

Influenza-related healthcare visits, hospital admissions, and direct medical costs for all children aged 2 to 17 years in a defined Swedish region, monitored for 7 years

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Abstract

Background: The seasonal variation of influenza and influenza-like illness (ILI) is well known. However, studies assessing the factual direct costs of ILI for an entire population are rare.

Methods: In this register study, we analyzed the seasonal variation of ILI-related healthcare visits and hospital admissions for children aged 2 to 17 years, and the resultant parental absence from work, for the period 2005 to 2012. The study population comprised an open cohort of about 78,000 children per year from a defined region. ILI was defined as ICD-10 codes: J00-J06; J09-J15, J20; H65-H67.

Results: Overall, the odds of visiting a primary care center for an ILI was 1.64-times higher during the peak influenza season, compared to the preinfluenza season. The corresponding OR among children aged 2 to 4 years was 1.96. On average, an estimated 20% of all healthcare visits for children aged 2 to 17 years, and 10% of the total healthcare costs, were attributable to seasonal ILI. In primary care, the costs per week and 10,000 person years for ILI varied – by season – from €3500 to €7400. The total ILI cost per year, including all physical healthcare forms, was €400,400 per 10,000 children aged 2 to 17 years. The costs for prescribed and purchased drugs related to ILI symptoms constituted 52% of all medicine costs, and added 5.8% to the direct healthcare costs.

The use of temporary parental employment benefits for caring of ill child followed the seasonal pattern of ILI ($r=0.91$, $P<0.001$). Parental absence from work was estimated to generate indirect costs, through loss of productivity of 5.2 to 6.2 times the direct costs.

Conclusions: Direct healthcare costs increased significantly during the influenza season for children aged 2 to 17 years, both in primary and hospital outpatient care, but not in hospital inpatient care. Primary care manages the majority of visits for influenza and ILI. Children 2 to 4 years have a larger portion of their total healthcare encounters related to ILI compared with older children. There is a clear correlation between ILI visits across the years and parental absence from work.

Abbreviations: CPP = cost per patient, HCR = healthcare register, ICD = International Classification of Diseases, ILI = influenza-like illness, OR = odds ratio, VAB = temporary parental benefit for staying home to take care of an ill child.

Keywords: children, direct medical costs, epidemiology, influenza-like illness, open cohort, seasonal influenza, societal costs

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1. Introduction

Influenza is a common epidemic disease, with an annual prevalence proportion around 40% in preschool-aged children and 30% in school-aged children.^[1–4] The disease varies in intensity and severity and can require medical care. The seasonal pattern of influenza might follow a similar pattern to the common cold. Medical complications, such as upper and lower respiratory tract problems and acute otitis media, often follow as part of the influenza illness itself. Apart from the burden of illness, children play an important role in the spread of influenza, as they can contract the virus at kindergarten or school and then transmit it to household members.^[5] The incidence of influenza is likely higher than reported, as not all children with infections attend a healthcare service; those who are not picked up by the surveillance systems are not recorded.^[6–8]

Hospital admission rates among children have varied widely during past epidemics of influenza, depending on the individual's medical history and age. In addition, different types of study report varying admission rates.^[9–13] Hospital admissions for influenza-like illness (ILI) and influenza follow the influenza season,^[10,12] and children with high-risk conditions usually constitute a larger proportion of those requiring inpatient care, compared with children who do not have high-risk conditions.^[10,11] However, vaccination status (full or partial) can reduce both in- and out-patient encounters.^[13]

Studies are available concerning vaccination, case reports, and hospital admissions related to influenza and childhood disease, but a limited number of studies describe the overall burden of the disease among children in well-defined populations across seasons.^[14] Actual direct costs are seldom used when estimating healthcare costs attributable to influenza. In a recent systematic review of 13 studies reporting the burden of influenza for children in terms of health and healthcare costs, Antonova et al^[14] concluded that “all cost estimates were not directly collected but imputed”. The indirect costs for parents may be considerable when they stay home from work to care for their sick children. Ortega-Sanchez et al (2012)^[15] found that caregivers lost an average of 73 work-hours when their children were admitted, and 6 for a single outpatient visit. If the child has to stay home, a parent must take a leave of absence from work, unless the care of the child can be arranged otherwise. In Sweden, there is a temporary parental benefit for staying home to take care of an ill child, abbreviated as VAB. The VAB is similar to the sickness compensation but without the qualifying period (of 1 day), and is available to all parents of children 1 to 12 years old (even if temporarily unemployed). Reimbursement is in proportion to income, with a limit at a monthly income above €3000. Official statistics report that an average episode of VAB lasts about 4 days (gross) and the majority occur during winter.^[16] The number of net VAB days equals the loss of production days, and there are about 3 net days per VAB. For more information regarding the Swedish VAB refer to the PDF Supplemental Digital Content 1 (SDC 1, <http://links.lww.com/MD/B216>) that describes Temporary Parental Benefits in Sweden.

1.1. Aim

The aims of this study were to analyze the seasonal variation in influenza-related visits for children aged 2 to 17 years and to assess the cost of physician visits, hospital admission, and influenza-related drug consumption, over a 7-year cycle (2005–2012), in a defined Swedish region. In addition, the study aimed to calculate the direct medical costs and to estimate the indirect costs due to loss of productivity attributable to seasonal ILI, for this group of children.

2. Materials and methods

2.1. The healthcare register

Data used in this study were obtained from the regional healthcare register (HCR) of the Östergötland County Council, located in southeast Sweden. The HCR contains information on all healthcare used in both primary and hospital care settings. The County Council provides publically financed healthcare to all 435,000 regional inhabitants, delivered through 44 primary healthcare centers and 3 hospitals. The HCR records all healthcare visits and links the information to a unique personal identification number. Records include data on the date of visit or admission, discharge date, diagnoses according to the International Classification of Diseases (ICD)-10, treatment received, X-ray examinations performed, etc. The medical costs for visits and inpatient care retrieved from the HCR were priced using a module Cost Per Patient (CPP) and are unique for each patient and encounter. In the HCR/CPP register, all treatments, operations, laboratory analyses, care efforts, etc. have a predefined price, as administrated by the Swedish Association of Local Authorities and Regions. The county HCR and the CPP module have been used in several studies for direct healthcare

costs calculations, for example, Wiréhn et al 2008,^[17] and in a study of influenza outbreaks by Timpka et al 2012.^[18] Data regarding visits to a primary care physician and outpatient and inpatient hospital care were retrieved from the HCR using a case-finding algorithm that retrospectively searched the register from August 1, 2005 to July 31, 2012. Children aged between 2 and 17 years were included by using the age as of August 1st of each year as inclusion criteria.

Records without a main diagnosis were omitted from the study, as were records from inpatient care where a main diagnosis, costs, and length of stay were missing. The quality of the HCR for outpatient data in terms of a main diagnosis being registered ranged from 92.6% to 97.8%. On average, 4.3% of registrations were excluded due to diagnosis omission (giving a quality of 95.7% valid posts); the majority was excluded from primary care. In total, 98.9% of inpatient care records were complete (98.4%–99.4% over the period).

Private primary healthcare is also recorded in the HCR, and constituted, on average, 12% of the primary care visits during the study period. However, these visits were not used in this study, mainly because Region Östergötland does not own these records. The exclusion of private primary records was compensated for by reducing the county population by (on average) 12% when calculating visits per 10,000 inhabitants (Table 1). The indirect cost calculations were sourced from elsewhere and were thus not affected by the type of primary care received. The HCR fulfills several purposes, and previous research has found it to be suitable and valid for population-based epidemiological studies.^[16]

2.2. The Register for prescribed and retrieved drugs

The National Board of Health and Welfare (Socialstyrelsen) maintains a register of all drug prescriptions that have been filled at a pharmacy by any Swedish inhabitant. This register also contains the actual cost for each drug issued. We obtained prescription drug data for all children aged 2 to 17 years during the study period, 2005 to 2012. The day of obtainment was used to determine seasonal classification (see below).

2.3. Study population

The study population included all children in the County of Östergötland. The number of children ranged from 79,653 in 2005 to 76,025 in 2012, contributing a total of 545,000 person-years to the study for outpatient and inpatient hospital care, and 479,200 person-years in primary care. A total of 637,700 visits to a physician with a recorded main diagnosis (irrespective of the diagnosis) were retrieved from primary and outpatient hospital care, together with 19,260 hospital admissions with complete records (Table 1).

2.4. Outcome definition

According to the European Centre for Disease Prevention and Control (ECDC), the disease behind an ILI visit may present and be characterized in different ways, with several terms being used.^[19] In this study, the term “ILI visit” was used to define the outcome of interest. Our definition was similar to those used in previous register studies,^[20,21] as described by Marsden-Haug et al 2007.^[22] In this study, we included patients according to the ICD-10 diagnosis registered in the HCR by the physician. An ILI visit was identified according to the 3 chosen groups defined in the ICD-10: acute upper respiratory infections (J00-J06),

Table 1**Population, outpatient visits (primary and hospital care), and hospital admission statistics for each year of study, from August 2005 to July 2012.**

	Year 1 (2005/2006)	Year 2 (2006/2007)	Year 3 (2007/2008)	Year 4 (2008/2009)	Year 5 (2009/2010)	Year 6 (2010/2011)	Year 7 (2011/2012)	Total PY (Average %)
Age 2–17 years								
Total population, n	79,653	78,969	78,518	77,844	77,358	76,646	76,025	545,013
Population in public primary care, n*	74,954	70,325	69,827	67,039	67,337	65,542	64,165	479,189
Primary care coverage, %	94.1	89.1	88.9	86.1	87.0	85.5	84.4	(87.9)
Males, %	51.4	51.3	51.3	51.2	51.2	51.3	51.3	(51.3)
Population aged 2–4 years								
Total, n	12,845	13,287	13,551	13,943	14,288	14,526	14,723	97,163
Males, %	51.2	51.3	50.8	50.7	51.0	51.4	51.5	(51.1)
Patients in outpatient care								
Total, n	39,252	39,816	39,019	39,642	40,518	40,923	39,835	279,005
Males, %	50.6	50.7	50.5	50.3	50.6	50.6	50.8	(50.6)
Outpatient care visits†								Visits
ILI-related, n	17,279	18,709	16,803	16,090	16,740	17,939	16,264	119,824
Other visits, n	70,612	72,512	71,255	70,298	76,571	78,958	77,671	517,877
Total visits, n	87,891	91,221	88,058	86,388	93,311	96,897	93,935	637,701
Proportion ILI-related visits, %	19.7	20.5	19.1	18.6	17.9	18.5	17.3	(18.8)
Patients in hospital care								Patients
Total, n	2568	2516	2321	2157	2128	2009	1999	15,698
Males, %	52.6	54.8	53.8	53.6	54.7	55.3	54.9	(54.2)
Hospital admissions								Admissions
ILI-related, n	106	92	103	106	129	78	111	725
Other, n	3038	2948	2781	2583	2539	2364	2282	18,535
Total, n	3144	3040	2884	2689	2668	2442	2393	19,260
Proportion ILI-related admissions, %	3.4	3.0	3.6	3.9	4.8	3.2	4.6	(3.8)

ILI=influenza-like illness, PY=person-years.

* Only data from the public primary care centers were available, thus 12% of the child population was excluded from the calculations of visits/10,000 residents in primary care.

† All visits to a physician in primary or outpatient hospital care where a diagnosis was registered.

influenza, pneumonia, and bronchitis (J09, J10, J11, J12, J13, J14, J15, J20), and otitis media (H65-H67). Physicians in primary care also use these ICD-10 codes, but with a varying degree of detail.

2.5. Seasonal classification

We used the “weeks” option in the statistical software package IBM SPSS, when extracting parts of a date variable (the date of visit or admission). The result was that week 1 for each year always started on January 1st, irrespective of the day of the week. The numbered weeks, therefore, do not completely equal the number of calendar weeks of the International Standard.^[23] Hence, we recategorized each “week 53” as belonging to week 52 in the same calendar year. For each year, the 3 main seasons were fixed in weeks: summer season (weeks 19–36), preinfluenza season (weeks 37–48), and the influenza season (weeks 49–18). For each year, we also defined the peak of the annual influenza season based on national statistics. This season was defined to last for 10 weeks every year, starting between weeks 1 and 6, depending on the year. The peak influenza season was defined by the highest incidence per week of ILI cases for the population aged 5 to 14 years during each season, as registered and reported by the Swedish Institute for Communicable Disease Control.^[24]

The type of influenza virus (H1N1) swine flu epidemic was most prevalent in our studied region in October and November 2009, near the start of year 5 (2009/10) in our study. Therefore, we chose to omit this year (2009/10) from the peak-of-influenza analyses, simply because no single peak of the influenza occurred later in year 5, according to the national statistics used for defining the peak period.^[24]

2.6. Cost calculations

2.6.1. Direct cost calculations for healthcare visits. The costs were expressed in Euro, in the price level of 2012. The costs for 2006 to 2011 were inflated using the consumer price index (CPI) to reflect the 2012 prices. The exchange rate from Swedish crowns (SEK) to Euro was set to 9 SEK per Euro. For each case in outpatient care where the cost for an outpatient care visit was less than 50 Euro (1.7% of all visits) or missing (2.3%), the cost was set at 50 Euro. If the cost of an outpatient visit during the study period exceeded 10,000 Euro the cost was set at 10,000 Euro, a valid substitute for 48 of 637,701 visits. For admissions that lasted fewer than 24 hours, the inpatient length of stay (LOS) was set at 1 day.

2.6.2. Direct cost calculations for prescribed and purchased drugs. The following 4 Anatomical Therapeutic Chemical (ATC) classification system groups^[25] were used to calculate the average cost of ILI-related treatment: J01, antibacterials for systemic use; R01, nasal preparations; R03, cough and cold preparations; and R05, respiratory system. Other relevant ATC groups did not vary by season or were used by such a small number of patients we chose to exclude them from the ILI ailment group, despite their relevance. These excluded ATC groups were: J02, J04, J05, D06, N02, and R02.

The drugs included in the calculations were delivered to the patient by the pharmacy. Any drugs administered during a healthcare encounter – during a hospital admission or while in the physician’s consulting room – were already calculated in the direct healthcare costs (as stated above). In addition to the total annual cost, the differences in cost were calculated as the average cost per week during the peak influenza season minus the average

cost per week during the preinfluenza season. All costs were expressed in Euro and adjusted to the price level of 2012 in the same manner as the costs for healthcare.

2.6.3. Indirect cost calculations and assumptions. The indirect costs of ILI were based on a fraction range (0.6–0.7) of the number of reimbursed VAB days (net). The number of childcare days were obtained via Statistics Sweden.^[16] The net childcare days (when parents stayed home from work) are equal to the loss of production at full time work, in contrast to the gross days of VAB, which are generated according to calendar days, and include part-time work. For more detailed information regarding the rules for VAB, please see the SDC 1, <http://links.lww.com/MD/B216> that describes Temporary Parental Benefits in Sweden.

In the county, the average number of reimbursed childcare days per year for the period 2006 to 2012 was 207,000, varying between 5140 net days in July and 27,160 net days in February (data for 2005 were unavailable). In a 2009 report of national figures for the Social Insurance, about 6% of all VAB reimbursements made were for children younger than 2 years, comprising about 7% of all days during 1 year (2009). Since our study excluded children younger than 2 years, the net days were reduced by 10%, resulting in an average of 186,300 days. Based on detailed statistics regarding reasons for absence (required by the Swedish Social Insurance Agency), we estimated ILI to be responsible for 60% to 70% of the days used (yearly average 2008–2012). The estimated loss of productivity amounted to 111,800 to 130,400 days per year, at an average cost of 155 Euro per day (2012) when using a human capital approach, including taxes for the employer. We also considered a mix of average wages for men (25%) and women (75%) when calculating the common average cost per day. These proportions reflect the parent in the family that makes most use of the benefit.

2.7. Statistical methods

A correlation analysis was performed between each diagnosis from primary/outpatient care that contributed to the variable “ILI visit” and the overall “ILI” variable itself. Diagnoses with 50 or fewer cases were excluded from the correlation analysis. Age-adjusted correlations between each single diagnosis within the outcome variable “ILI visit” and the outcome variable “ILI visit” itself were assessed using the option of “Partial correlation.” In statistic methodology terms, a partial correlation is done in the same way as a linear regression but the outcome (result) is presented as correlation coefficients, and not as beta coefficients. For all analyses in this study a (2-sided) probability (P) < 0.050 was considered statistically significant. All P -values below 0.001 are reported as P < .001. Odds ratios (ORs) and 95% confidence intervals were estimated using logistic regression for ILI visits across seasons, using the logistic regression option in IBM SPSS without covariates. The correlation between ILI visits and the VAB-reimbursed days was tested with a Pearson correlation coefficient. The number of months (N) in the correlation analysis was 84.

All statistics and dataset arrangements were performed using IBM SPSS (version 20 and 22), and MS Excel.

2.8. Ethical approval

This study was approved by the Regional Ethics Committee at Linköping University, Sweden, on January 23, 2013 [No: 2012/442–31].

3. Results

The ICD-diagnoses used for measuring ILI visits, and the distributions of these diagnoses, are shown in Table 2. The most common ILI-visit in the primary care setting for the children in this study was J06 (acute upper respiratory infections of multiple and unspecified sites) while H65 (nonsuppurative otitis media) was most common in the outpatient hospital care setting. For children admitted to a hospital, J15 (bacterial pneumonia) was the main diagnosis (30% of patients). The prevalence of each diagnosis varied across different levels of healthcare. Each of these unique ILI-diagnoses were significantly correlated with the outcome variable – overall ILI visits – in primary and outpatient hospital care settings (P < 0.001), but the strongest correlation was found for the diagnoses; J03, J06, H65, and H66. A high correlation indicates that the separate diagnosis followed a similar seasonal variation to the overall variable, while a low correlation indicates more unpredictable seasonal pattern. Seasonal variation was less evident for the other diagnoses, but none of the tested diagnoses had a negative correlation with the overall ILI visits variable. In general, inpatients with an ILI diagnosis were significantly younger than the average (7.4 vs 10.2 years). Inpatients with J15 had the longest length of stay (an average of 8.0 days), while the group J03 (acute tonsillitis) patients were the oldest (10.4 years). The youngest children had the highest frequency of ILI visits, followed by a decline during the early teens. Among the youngest children, boys had a higher frequency of ILI visits than girls, while girls showed an increase in ILI visits from the age of 14 (Fig. 1). The average number of ILI visits per month varied from about 150 to 600 per 10,000 children aged 2 to 4 years, and 100 to 200 for children aged 5 to 17 years. The influenza incidence peaked during the winter months (December to March) and was at its lowest during the summer. Visits related to the diagnosis of otitis media (H65–H67) showed the highest increase related to the peak of influenza (Fig. 2).

In the primary care setting, the number of ILI visits per week per 10,000 varied from 30 in the summer to 63 during the influenza peak season. The number of visits for hospital outpatient care was about 10 times less; 4 to 7 visits per week per 10,000 residents (Table 3). The youngest children (2–4 years old) had relatively more ILI visits than the older children (5–17 years old). Overall, 20% of the healthcare costs of children aged 2 to 4 years were related to ILI versus 10% for those aged 2 to 17 years (Table 3). During the 6-year study period (year 5 [2009/10] was excluded from these calculations), 20% of all visits or admissions were ILI-related, but these encounters accounted for 10% of the healthcare costs. For children aged 2 to 17 years, in the primary care setting the visit-to-cost ratio approached 1:1, with 32% of all visits made to a physician and 29% of the total costs, related to ILI.

Using the preinfluenza season as a reference category, during the peak season there was a significant increase in ILI visits by children aged 2 to 17 years to primary (OR 1.64, P < 0.001) and outpatient hospital (OR 1.43, P < 0.001) care. The increase in ILI-related visits from the preinfluenza season to the influenza season (excluding the peak) was also statistically significant (Table 4). Children aged 2 to 4 years had a greater seasonal variation of ILI visits compared with children \geq 5 years old. The OR in the primary care setting for visits during the season peak was almost doubled (OR 1.96) for these children, compared to the preinfluenza season. The corresponding OR for children aged 5 to 17 years was lower (OR 1.47), but still

Table 2

Visit and admission statistics across the ICD-10 diagnoses constituting an ILI-encounter (main diagnosis) and the partial correlations for each of the main diagnoses with the ILI-visit variable (0/1).

ICD-10 main diagnosis	Visits per 1000 ILI visits, ‰		Age adjusted correlation*		Hospital admissions, ‰	N
	Primary care	Hospital care	ICD-10 main with ILI visit	N		
J00 Acute nasopharyngitis [common cold]	0.02	0.40	–	50	0	0
J01 Acute sinusitis	13.09	1.61	0.118	1762	49.66	36
J02 Acute pharyngitis	25.73	2.33	0.157	3362	24.83	18
J03 Acute tonsillitis	214.92	9.38	0.441	26,876	187.59	136
J04 Acute laryngitis and tracheitis	2.54	0.45	0.050	358	13.79	10
J05 Acute obstructive laryngitis [croup] and epiglottitis	14.48	11.73	0.135	3141	162.76	118
J06 Acute upper respiratory infections of multiple and unspecified sites	350.95	16.33	0.562	44,009	122.76	89
J09 Influenza due to identified avian influenza virus	0.06	0.23	–	34	16.55	12
J10 Influenza due to identified influenza virus	0.00	0.02	–	2	2.76	2
J11 Influenza virus not identified	7.39	0.48	0.080	943	8.28	6
J12 Viral pneumonia	0.02	0.27	–	34	5.52	4
J13 Pneumonia due to Streptococcus pneumonia	0.01	0.05	–	7	6.90	5
J14 Pneumonia due to Hemophilic influenza	0.00	0.01	–	1	5.52	4
J15 Bacterial pneumonia, not elsewhere classified	0.07	4.20	0.058	511	286.90	208
J20 Acute bronchitis	0.16	1.98	0.040	256	49.66	36
H65 Nonsuppurative otitis media	34.83	48.24	0.251	9953	13.79	10
H66 Suppurative and unspecified otitis media	223.19	14.82	0.431	28,520	42.76	31
H67 Otitis media in diseases classified elsewhere	0.02	0.03	–	5	0	0
Total = 1000.00	887.46	112.54			1000.00	
Total N				119,824		725

ICD-10=International Classification of Diseases, version 10, ILI=influenza-like illness.

*Some diagnoses had such a small number of cases which motivated to omit any partial correlation test (–).

significant ($P < 0.001$). There was a significant decrease in ILI-related admissions during the summer, and a significant increase during the peak period of the influenza season when tested for the whole children population ($P = 0.036$ and $P = 0.012$, respectively). No similar pattern was seen when age-groups were tested separately, apart from a significant decrease during the summer period for the youngest children ($P = 0.018$).

Of the total ILI-related healthcare costs, the primary care setting generated two-thirds (63.9%), the hospital outpatient care setting one-quarter (25.5%), and hospital admissions one-tenth (10.6%). The healthcare average cost per week per 10,000 person years was 74,400 Euro overall. Of this 7700 Euro (10.3%) was related to ILI visits and hospital admissions

(Table 3). In primary care, the costs per week per 10,000 person years for ILI varied from 3500 to 7400 Euro, depending on the season. The total annual ILI costs, including all healthcare, amounted to 400,400 Euro per 10,000 children aged 2 to 17 years. There was no difference in average LOS (2, 3 days) between children admitted to hospital with ILI as the main diagnosis and those admitted with other diagnoses. However, the costs for ILI patients were lower than those of other patients (2910 Euro vs 3,490 Euro, $P = 0.051$). Drugs from the 4 ATC codes J01, R01, R03, and R05 were responsible for about half (23,200 Euro per 10,000 inhabitants) of the total annual cost for prescribed and obtained medicine during the study period (44,360 Euro per 10,000 inhabitants). The costs for the

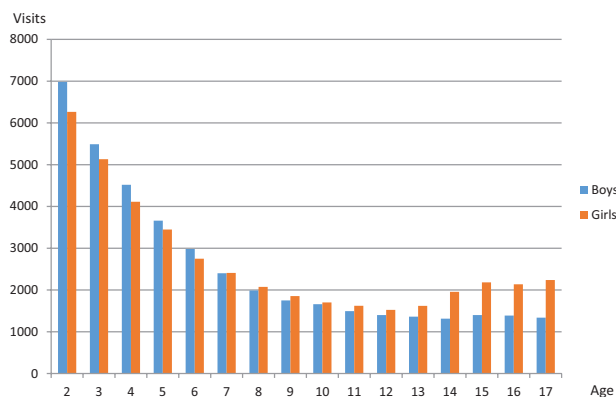


Figure 1. Total number of influenza-like illness (ILI) visits to a physician per 1000 person years, stratified by age and gender (including all years of study). This illustrates the decline in the number of visits with increasing age.

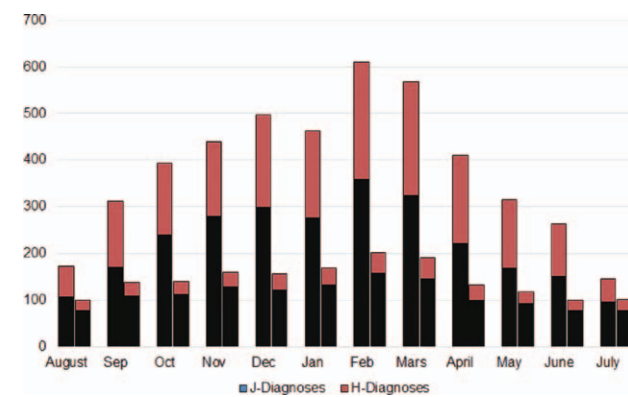


Figure 2. Average number of influenza-like illness (ILI) visits to a physician in primary care per 10,000 person-years, stratified by month (aggregated for all years of study) and age-group: 2–4 years (left bars) and 5–17 years (right bars).

Table 3**Average number of visits to primary or hospital outpatient care or hospital admissions and the total associated medical costs (data from 2009/2010 excluded).**

	Healthcare visits or admissions per week per 10,000 person-years				Cost (×1000 Euro)			
	Other	ILI	Total	% ILI-visits	Other	ILI	Total	% ILI-visits
Age 2–17 years								
PC								
Summer	91	30	121	24.8	11.9	3.5	15.4	22.7
Preinfluenza season	101	45	146	30.8	13.6	5.3	18.8	28.0
Influenza season excl. peak	91	49	140	35.0	12.0	5.7	17.7	32.2
Influenza peak season	100	63	163	38.7	13.3	7.4	20.7	35.7
Hospital outpatient (HC)								
Summer	87	4	91	4.4	28.3	1.2	29.5	4.2
Preinfluenza season	107	6	113	5.3	34.4	2.0	36.4	5.5
Influenza season excl. peak	93	6	99	6.1	30.7	1.9	32.7	5.9
Influenza peak season	102	7	109	6.4	28.1	2.4	30.4	7.8
HA								
Summer	7.4	0.2	7.6	2.6	21.9	0.5	22.4	2.4
Preinfluenza season	8.1	0.3	8.4	3.6	24.2	1.0	25.2	3.8
Influenza season excl. peak	8.3	0.4	8.7	4.6	21.8	0.7	22.5	3.2
Influenza peak season	6.6	0.3	7.0	4.3	23.6	0.9	24.6	3.8
Age 2–17 years								
In PC	95	44	139	31.6	12.6	5.2	17.7	29.1
In hospital outpatient care	96	6	101	5.5	31.4	1.8	33.2	5.4
PC and HC	191	50	241	20.6	44.0	7.0	50.9	13.6
HAs	8	0.3	8	3.8	22.7	0.8	23.5	3.2
Total week average PC, HC, and HA	199	50	248	20.1	66.7	7.7	74.4	10.3
Age 2–4 years								
In PC	109	90	198	45.2	13.1	10.2	23.3	43.7
In hospital outpatient care	92	14	105	13.0	29.7	4.6	34.4	13.5
PC and HC	201	103	304	34.0	42.8	14.8	57.6	25.7
HAs	7	1	8	7.8	23.0	1.6	24.5	6.4
Total week average PC, HC, and HA	208	104	312	33.4	65.8	16.4	82.2	19.9

HA=hospital admission, HC=hospital care, ILI=influenza-like illness, PC=primary care.

drugs in the 4 ATC groups delivered by pharmacies corresponded to 5.8% of the annual direct healthcare costs for ILI. These drugs costs were not included in the annual total direct costs for healthcare (0.4 million Euro per 10,000 children), although they are direct costs. The number of medicine packages delivered increased on average from 126 to 164 packages per week per

10,000 children aged 2 to 17 years. The costs for the drugs in the 4 ATC groups increased an average of 30.3% per week from the preinfluenza season to the peak influenza season. This 30% increase of delivered drugs during the peak influenza season amounted to an increased cost of 850 Euro per week per 10,000 inhabitants.

Table 4**Odds ratios for ILI visits to primary- and hospital-level care, stratified by season and age (year 2009/2010 excluded).**

Season and age-group	Primary care			Hospital outpatient care			Hospital inpatient care		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
2–17 years									
Summer	0.85	0.83–0.87	<0.001	0.95	0.90–0.99	0.040	0.80	0.65–0.98	0.036
Preinfluenza season	Ref.			Ref.			Ref.		
Influenza season	1.21	1.18–1.24	<0.001	1.07	1.02–1.12	0.009	1.21	0.98–1.48	0.074
Peak of influenza season	1.64	1.61–1.68	<0.001	1.43	1.36–1.50	<0.001	1.33	1.07–1.66	0.012
2–4 years									
Summer	0.82	0.79–0.85	<0.001	0.98	0.90–1.05	0.530	0.66	0.46–0.93	0.018
Preinfluenza season	Ref.			Ref.			Ref.		
Influenza season	1.18	1.14–1.23	<0.001	1.14	1.06–1.23	0.001	1.32	0.96–1.80	0.089
Peak of influenza season	1.96	1.89–2.04	<0.001	1.67	1.54–1.80	<0.001	1.33	0.94–1.89	0.113
5–17 years									
Summer	0.85	0.83–0.88	<0.001	0.92	0.86–0.98	0.011	0.88	0.68–1.15	0.355
Preinfluenza season	Ref.			Ref.			Ref.		
Influenza season	1.19	1.16–1.23	<0.001	0.99	0.93–1.06	0.812	1.04	0.79–1.37	0.768
Peak of influenza season	1.47	1.44–1.23	<0.001	1.28	1.19–1.36	<0.001	1.30	0.97–1.74	0.074

CI=confidence interval, ILI=influenza-like illness, OR=odds ratio, Ref.=reference category.

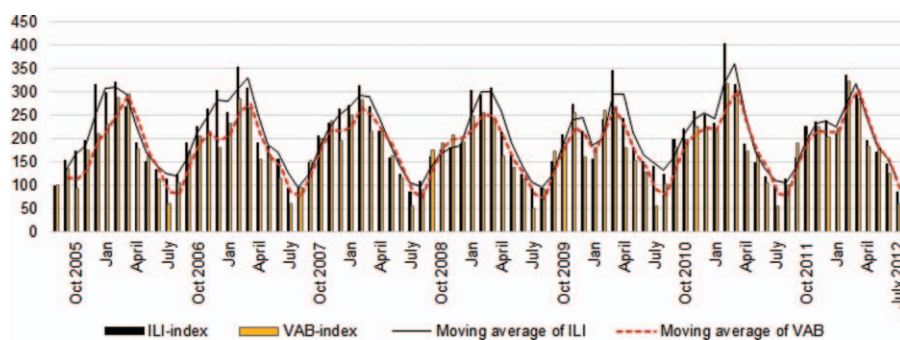


Figure 3. Seasonal variation of ILI visits in the county (ILI index) and the national number of reimbursed days for parental care of their sick children in Sweden (VAB index) during the study period. ILI=influenza-like illness, VAB=temporary parental benefit for staying home to take care of an ill child.

The number of days used for VAB displayed a strong seasonal variation, with the majority of days used during the influenza season (Fig. 3). The Pearson correlation between ILI visits in the study and VAB days used per month was $r=0.91$ ($P < 0.001$, $N=84$). The correlation between the VAB days used in the county compared to the national figures approached 1 ($r=0.993$, $P < 0.001$, $N=72$). However, data on VAB for the county were available for only 6 (of the 7 study) years, which explains smaller value of N . With the estimated figures for the loss of production due to VAB – stated in the Section 2 – these indirect costs were in the range of 17.3 to 20.2 million Euro per year for the county. This loss of production equals 2.2 to 2.6 million Euro per year per 10,000 children aged 2 to 17 years. The annual indirect costs in loss of production related to VAB are thus 5.2 to 6.2 times greater than the direct costs (2.2–2.6 million Euro vs €0.42 million Euro per 10,000 children annually).

4. Discussion

The results showed to what degree the number of ILI-visits and pharmacy drug purchases increased during the peak influenza season, compared with preinfluenza season, in children aged 2 to 17 years. Our analyses of healthcare costs related to ILI visits among children in a defined region included all levels of healthcare – primary and hospital in- and outpatient care settings – and incorporated pharmacy drug consumption. This, to our knowledge, is a unique design.

We found a strong correlation between the influenza season and parental leave of absence for taking care of ill children. This constitutes an indirect cost to both the individual and society. The parental leave figures for VAB were taken from official statistics and were not directly linked at patient level to the patients in the HCR. Indeed, they should not be since the clinical cases of ILI are always only a fraction of all children who experience an influenza episode, as stated above.^[2] A study in Finland found that for every 100 children aged 3 to 6 years with influenza, the parents were absent on average 146 days per influenza season (October to May). For the younger children, parental absence from work was even greater.^[9] Our results are consistent with results from a previous study by Fraaij and Heikkinnen, 2011.^[26] In that study, the authors described a similar morbidity pattern, also found that the bulk of the influenza-related disease burden is experienced in the outpatient setting, and reported substantial parental work absenteeism related to (their) children's ILI.

In terms of epidemiology, medical attention is not sought for every child with an ILI as many families will self-medicate. This

percentage of the population is unknown to public healthcare statistics. However, 1 Swedish study reported that only 8% of symptoms of sickness displayed by children aged 4 to 6 years led to consultation with a physician. During 1 winter month in that same study, >80% of the children younger than 6 years were reported to have had at least 1 symptom of illness, with a runny nose being the most frequently reported symptom.^[7]

The indirect costs in this study were derived from parental absence from work due to child illness, regardless whether they sought medical attention or not. However, there are more indirect costs than simply this loss of productivity. Children, especially the youngest children, may often act as vectors, and will spread ILIs to older family members, resulting in school and work absence due to ILI for the adults themselves. This implies that the total societal costs related to ILI are greater than what our study can present.

Primary care settings managed the majority of ILI visits for children and generated, in our study, around two-third of its costs. The number of visits related to ILI in primary care, and therefore the workload, peaked in late winter (January to March). However, the peak of visits made by children did not seem to affect the workload at the primary care centers to any significant degree. Two year statistics (from the HCR) of all medical encounters, including visits to a physician in primary care and paramedical encounters, show the highest workload to be in November.

Our results demonstrate the typical seasonal characteristics of ILI in north European countries. The region studied is located in the southern part of Sweden and due to climate variations there may be a certain north–south differences in Sweden. The winter season is both colder and longer further north in Sweden and the influenza virus is known to thrive better in a colder climate. The studied region, the county of Östergötland, accounts for 4.6% of the total Swedish population. The sociodemographic profile of the studied region is similar to that of the general Swedish population. We therefore consider this region generalizable to the rest of Sweden and possibly also to other countries in northern Europe.

Previous studies in this field used diagnostic definitions derived from ICD-9.^[20,21] Our definition of ILI follows the same general pattern as ICD-9 in these references, but is updated to correspond with ICD-10 (additional information is found in SDC 2, <http://links.lww.com/MD/B216>, a PDF-document describing ILI-diagnosis codes for computer algorithms). In our material, the difference due to diagnostic inclusion was shown to affect only a very small number of cases. The number of diagnoses

included in the ILI concept may have some impact on the analysis. A wider set of diagnostic codes could identify more ILI cases and yield an increased sensitivity, but would probably give a lower signal-to-noise ratio, as described by Marsden-Haug et al, 2007.^[22] With more “noise” there would be lower specificity, with a reduced proportion of true positive cases within all cases. Conversely, if the definition was set too narrow, we would miss a number of ILI cases, and instead, achieve a low sensitivity.

4.1. Strengths and limitations

Our study was based on register data of healthcare visits from all healthcare levels, including primary care, inpatient hospital care, and outpatient hospital care settings, thus eliminating biases related to self-reported events, missing data from follow-up periods, and selection procedures. To the best of our knowledge, our study is the only burden of ILI study using such a comprehensive database that also includes unique prices per procedure and patient (CPP). The costs for drugs are also not only based on prescription, but prescription and purchase through any pharmacy. This increases the validity of the costs for drugs because prescribed medicine is not always retrieved by the patient. The use of a population-based, longitudinal, open cohort also makes the outcomes robust.

We have no data for children <2 years of age in this study. For children <1 year of age, breastfeeding rates and duration may vary between different cultures and countries. Breast milk contains important immune factors that can prevent illness in breastfeeding children. Had we included children <1 year of age we may have decreased the generalizability to populations other than Swedish children aged up to 4 years (0–4 years). That, we do not have data for children >1 year but <2 years of age, can truly be seen as a limitation, as breastfeeding is not as common after the age of 1 year. Unfortunately, we do not have any HCR data available for children in this age group. Although inclusion or exclusion of data from 1-year-old children would hardly affect the outcome for the total cohort (2–17 years of age), it could possibly have some impact on the subgroup analysis of the youngest children (1–4 years old). However, to have any impact, even in this smaller and younger subgroup, the outcomes for the 1-year-old children would have to differ significant compared to the other 3 age-groups (2, 3, and 4 years old), to have any real impact. This seems unlikely to us.

Our findings depend on the quality of the HCR registry data, although nondifferential error would probably not affect internal validity. The quality and completeness of the registrations in the HCR are reported to be high, and it has proven to be a valid data source for other epidemiological studies.^[17] The physicians in primary care manage a large portion of patients with ILI-symptoms, which can, in some sense, be regarded as their area of expertise. We have great confidence that their use of stating diagnoses is similar to the use of stating diagnoses in the outpatient hospital setting. The wide range of diagnoses that we included in the ILI also ensured that specificity was maintained, since the doctor could use one of 18 ICD-10 codes within the ILI-definition used. When interpreting the results of the present study, it is important to note that we have a wide range of diagnostic codes and that the “real influenza cases” constitute a hidden proportion of all visits to a physician. The largest confounder is most probably the common cold, followed by other infections affecting the ear–nose–throat area. This means that besides influenza viruses there are other viruses and bacteria at play.^[18] Another limitation is that residents seeking healthcare outside the

region (or the nation) will not be registered in the HCR. This constitutes a theoretical under-representation in HCR for the studied region and period. However, we consider this to have a negligible effect on our findings. Visitors seeking healthcare in the region are included in the HCR, but were excluded from the analysis as nonresidents, including visitors would bias the outcome of population figures per 10,000 residents.

The direct costs calculated in this study are the actual costs, unique for each patient and derived from the CPP-database, and the total costs for the drugs, excluding any patient discounts. This makes our cost calculations more accurate than studies that use cost-estimates based on average or template costs.^[14] Indirect costs are usually not easy to calculate, though here we could use official statistics of reimbursed days for VAB for parents as a proxy for the loss of productivity costs, in the calculation of this particular indirect cost. We assumed ILI to be the cause of absence for at least 60% to 70% of total days reimbursed. This is our own estimate, inspired by analysis of the detailed statistics of reasons for VAB that we obtained personally from the Swedish Social Insurance Agency.

4.2. Limiting the burden of influenza in the society?

Several measures may help to reduce the incidence of seasonal influenza for children in a community. Better hygiene at kindergartens and schools and parental leave to take care of ill children can help reduce influenza rates. During the H1N1 swine flu epidemic, public health authorities launched a large campaign to promote hygiene in general and hand hygiene in particular. Campaigns like this are believed to have a long-term behavioral effects.^[27] Many kindergartens have mandatory leave for children with various infectious diseases, but the effects of that mandate are largely unknown. The welfare systems in Scandinavia, where employees (and people seeking employment) can stay at home when their children or they themselves are ill, can probably affect and slow down the spread of infectious diseases. One option to limit the impact of a seasonal influenza might be through different vaccination programs. Such vaccination programs have, for example, been launched in Finland and the UK, with varying results.^[28–30] If there is an outbreak of a serious infectious disease, 1 option can be simply to close down public areas, such as schools, kindergartens, and libraries.

5. Conclusions

Our results demonstrate a significant increased burden of disease during the influenza season and its peak period, with increased direct medical costs, especially in the primary care setting. The largest impact of ILI was identified among the youngest children (2–4 years). Increased parental absence from work to take care of ill children was also clearly demonstrated to correlate strongly with the ILI-related healthcare encounters; this loss of productivity constitutes major part of the societal costs.

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