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Article

Population-Based Study on Incidence, Risk Factors, Clinical Complications and Drug Utilisation Associated with Influenza in the United Kingdom

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Abstract This large population-based study using the UK-based General Practice Research Database was conducted to quantify influenza-related physician visits, clinical complications of and risk factors for influenza, and related drug use in all age groups from 1991 to 1996. A total of 141,293 subjects who had one or more diagnoses of influenza or influenza-like illness during the study period as well as the same number of age-, sex-, practice and calendar time-matched controls were identified. Adults aged 15–64 years had the highest influenza incidence rate. The risk of getting influenza was particularly increased for subjects with chronic respiratory conditions (asthma or chronic obstructive pulmonary disease, odds ratio 1.65, 95% confidence interval 1.60–1.70). Subjects with influenza were more likely to have a diagnosis of clinical complications than control subjects (relative risk 3.4, 95% confidence interval 3.3–3.6). The risk of developing clinical complications was highest for children and was elevated for subjects with certain underlying chronic conditions. In absolute terms, otherwise healthy adults (15–64 years) accounted for the greatest proportion of all influenza-related physician visits as well as clinical complications in this study population. Of the 141,293 subjects with influenza, 83,911 (59.4%) received drugs on prescription. The most frequently prescribed drugs were antibiotics (45.2%), followed by antipyretics/analgesics (22.5%). Influenza patients were approximately six times more likely to use drugs on prescription than controls. This analysis may lead to further analyses on the economic impact of influenza and the contribution of different population groups to that burden.

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Introduction

Influenza outbreaks occur annually across the world, causing excess morbidity and mortality [1–4]. Influenza is a substantial socioeconomic burden for society in terms of medical treatments (increase in practice visits, hospitalisations, clinical complications, drug use) and work absenteeism [5–12]. Many studies have primarily been directed at investigating the effects and complications of influenza in elderly persons [13, 14], children [15, 16], other particular age or gender groups [4], or subjects with preexisting comorbidities [14, 17]. This is in line with the commonly held perception that influenza is of scant importance to otherwise healthy adults. Previous studies, however, have noted that subjects between the ages of 15 and 64 years may substantially experience clinical complications asso-

ciated with influenza, such as severe respiratory tract infections requiring hospitalisations during winter epidemics [18].

Most previous studies on influenza and influenza-related clinical complications have focused on hospitalisation rates in relation to influenza epidemics [4, 19, 20]. Relatively little research has been done using data from the primary care setting, although influenza is an infectious disease that is predominantly dealt with in primary care facilities. Community-based surveys have assessed influenza incidence rates and suggested that acute respiratory infections (bronchitis, pneumonia), otitis media, and heart failure are the most frequently observed clinical complications of influenza [21–25]. The clinical course of such complications can be more severe in subjects with underlying chronic diseases of the respiratory tract or cardiovascular system [4, 13, 14, 17, 23].

There are limited data on the association between chronic diseases, the risk of contracting influenza, and the risk of developing influenza-related clinical complications. This large study using the General Practice Research Database (GPRD) was conducted to explore the incidence of influenza-related physician visits in the UK, to analyse whether the presence of chronic diseases is associated with an increased risk of getting influenza, to quantify influenza-related clinical complications for all age groups, and to explore prescription drug use for influenza and its clinical complications in the UK.

Materials and Methods

Data Source. This study was based on information derived from the large UK-based GPRD. General practitioners (GPs) from some 300 primary care practices record medical information on over 3 million currently registered patients in a standard manner and supply it anonymously to provide data for research purposes. The computer records contain patient demographics, symptoms and diagnoses (by OXMIS codes [Oxford Medical Information System], which are mapped onto ICD codes [International Classification of Diseases]), referrals, hospitalisations, and drug prescriptions in chronological order. Computerised recording was started by many GPs in the late 1980s and replaced the previously hand-written records. The GPRD is currently owned by the UK Department of Health and administered by the UK Medicines Control Agency. The accuracy and comprehensiveness of diagnoses and drug prescriptions in the GPRD has been validated and described elsewhere [26–29], and the GPRD has been the data source for numerous epidemiological research projects.

Base Population and Study Population. The base population consisted of all subjects registered in the GPRD until December 1996 (approximately 3.2 million subjects). The study population encompassed all subjects within the base population who had at least one clinical diagnosis of influenza or influenza-like illness (subsequently referred to as influenza) recorded in the GPRD between 1 January 1991 and 31 December 1996.

All subjects with a history of cancer of the haemopoietic system, AIDS, organ transplantation, or exposure to the immunosuppressants cyclosporine or azathioprine prior to the first influenza diagnosis were excluded from the study population. In addition, all subjects who were current users of oral steroids at the time of the influenza diagnosis were also excluded. These patients were removed from the study because the above conditions and medications are usually associated with an increased risk of infectious complications [30].

For each patient with influenza (hereafter referred to as cases), one control subject was selected from the base population. This control was a person who was registered with the same GP at the same time as the case but who did not get a GP-recorded diagnosis of influenza during the entire 6-year study period. In addition to attending the same general practice, the control was matched to the case on age (same year of birth) and gender, and the exact same date of the case's first influenza diagnosis during the study period was also the "index date" for the matched control. The same exclusion criteria were applied to controls and to cases.

Number of Influenza Cases Over Population Denominator (by Age), and Influenza Incidence Rates. The proportion of influenza cases over the denominator (i.e. the number of subjects in the entire database) was assessed separately for four different age strata (<15, 15–49, 50–64, and $65+$ years of age). In addition, monthly influenza incidence rates over time were assessed. For this purpose, influenza diagnoses separated by at least 30 days in the computer record were identified (if 2 or more influenza diagnoses were recorded within 30 days, these events were regarded as a single event). Subjects who were alive and actively registered in the GPRD in a given year during the study period formed the denominator. Influenza incidence rates in the GPRD were compared with data from the surveillance system of the Royal College of General Practitioners in the UK [24, 31] over the entire 6-year study period.

Chronic Diseases and the Risk of Getting Influenza. The prevalence of chronic diseases prior to the index date was compared between influenza cases and the matched control sample. For all cases and controls, it was assessed whether they had a diagnosis of a chronic respiratory disease (i.e. asthma, chronic obstructive pulmonary disease [COPD]), heart disease (i.e. congestive heart failure, ischemic heart disease), diabetes mellitus, Parkinson's disease, or cancer (except nonmelanoma skin cancer) recorded in the computer record prior to the index date. In order to explore whether the presence of any of these diseases may be associated with an altered risk of getting an influenza diagnosis, a conditional logistic regression analysis using the SAS software (release 6.12; SAS Institute, USA) was conducted.

Clinical Complications Associated with Influenza. All cases with influenza and all matched control subjects with influenza were followed-up for 30 days after the date of the GP-recorded influenza diagnosis. It was assessed whether they developed clinical complications of the respiratory tract (sinusitis, bronchitis, pneumonia, unspecific upper respiratory tract infection, acute asthma attack, croup, lung abscess, or pneumothorax), heart (myocarditis or pericarditis), central nervous system (meningitis, psychosis, epilepsy, or Guillain-Barré syndrome), kidneys (acute renal failure, glomerulonephritis, or nephrotic syndrome), or other complications (parotitis, aplastic anaemia, gastrointestinal bleeding, myositis, otitis media, or death) in the 30-day time-window after a computer-recorded influenza diagnosis. A comparison of the 30-day incidence rates between cases and controls yielded a relative risk estimate of developing clinical complications directly attributable to influenza.

Association Between Predisposing Diseases, Age, and Gender, and the Risk of Developing Clinical Complications. Within the entire case population, subjects who had a diagnosis of a chronic respiratory disease (i.e. asthma, COPD), heart disease (i.e. congestive heart failure, ischemic heart disease), diabetes mellitus,

Parkinson's disease, or cancer (except nonmelanoma skin cancer) recorded in the computer record prior to the first influenza diagnosis were identified and quantified. In an additional case-control analysis restricted to influenza cases only, it was evaluated whether the presence of such chronic diseases was associated with a higher risk of developing clinical complications. An unconditional logistic regression analysis was conducted, adjusting for gender (male, female) and age (1–14, 15–49, 50–64, 65+ years), comparing the prevalence of pre-existing diseases between influenza cases with clinical complications and those who did not develop clinical complications within 30 days after the index date.

Drug Use After Influenza Diagnoses. We assessed for each case and control whether they received drug prescriptions for antibiotics, antiviral agents (i.e. amantadine), antipyretics/analgesics (i.e. paracetamol, aspirin, ibuprofen, or naproxen), decongestants/nose preparations, cough medication, ear drops, or throat preparations within the 30 days after the influenza diagnosis. We also stratified drug use by the presence of clinical complications recorded in the computer profile in association with the influenza diagnosis.

Results

Number of Influenza Cases Over Population Denominator (by Age), and Influenza Incidence Rates. Within the entire base population of 3,298,045 subjects in the GPRD, 141,293 (4.3%) subjects had one or more diagnoses of influenza or influenza-like illness during the 6-year study period (14.8%, 57.6%, 15.2%, and 12.4% in the 4 age groups of <15, 15–49, 50–64 and 65+ years of age, respectively). There were 20,869 influenza cases in a base population of 685,443 subjects (0.03) in the young age group below 14 years of age, 81,426 cases in 1,668,623 subjects (0.049) in the age group of 15–49 years, 21,419 cases in 436,423 subjects (0.049) in the age group of 50–64 years, and 17,552 cases in 507,556 subjects (0.035) in the oldest age group of 65+ years. Thus, the number of influenza cases over the number of subjects in the base population (i.e. the proportion) in the four age strata was highest for the two middle age strata. Overall, 55.5% of influenza cases were female.

Of the 141,293 subjects with a diagnosis of influenza, 126,591 (89.6%) had a single influenza diagnosis recorded during the study period, 13,638 (9.6%) had two or three diagnoses, and 1,064 (0.8%) subjects had four or more separate influenza diagnoses during the 6-year study period. The total number of influenza events in the case population ($n=141,293$) during the study period was 161,198. Overall, the incidence rate of physician consultations due to influenza was 14.5/1,000 person-years (95% confidence interval [CI], 14.4–14.6) for the entire study period. The incidence rate was highest in the combined adult age group of 15–64 years (16.4/1,000 person-years), lowest in the older age group above age 65 (9.9/1,000 person-years), and 12.2/1,000 in the younger age group below the age of 14. The incidence rates derived from GPRD data were closely similar to the ones reported by the surveillance system of the Royal College of General Practitioners [14, 19] (Figure 1).

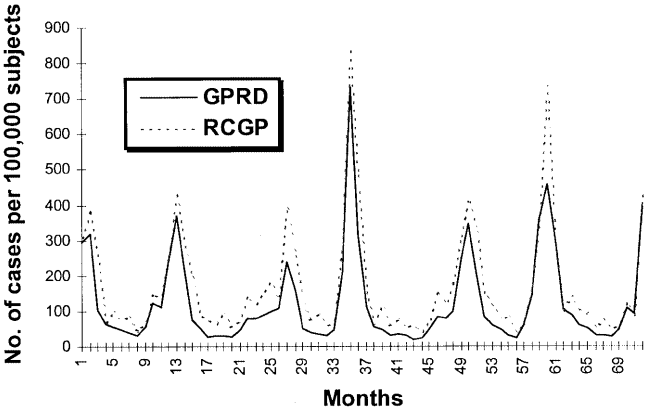

Figure 1 Influenza incidence rates in the UK during 1991–96 identified in the General Practice Research Database and reported by the Royal College of General Practitioners

Chronic Diseases and the Risk of Getting Influenza. Among all cases with an influenza diagnosis, 28,699 (20.3%) had at least one chronic disease recorded prior to the index date. Respiratory diseases (i.e. asthma, COPD) were most frequently recorded (9.1%), followed by cancer (4.6%), cardiovascular diseases (i.e. ischemic heart disease, congestive heart failure, 3%), diabetes mellitus (1.3%), and Parkinson's disease (0.1%). There were 3,079 (2.2%) subjects who had more than one of the above-mentioned diseases recorded prior to the first influenza diagnosis.

The prevalence of chronic diseases prior to the index date was slightly higher in cases than controls (odds ratio [OR], 1.37; 95% CI, 1.34–1.39). The risk was particularly increased for subjects with respiratory conditions, yielding an adjusted OR of 1.65 (95% CI, 1.60–1.70). It was only marginally increased in association with chronic cardiovascular diseases (adjusted OR, 1.23; 95% CI, 1.17–1.29), diabetes (adjusted OR, 1.11; 95% CI, 1.04–1.18), or cancer (adjusted OR, 1.08; 95% CI, 1.03–1.11) (Table 1).

Clinical Complications Associated with Influenza. Within the case population, 13,457 (9.5%) had clinical complications recorded within 30 days after an influenza diagnosis. Among the influenza cases with complications, 274 (0.2% of the total study population) died within 30 days of a recorded influenza diagnosis. There were 2,090 (1.5%) subjects who developed bronchitis, 540 (0.4%) who developed pneumonia, and 7,783 (5.5%) who developed an unspecified upper respiratory infection within 30 days after the influenza diagnosis. Furthermore, there were 1,479 (1%) patients who had a diagnosis of otitis media and 45 (0.03%) who had a diagnosis of sinusitis recorded during the follow-up period of 30 days after the index date. All other clinical complications were rare (Table 2).

Compared to the 13,457 (9.5%) influenza cases who developed clinical complications within 30 days after an

Table 1 Chronic diseases and the risk of developing influenza

Disease	Cases (141,293)	Controls (141,293)	OR (95% CI)
None	112,594 (79.7%)	118,652 (84.0%)	1.0 (reference group)
Respiratory tract	12,783 (9.1%)	8,270 (5.9%)	1.65 (1.60–1.70)
Cardiac	4,246 (3.0%)	3,773 (2.7%)	1.23 (1.17–1.29)
Diabetes	1,858 (1.3%)	1,792 (1.3%)	1.11 (1.04–1.18)
Parkinson	170 (0.1%)	219 (0.2%)	0.86 (0.70–1.05)
Cancer	6,563 (4.6%)	6,472 (4.6%)	1.08 (1.03–1.11)
Mixed	3,079 (2.2%)	2,115 (1.5%)	1.60 (1.51–1.69)
Any of the above	28,699 (20.3%)	22,641 (16.0%)	1.37 (1.34–1.39)

Table 2 Clinical complications in cases and controls, and relative risk (RR) estimates. Numbers in parentheses do not add up to 100% because subjects could have had more than one clinical complication

Type of complication	Cases ($n=141,293$)	Controls ($n=141,293$)	RR (95% CI)
Respiratory tract	11,367 (8.04%)	3,034 (2.15%)	3.8 (3.6–3.9)
Bronchitis	2,090 (1.48%)	341 (0.24%)	6.1 (5.5–6.9)
Pneumonia	540 (0.38%)	28 (0.02%)	19.3 (13.2–28.2)
URTI	7,783 (5.51%)	2,415 (1.71%)	3.2 (3.1–3.4)
First asthma attack	1,277 (0.9%)	266 (0.19%)	4.8 (4.2–5.5)
Lung abscess	3 (<0.01%)	0	NC
Pneumothorax	7 (<0.01%)	0	NC
Croup	46 (0.03%)	21 (0.01%)	2.2 (1.3–3.7)
Sinusitis	45 (0.03%)	15 (0.01%)	3.0 (1.7–5.4)
Cardiac	108 (0.08%)	52 (0.04%)	2.1 (1.5–2.9)
Myocarditis	107 (0.08%)	51 (0.04%)	2.1 (1.5–2.9)
Pericarditis	1 (<0.01%)	1 (<0.01%)	NC
Central nervous system	177 (0.13%)	89 (0.06%)	2.0 (1.5–2.6)
Meningitis	21 (0.01%)	2 (<0.01%)	10.5 (2.5–44.8)
Psychosis	46 (0.03%)	27 (0.02%)	1.7 (1.1–2.7)
Epilepsy	110 (0.08%)	60 (0.04%)	1.8 (1.3–2.5)
Guillain-Barré syndrome	2 (<0.01%)	0	NC
Renal	33 (0.02%)	5 (<0.01%)	6.6 (2.6–16.9)
Acute renal failure	29 (0.02%)	4 (<0.01%)	7.3 (2.6–20.6)
Glomerulonephritis	2 (<0.01%)	0	NC
Nephrotic syndrome	2 (<0.01%)	1 (<0.01%)	NC
Other	2,202 (1.56%)	841 (0.6%)	2.6 (2.4–2.8)
Otitis media	1,479 (1.05%)	572 (0.4%)	2.6 (2.4–2.9)
Parotitis	2 (<0.01%)	5 (<0.01%)	NC
Myositis	3 (<0.01%)	1 (<0.01%)	NC
Aplastic anaemia	1 (<0.01%)	0	NC
GI bleeding	453 (0.32%)	176 (0.12%)	2.6 (2.2–3.1)
Death	274 (0.19%)	91 (0.06%)	2.0 (2.4–3.8)
Total	13,457 (9.52%)	3,924 (2.78%)	3.4 (3.3–3.6)

URTI, unspecific respiratory tract infection; GI, gastrointestinal
NC, not calculated due to low numbers

influenza diagnosis, 3,924 (2.8%) of subjects in the matched control population had clinical complications recorded during the same 30-day interval after the same index date (Table 2). Thus, subjects with influenza were 3.4-times (95% CI, 3.3–3.6) more likely to have a diagnosis of clinical complications recorded in a 30-day time-window after the index date than controls. The difference, and therefore the number of subjects with clinical complications potentially attributable to influenza in 141,293 subjects, was 9,533 (6.7%).

Association Between Predisposing Diseases, Age, and Gender, and the Risk of Developing Clinical Complications. As compared to the reference group of cases who did not have any pre-existing diseases recorded, the relative risk estimates of developing clinical complications were highest for cases with chronic respiratory diseases (OR, 1.89; 95% CI, 1.80–1.99), Parkinson's disease (OR, 1.58; 95% CI, 1.02–2.46), and cardiovascular diseases (OR, 1.42; 95% CI, 1.29–1.58), after adjusting for age and gender. The adjusted relative risk estimate of developing clinical complications was not materially altered for subjects with diabetes (OR, 1.09; 95% CI, 0.93–1.28) or cancer (OR, 0.97; 95% CI, 0.89–1.06) (Table 3).

Within the group of influenza cases with predisposing respiratory diseases who developed respiratory complications (predominantly respiratory infections such as

Table 3 Risk of developing complications in relation to pre-existing chronic diseases in the case population (141,293)

Pre-existing disease or variable	Risk (odds ratio[a])	95% CI
None	1.0[b]	
Respiratory disease	1.89	1.80–1.99
Cardiovascular disease	1.42	1.29–1.58
Diabetes mellitus	1.09	0.93–1.28
Parkinson's disease	1.58	1.02–2.46
Cancer	0.97	0.89–1.06
Mixed complications	1.78	1.60–1.98
Age group 1–14 years	1.0[b]	
Age group 15–49 years	0.56	0.54–0.59
Age group 50–64 years	0.61	0.57–0.64
Age group 65+ years	0.69	0.64–0.74
Male	1.0[b]	
Female	1.14	1.10–1.18

[a] Adjusted for all other factors in the table
[b] Reference group

bronchitis or pneumonia), asthma was the most prevalent risk factor (>90%), while the remainder were subjects with COPD or a combination of both asthma and COPD.

The proportions of subjects who developed clinical complications in the age groups <15, 15–49, 50–64, and 65+ years were 14.2%, 8.2%, 9%, and 10.9%, respectively. Compared with the relative risk estimates (ORs) of developing clinical complications for the young age group below 14 years of age, the ORs for the other age groups were as follows: 0.56 (95% CI, 0.54–0.59) for 15–49 years, 0.61 (95% CI, 0.57–0.64) for 50–64 years, and 0.69 (95% CI, 0.64–0.74) for 65+ years. Females were slightly more likely to develop clinical complications within 30 days after an influenza diagnosis than males (OR, 1.14; 95% CI, 1.10–1.18) (Table 3).

While the young age group (<15 years old) had the highest proportion of subjects who developed clinical complications, the healthy middle-aged adults combined (15–64 years of age) without underlying chronic conditions accounted – in absolute terms – for the largest proportion (6,437=47.8%) of the total number of 13,457 influenza-related clinical complications in the entire study population (Table 4).

Drug Use After Influenza Diagnoses. Overall, 83,911 (59.4%) influenza cases received some of the above-defined drug treatments on prescription. The most frequently prescribed drugs were antibiotics (45.2%), followed by antipyretics/analgesics (22.5%). While 43.7% of the study subjects with influenza received drugs from only one of the above-mentioned categories, 22,230 (15.7%) received a combination of drug treatments. The proportion of subjects who received drug prescriptions was highest in the oldest age category, 65+ years (75.2%). In absolute terms, adults aged 15–64 years accounted for 69% of all drug prescriptions associated with influenza. Penicillins were the antibiotics used most often (Table 5).

Table 4 Clinical complications in influenza cases (141,293) by age and by presence of pre-existing chronic diseases. Percentages in parentheses are column percentages

Complication	Age group							
	1–14 years (20,896)		15–49 years (81,426)		50–64 years (21,419)		65+ years (17,552)	
	Healthy (17,201)	Predisposed[a] (3,695)	Healthy (69,231)	Predisposed[a] (12,195)	Healthy (16,017)	Predisposed[a] (5,402)	Healthy (10,145)	Predisposed[a] (7,407)
Respiratory tract	1,697 (9.9%)	520 (14.1%)	4,530 (6.5%)	1,337 (11.0%)	1,106 (6.9%)	604 (11.2%)	819 (8.1%)	754 (10.2%)
Bronchitis	113 (0.7%)	21 (0.6%)	748 (1.1%)	203 (1.7%)	309 (1.9%)	167 (3.1%)	273 (2.7%)	256 (3.5%)
Pneumonia	29 (0.2%)	9 (0.2%)	185 (0.3%)	35 (0.3%)	52 (0.3%)	27 (0.5%)	106 (1.0%)	97 (1.3%)
URTI	1,470 (8.6%)	302 (8.2%)	3,502 (5.1%)	684 (5.6%)	722 (4.5%)	300 (5.6%)	457 (4.5%)	346 (4.7%)
Cardiovascular	0	0	4 (0.01%)	9 (0.07%)	7 (0.04%)	20 (0.4%)	9 (0.1%)	59 (0.8%)
CNS	17 (0.1%)	0	85 (0.1%)	10 (0.1%)	16 (0.1%)	5 (0.1%)	21 (0.2%)	23 (0.3%)
Renal	2 (0.01%)	0	5 (0.01%)	3 (0.02%)	4 (0.02%)	2 (0.04%)	5 (0.1%)	12 (0.2%)
Other	701 (4.1%)	156 (4.2%)	646 (0.9%)	143 (1.2%)	141 (0.9%)	49 (0.9%)	195 (1.9%)	171 (2.3%)
Otitis media	684 (4.0)	153 (4.1%)	454 (0.7%)	94 (0.8%)	46 (0.3%)	16 (0.3%)	21 (0.2%)	11 (0.2%)
GI bleeding	17 (0.1%)	2 (0.1%)	171 (0.3%)	44 (0.4%)	81 (0.5%)	22 (0.4%)	67 (0.7%)	49 (0.7%)
Death	0	1 (0.03%)	21 (0.03%)	5 (0.04%)	12 (0.07%)	11 (0.2%)	110 (1.1%)	114 (1.5%)
Total	2,311 (13.4%)	650 (17.6%)	5,185 (7.5%)	1,472 (12.1%)	1,252 (7.8%)	670 (12.4%)	981 (9.7%)	936 (12.6%)

[a] Predisposed subjects had ≥1 chronic diseases recorded prior to the date of the influenza diagnosis
URTI, unspecific respiratory tract infection; CNS, central nervous system; GI, gastrointestinal

Table 5 Drug use in the study population, by age group. Numbers in parentheses are column percentages; they do not add up to 100% because subjects could have used multiple drugs

	Age 1–14 yrs. (20,896)	Age 15–64 yrs. (102,845)	Age 65+ yrs. (17,552)	Total (141,293)
Any drug use	12,548 (60.0%)	58,172 (56.6%)	13,191 (75.2%)	83,911 (59.4%)
Antipyretics/analgesics	7164 (34.3%)	18,179 (17.7%)	6474 (36.9%)	31,817 (22.5%)
Antibiotics	7180 (34.4%)	46,605 (45.3%)	10,071 (57.4%)	63,856 (45.2%)
Penicillins	5256 (25.2%)	28,922 (28.1%)	6173 (35.2%)	40,351 (28.6%)
Cephalosporins	724 (3.5%)	4989 (4.9%)	1463 (8.3%)	7176 (5.1%)
Macrolides	1418 (6.8%)	7872 (7.7%)	1504 (8.6%)	10,794 (7.6%)
Quinolones	4 (0.02%)	1057 (1.0%)	482 (2.7%)	1543 (1.1%)
Tetracyclines	48 (0.2%)	6977 (6.8%)	1518 (8.6%)	8543 (6.0%)
Sulfonamides	503 (2.4%)	3525 (3.4%)	883 (5.0%)	4911 (3.5%)
Amantadine	0 (0%)	45 (0.04%)	12 (0.1%)	57 (<0.1%)
Nasal decongestants	1603 (7.7%)	3893 (3.8%)	708 (4.0%)	6204 (4.4%)
Ear drops	36 (0.2%)	66 (0.1%)	56 (0.3%)	158 (0.1%)
Cough medication	1791 (8.6%)	4514 (4.4%)	1829 (10.4%)	8134 (5.8%)
Throat preparation	13 (0.06%)	42 (0.04%)	9 (0.05%)	64 (<0.1%)

Table 6 Drug use in the study population by presence of complications after influenza (by age group). Numbers in parentheses are column percentages; they do not add up to 100% because subjects could have used multiple drugs

Age group	Type of drug	No complications		Complications		Total study population	
		Cases	Controls	Cases	Controls	Cases	Controls
1–14 yrs.	any drug	9,927 (55.4%)	1,066 (5.5%)	2,621 (88.5%)	1,185 (81.2%)	12,548 (60.1%)	2,251 (10.8%)
	antibiotics	4,997 (27.9%)	717 (3.7%)	2,183 (73.7%)	1,041 (71.3%)	7,180 (34.4%)	1,758 (8.4%)
	analgesics	5,793 (32.3%)	326 (1.7%)	1,371 (46.3%)	320 (21.9%)	7,146 (34.3%)	646 (3.1%)
15–64 yrs.	any drug	50,664 (53.8%)	6,530 (6.5%)	7,508 (87.5%)	1,530 (74.1%)	58,172 (56.6%)	8,060 (7.8%)
	antibiotics	39,622 (42.0%)	3,381 (3.4%)	6,983 (81.4%)	1,423 (68.9%)	46,605 (45.3%)	4,804 (4.7%)
	analgesics	15,927 (16.9%)	3,261 (3.2%)	2,252 (26.3%)	229 (11.1%)	18,179 (17.7%)	3,490 (3.4%)
65+ yrs.	any drug	11,518 (73.7%)	3,069 (17.9%)	1,673 (87.3%)	276 (69.4%)	13,191 (75.2%)	3,345 (19.1%)
	antibiotics	8,544 (54.7%)	670 (3.9%)	1,527 (79.7%)	221 (55.5%)	10,071 (57.4%)	891 (5.1%)
	analgesics	5,714 (36.6%)	2,546 (14.8%)	760 (39.7%)	106 (26.6%)	6,474 (36.9%)	2,652 (15.1%)
All groups	any drug	72,109 (56.4%)	10,665 (7.8%)	11,802 (87.7%)	2,991 (76.2%)	83,911 (59.4%)	13,656 (9.7%)
	antibiotics	53,163 (41.6%)	4,768 (3.5%)	10,693 (79.5%)	2,685 (68.4%)	63,856 (45.2%)	7,453 (5.3%)
	analgesics	27,434 (21.5%)	6,133 (4.5%)	4,383 (32.6%)	655 (16.7%)	31,817 (22.5%)	6,788 (4.8%)

Table 6 shows the distribution of total drug use and of use of antibiotics or antipyretics/analgesics by age for cases and controls, stratified by the presence of clinical complications. Overall, 87.7% of influenza cases with clinical complications received some drugs on prescription. Antibiotics were prescribed to 79.5% of influenza cases with clinical complications, while 41.6% received antibiotics in the absence of any computer-recorded clinical complications ($P<0.0001$). The proportion of subjects in the matched control group who received any of the study drugs within 30 days after the index date was 9.7%, as compared to 59.4% in the influenza cases ($P<0.0001$). Thus, influenza cases were approximately six times more likely to use drugs on prescription than an age- and sex-matched random sample of the general population at the same point in time registered in the same general practice. Overall, 45.2% of influenza cases and 5.3% of subjects in the matched control population received antibiotics in the 30-day time-window immediately following the index date ($P<0.0001$). In absolute numbers, there was an excess number of 70,255 prescriptions for any drugs, and of 56,403 prescriptions for antibiotics directly attributable to influenza and its clinical complications.

Discussion

To our knowledge, this is the largest population-based primary-care survey on influenza describing and quantifying influenza-related complications, health resource utilisation, and drug use on prescription in all age groups. In the early 1970s Kavet [32] described the burden of illness of influenza in the USA over the three "seasons" 1963, 1966, and 1969, but we are not aware of any observation of the burden for different age groups.

Most findings are consistent with previous studies. We found an increased risk of developing complications in subjects with predisposing illnesses [14, 17, 33]. Respiratory tract infections were the most frequent clinical complications, and chronic respiratory diseases the strongest risk factors for developing clinical complica-

tions [33]. A finding of particular interest, which is not necessarily in line with previously published results, is the fact that subjects between the ages of 15 and 64 had the highest consultation rates for influenza during the 6-year study period, higher than children below the age of 14 and higher than elderly people above the age of 65 years. On the other hand, children had the highest complication rates (particularly respiratory tract infections), followed by the elderly and the middle-aged adults. In absolute numbers, however, adults aged 15–64 were responsible for most consultations for influenza as well as for the majority of clinical complications. This finding is of particular interest with regard to the economic burden of influenza in the community, and it may lead to further economic analyses about the impact of influenza on the community and the contribution of different population groups to that burden.

In the current investigation, the monthly incidence rates derived from GPRD data were highly consistent with data from the influenza surveillance system of the Royal College of General Practitioners (RCGP), a UK-based sentinel system. A group of general practitioners report the number of influenza cases seen in their surgery on a weekly basis to the RCGP, which allows the assessment of population-based incidence rates [24, 31]. Johnson et al. [34] analysed influenza incidence rates based on a UK-based computer database (Meditel) and compared them with those from the RCGP. The peak incidence rates from the computerised system occurred around the same time, but they were only approximately a third to a quarter of those derived from the RCGP's surveillance system. The GPRD data yielded incidence rates that were closely similar to the RCGP data, even though some of the peaks in the GPRD were also somewhat lower during the 6-year study period. The high concordance between the two data systems indicates that diagnosis misclassification in the GPRD in the current investigation is not likely to be substantial, since the majority of all influenza diagnoses was recorded during documented influenza peaks, i.e. at times when influenza viruses most likely circulated in the community.

Any assessment of influenza incidence rates based on data from general practices is likely to underestimate the real incidence rate in a population, because an unknown proportion of subjects with influenza may not see a doctor, choosing instead to treat themselves at home. On the other hand, there is also some misclassification with regard to the correct diagnosis of influenza in a general practice setting. Influenza is a rather subjective diagnosis that is based on a combination of symptoms during a given time period when influenza is most likely to occur. In this large population-based study, it was not possible to verify influenza diagnoses by serologic tests, and some clinical occurrences of influenza may have been caused by other infective agents [21, 35, 36]. Furthermore, subjects with severe symptoms, complications, high fever, advanced age, and/or pre-existing comorbidities may be more likely to see their GP for influenza-related symptoms compared to the "average" population. This might have led to some overestimation of the burden of illness of flu in this study. On the other hand, it is possible that some complications may have been missed due to possible nonspecific coding by the GPs (e.g. cough, which may have reflected an uncoded underlying bacterial superinfection). It is not possible to estimate to what extent these sources of misclassification may counterbalance each other, but it is certain that there is some misclassification in a large computer-based survey like this.

The relative risk estimates of developing clinical complications in association with pre-existing diseases (i.e. chronic respiratory, cardiovascular, or other illnesses) need careful interpretation. The approximately 1.5- to 2-fold increased risk of developing clinical complications for subjects with a history of chronic respiratory or cardiovascular diseases and for those with Parkinson's disease may reflect a real increased risk. Alternatively, it may simply reflect a higher likelihood of getting an influenza diagnosis recorded (diagnostic bias) because such patients are more likely to see the GP on a regular basis or because they are more careful about their health and more likely to report fever and cold symptoms to their GP. However, it may be noted that there was no suggestion of a materially altered complication risk for subjects with cancer (OR, 0.97; 95% CI, 0.89–1.06), and only a weakly increased risk for subjects with diabetes mellitus (OR, 1.09; 95% CI, 0.93–1.28), both diseases that may also be associated with increased medical attention. The fact that we did not find evidence of a substantially increased complication risk for subjects with diabetes does not necessarily contradict previous findings indicating that diabetics are susceptible to more severe complications, if developed, and at increased risk of dying from respiratory complications [37, 38].

Drug utilisation patterns in the study population need to be interpreted cautiously, since some underrecording of drug use may have occurred. This may have affected drugs that can also be purchased over the counter, such as certain analgesics (paracetamol, aspirin, ibuprofen) as well as some cough medication or nasal decongestants. On the other hand, exposure to antibiotics is most likely comprehensive since antibiotics are available only on prescription. The findings of this analysis indicate that drug use for influenza, particularly in association with clinical complications, is substantial in the study population and causes substantial direct costs to society. Antibiotic use for influenza infections has been assessed previously [16, 39], but has not been directly quantified to the level of sensitivity of this study. It is difficult to firmly distinguish between use of antibiotics for the treatment or for the prevention of complications in a large and retrospective obser-

vational study. Even though antibiotic use was much higher in subjects with clinical complications, it can be assumed that prophylactic use was substantial in the current study population.

Most previous observational studies compared excess morbidity, mortality, or drug use between influenza epidemics and nonepidemics to quantify the risks attributable to influenza [4, 16, 40]. It is a strength of this study that we were in a position to directly compare complication rates and drug use between influenza cases and matched controls at the same season in the same year, leading to a direct assessment and quantification of the burden attributable to influenza.

In summary, this large population-based investigation quantified consultation rates, clinical complications, and drug use directly related to influenza and suggests that influenza-associated health resource utilisation as well as drug use is substantial in all age groups. Adults (15–64 years) caused most influenza-related physician visits, clinical complications, and drug use in absolute numbers. These data will provide evidence for further economic studies exploring the influenza-related economic burden of illness to society and for economic evaluations assessing the benefits of interventions to prevent and/or treat influenza and influenza-like illness.

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