 3.4	3.4 ± 3.1
Further examinations, No. (%)	441 (25.2)^	73 (18.6)
Impact on households		
Similar disease within household, No. (%)	791 (45.2)*	131 (33.4)
Mothers who remained absent from work, No. (%)	316 (18.0)^	33 (8.4)
Working days lost by mothers, mean days ± SD	4.57 ± 2.43^	2.99 ± 1.90
Fathers who remained absent from work, No. (%)	122 (7.0)^	8 (2.0)
Working days lost by fathers, mean days ± SD	4.41 ± 3.10^	3.00 ± 2.71

*$p < 0.001$ and ^$p < 0.05$ *vs* influenza B-positive cases; no other significant differences.
[a] An axillary temperature of ≥37.6 °C or a rectal temperature of ≥38 °C.
[b] an axillary temperature of ≥39 °C or a rectal temperature of ≥39.5 °C. SD: standard deviation.

affected than those of influenza-negative children. All of these findings have substantial medical and socio-economic consequences that seem to justify the implementation of universal paediatric immunisation. Given the age-related differences in the impact of influenza, this is particularly true in the case of children aged 6—59 months in whom influenza seems to give rise to the highest economic costs.

During the influenza season of 2008—2009, the incidence of influenza in our study population was about 10%, which is highly consistent with that reported by the active

Table 4 Cost of influenza infection compared with influenza-negative cases among the study children and their households.

	Influenza-positive cases ($n = 2143$)	Influenza-negative cases ($n = 4845$)	Difference
Paediatric examinations	33.0 ± 4.0	30.6 ± 4.2	+2.4 ± 4.1
Antibiotic use	3.7 ± 4.3	4.4 ± 4.9	−0.7 ± 4.6
Antipyretic use	2.4 ± 2.0	1.9 ± 1.4	+0.5 ± 1.7
Hospitalisation	22.4 ± 238.1	22.5 ± 251.0	−0.1 ± 244.6
Working days lost by mothers	47.9 ± 90.1^	26.7 ± 89.9	+21.2 ± 90.0
Working days lost by fathers	22.3 ± 89.7^	3.3 ± 39.9	+19.07 ± 64.8
Total cost	131.7 ± 71.4*	89.4 ± 65.2	+42.3 ± 68.3

Mean costs ± SD in euros. ^$p < 0.05$ and *$p < 0.001$ *vs* influenza-negative cases; no other significant differences.

Table 5 Cost of influenza infection among the study children and their households, by viral type and children's age.

	Viral type		Children's age		
	Influenza A-positive cases ($n = 1751$)	Influenza B-positive cases ($n = 392$)	Influenza-positive cases <2 yrs ($n = 343$)	Influenza-positive cases 2–5 yrs ($n = 1071$)	Influenza-positive cases 2–5 yrs ($n = 729$)
Paediatric examinations	33.3 ± 4.6	30.9 ± 3.4	33.5 ± 5.6	32.9 ± 4.2	33.0 ± 2.5
Antibiotic use	3.7 ± 3.3	3.4 ± 3.1	3.2 ± 3.9	4.0 ± 4.6	3.3 ± 3.9
Antipyretic use	2.5 ± 2.1	2.0 ± 1.9	2.4 ± 1.9	2.3 ± 2.2	2.1 ± 2.5
Hospitalisation	22.4 ± 243.4	14.2 ± 216.7	40.8 ± 238.8	23.9 ± 268.9	11.5 ± 153.4
Working days lost by mothers	54.4 ± 94.8^	16.6 ± 61.4	46.7 ± 96.4°	55.6 ± 106.7°	19.8 ± 49.6
Working days lost by fathers	26.3 ± 97.7^	5.7 ± 33.3	26.6 ± 90.4°	29.4 ± 111.4°	4.2 ± 39.1
Total cost	142.6 ± 74.3*	72.8 ± 53.3	153.2 ± 72.8°	148.1 ± 83.1°	73.9 ± 41.9

Mean costs ± SD in euros. ^$p < 0.05$ and *$p < 0.001$ *vs* influenza B-positive cases; °$p < 0.05$ *vs* age >5 years; no other significant differences.

virological surveillance system of the European Centre for Disease Control and Prevention during the same season.[25] This supports the reliability of the methods used to enrol the patients and identify influenza, and allows us to calculate that no fewer than 800,000 paediatric cases of influenza occurred in Italy during the 2008–2009 influenza season (about 8.5 million of children aged <14 years live in Italy[26] and the incidence of influenza was quite similar throughout the country in that period).[27] Moreover, given the number of cases requiring more than one examination, it can be estimated that about one million paediatric examinations were needed during the same period to deal with influenza among healthy children in the community. In practical terms, about one-third of all of the examinations of healthy children due to ILIs were caused by influenza, which clearly underlines the significant impact of the disease on the National Health System.

Fortunately, despite its frequency, influenza seems to be mild among healthy children because very few patients had to attend an Emergency Room or be hospitalised. However, it was clinically more important than the influenza-negative ILIs because the influenza-positive children more frequently had high-grade and long-lasting fever and long-lasting symptoms, needed further examinations after diagnosis, and received more antipyretic doses. The significant incidence of influenza among children in the community, and its greater seriousness in comparison with other respiratory infections, have been reported by Heikkinen et al.[15] and Tsolia et al.[16] However, as these studies were carried out at different times and in different countries, our findings confirm that the clinical importance of influenza is constant and largely independent of temporal or geographical factors.

More than 40% of our children with influenza received antibiotics, which is in line with the findings of previous studies of the impact of influenza infection on the out patients use of antibiotics.[7,14–16] However, antibiotics were prescribed less frequently to the influenza-positive children than the influenza-negative patients. This can be explained by the fact that many PCPs use rapid antigen detection tests to identify influenza viruses in nasopharyngeal secretions, and this can significantly reduce antibiotic use in influenza-positive cases.[28–30]

The clinical presentation of influenza was quite similar in the children of all age groups, although the younger children had significantly fewer URTIs and more episodes of AOM and gastrointestinal manifestation. The similar severity of influenza in younger and older children contrasts with the findings of hospital-based studies showing that disease severity as inversely proportional to age,[6–11] but this can be explained by the fact that these studies included more young children at risk because of underlying chronic diseases. In the case of AOM, our data confirm previous findings by us[14] and Tsolia et al.[16] and indicate that other pathogens mainly favour its development.

Influenza A virus caused more severe diseases than influenza B virus. This is not surprising because, during the 2008–2009 influenza season, most of the cases of influenza A diagnosed in Italy were due to the A/H3N2 subtype, which was significantly more virulent than the A/H1N1 subtype or type B.[31] However, this finding underlines the fact that the circulating viral strain conditions the impact of the disease.

The effect of paediatric influenza on the family is clearly demonstrated by the greater number of ILIs suffered by the households of the influenza-positive children. This confirms what has previously been reported by us[14] and others[15,16] and is probably due to the longer and greater shedding of influenza viruses in younger patients. The loss of parental working days contributes most to the costs arising from a single case of influenza which, in this study, was calculated to be about €132. The real economical importance of the absenteeism can vary according to the type of work because in some cases production can be continued with a smaller work force and the worker loses sick leave time without real financial losses. However, when production has to be reduced for absenteeism it can be very relevant. In this case, on the basis of the total number of children who presumably acquired influenza in Italy during the 2008–2009 season, it can be estimated that the global cost of influenza among healthy children was no less than €100,000,000, and probably more because our calculations did not include the costs of the medical examinations and drug prescriptions relating to the other members of the households. Our analysis of costs by viral type and children's age indicates that the families with children infected

by influenza A virus have the highest costs, and those with older children the lowest. This seems to suggest that both the severity and spread of influenza depend on the virulence of the circulating viral strain, and that family involvement is greater when it includes younger children, probably because the parents of lose working days not only because of their own diseases but also because they have to stay at home to look after their ill child.

In conclusion, our findings confirm that influenza among healthy children is frequent and has indirect consequences on their households. This strongly supports the view that influenza vaccination should not only be given to children at risk of complications because of underlying chronic diseases, but also to healthy children, especially those aged between six months and five years.

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