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Influenza-attributable burden in United Kingdom primary care

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SUMMARY

Influenza is rarely laboratory-confirmed and the outpatient influenza burden is rarely studied due to a lack of suitable data. We used the Clinical Practice Research Datalink (CPRD) and surveillance data from Public Health England in a linear regression model to assess the number of persons consulting UK general practitioners (GP episodes) for respiratory illness, otitis media and antibiotic prescriptions attributable to influenza during 14 seasons, 1995–2009. In CPRD we ascertained influenza vaccination status in each season and risk status (conditions associated with severe influenza outcomes). Seasonal mean estimates of influenza-attributable GP episodes in the UK were 857 996 for respiratory disease including 68 777 for otitis media, with wide inter-seasonal variability. In an average season, 2·4%/0·5% of children aged <5 years and 1·3%/0·1% of seniors aged ⩾75 years had a GP episode for respiratory illness attributed to influenza A/B. Two-thirds of influenza-attributable GP episodes were estimated to result in prescription of antibiotics. These estimates are substantially greater than those derived from clinically reported influenza-like illness in surveillance programmes. Because health service costs of influenza are largely borne in general practice, these are important findings for cost-benefit assessment of influenza vaccination programmes.

Key words: Epidemiology, GP surveillance systems, infectious disease, influenza, influenza vaccines.

INTRODUCTION

In most winters, influenza causes substantial morbidity and mortality [1, 2], with widely variable clinical manifestations ranging from subclinical infection to fatal illness [3]. Although many persons become infected, seroprevalence studies indicate that only a minority make use of health services [4]. Nevertheless, those that do create considerable pressure on both primary- and secondary-care services [5, 6]. The risk of serious illness involving hospital admission or death is thought to be higher in persons with chronic illness [7], but the total impact of influenza on health services comes at least as much from otherwise healthy persons [8]. In the UK this impact is concentrated in a comparatively short epidemic period of around 8 weeks [9], creating surge pressures on health services, commonly in midwinter, when the impact of other respiratory viral infections is also highest [10].

Policies to prevent and treat influenza need to accommodate the varying threat from different virus strain types, changes in severity of epidemics over time,

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advances in vaccines, the ageing population, increasing population expectancies from healthcare and changes in healthcare delivery. These factors interact to influence the cost effectiveness of medical intervention, and create the need to update burden assessments on a continuing basis using measurements from several seasons.

Most estimates of the influenza burden employ modelling methods in which the identification of the influenza epidemic period is determined from available virology data and the impact measured in the commensurate changes in the chosen outcome [11–15]. In some modelling studies, influenza virus data have been used exclusively, but the confounding effect of other viruses has prompted the inclusion of data for other viruses, especially respiratory syncytial virus (RSV). In a few studies, meteorological data has been incorporated as well [13, 14]. This study aims to provide a comprehensive analysis of the burden of persons consulting a general practitioner (GP) for a cause attributable to influenza over many seasons, to inform cost-benefit analyses of vaccination and treatment interventions. We used consultation data from the Clinical Practice Research Datalink (CPRD) and virology data from Public Health England (PHE) in a linear regression model to estimate influenza-attributable consultations and antibiotic prescriptions over 14 seasons, while controlling for RSV and other seasonal variables, and stratifying the analyses by age, comorbidity risk and influenza vaccination status.

METHODS

Study design

Viral surveillance time-series regression models were used to estimate the number of persons consulting a GP for influenza-attributable respiratory disease in England in each season (July in the index year through June the following year), from 1995 to 2009, stratifying by age, risk status and vaccination status (www.clinicaltrials.gov: NCT01520935). Seasons after July 2009 were not included as we were concerned to establish the normal or average seasonal burden of influenza, which was disturbed by the pandemic experience in summer 2009.

Data sources

At the midpoint of the study (January 2001) the monitored population was around 3·7 million. Patients included in the study were registered in approximately 550 general practices [16]. Individual patients could be followed for varying durations during this period. CPRD diagnoses and interventions are summarized and stored as READ codes.

Weekly influenza and RSV counts were obtained from PHE. Influenza reports are based on regular returns of virus swab-positive tests to PHE, mainly from community-based investigation of persons with influenza-like illness. RSV reports are mainly confirmed infections in young children admitted to hospital with respiratory infections. We used only counts of positive nose/throat swabs or nasopharyngeal aspirates. Viruses were classified as A or B without further classification.

All analyses of CPRD were restricted to English practices to match the coverage of virology data.

Outcome definitions

A GP episode was counted as the first in a series of consultations for a particular diagnosis/diagnostic group. A minimum of 28 days was required following any previous consultation for that same diagnosis/diagnostic group before defining a new episode.

Diagnostic READ codes were combined into respiratory diagnoses consistent with recognized ICD-10 groupings (Table 1) (see Supplementary material). We undertook a preliminary search of records to find codes that increased during influenza active periods. Our ‘respiratory disease broadly defined’ outcome included all disorders in the ICD-10 respiratory disease chapter, otitis media, as well as selected presenting symptom codes we found were used by some GPs in lieu of specifying a clinical diagnosis. A negative control outcome (urinary tract infection) with no seasonal pattern and association with influenza was included to control for the possibility of bias in model attribution over the entire study period.

Time-series of numbers of prescriptions of broad spectrum penicillin, tetracycline and macrolide antibiotics, which are widely prescribed for acute respiratory infections, were also examined as an outcome category.

Vaccination and risk status

The CPRD dataset contains unique patient identifiers, allowing patients to be followed longitudinally. Since almost all influenza vaccination during the study period was undertaken by GPs and recorded using specific codes, we were able to check the vaccination

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Table 1. *Outcomes: general practitioner consultations (CPRD)**

Outcome	ICD-10 codes
Respiratory diseases	
Respiratory disease broadly defined: Resp dis + symptoms + sepsis	J00–99, R05–06, B34, A40–41, P36
Respiratory disease	J00–99
Acute upper respiratory disease	J00, J02–06
Pneumonia and influenza	J09–18
Bronchitis/bronchiolitis	J20–22, J40
Influenza-like illness	J09–11, B34
Non-respiratory diseases	
Otitis media	H65–66, H70
Urinary tract infection	N39
Drug prescriptions	
Antibiotics (broad spectrum penicillins, macrolides, tetracyclines)	
Risk factor definitions	Chronic heart disease; renal; diabetes (diagnosis/ monitoring); liver; stroke/ TIA; MS-CNS; COPD_no_asthma; asthma; immuno; immuno_suppressant treatment; anti-asthmatic treatment

* Any Clinical Practice Research Datalink (CPRD) GP episode, including office visits, home visits, telephone consults and other types, for subjects registered with research quality data in CPRD. CPRD diagnostic data are coded using READ codes selected to correspond to ICD-10 definitions.

status for each person in each season. Vaccine coverage in the CPRD population was used to estimate the vaccination coverage in each age-risk stratum. We also externally validated the CPRD vaccination coverage estimates against national data on vaccination coverage [17]. We classified each patient as 'high' or 'low' risk by the prior occurrence of diagnoses that would prioritize the patient to receive influenza vaccination by reference to the accumulated historical records in the database (Table 1) [18].

Denominators

The CPRD covers a population which is representative of England in age and gender distribution and is thus a suitable population-denominated database for the assessment of vaccination status and national patterns of comorbidity in age- and gender-specific groups [19]. We found excellent agreement between CPRD and independent data sources for the UK with respect to the population age structure, the prevalence of various risk factors, and influenza vaccination coverage; for example, CPRD data yielded an average vaccination rate of 71% for persons aged $\geqslant 65$ years for the years 2001–2008, in close agreement with PHE estimates [17]. The 2001 UK population (Office of National Statistics [20]) was thus used to weight the English CPRD population by age to reflect the UK profile.

Statistical methods

Statistical analyses were performed using SAS v. 9.2 (SAS Institute Inc., USA). Weekly time-series of the number of specimens positive for influenza A, influenza B and RSV were generated using PHE virology surveillance data. Weekly time-series for multiple influenza-related health outcomes (Table 1) were generated from the CPRD for age groups <5, 5–17, 18–49, 50–64, and $\geqslant 65$ years (for selected analyses age groups 65–74 and $\geqslant 75$ were examined separately) and low-/high-risk groups. A multiple linear regression model was applied to each age group to associate GP episodes to influenza A or B, while controlling for RSV and unspecified seasonal factors (Fig. 1). Major changes in virus detection methodology were undertaken by PHE in 2001; thus, to avoid bias the model separated the periods before and after this date:

$$\begin{aligned} Y = {} & \beta_0 + \beta_{s1} t + \beta_{s2} t^2 + \beta_{s3} t^3 + \beta_{s4} \sin(2\pi t/52{\cdot}18) \\ & + \beta_{s5} \cos(2\pi t/52{\cdot}18) \\ & + \beta_{p1a} \text{InfluenzaA}(\text{pre-July 2001}) \\ & + \beta_{p1b} \text{InfluenzaA}(\text{post-July 2001}) \\ & + \beta_{p2a} \text{InfluenzaB}(\text{pre-July 2001}) \\ & + \beta_{p2b} \text{InfluenzaB}(\text{post-July 2001}) \\ & + \beta_{p3a} \text{RSV}(\text{pre-July 2001}) \\ & + \beta_{p3b} \text{RSV}(\text{post-July 2001}), \end{aligned}$$

where, Y is the incidence (rate) of outcome definition for each time period t (weeks), RSV and influenza are the proportion of laboratory isolates during t, sin and cos are harmonic functions of t, and the remaining terms track other types of secular trends in the data. The time period t used in the model is a running index of weeks starting 1 October 1997 and ending 31 March 2009.

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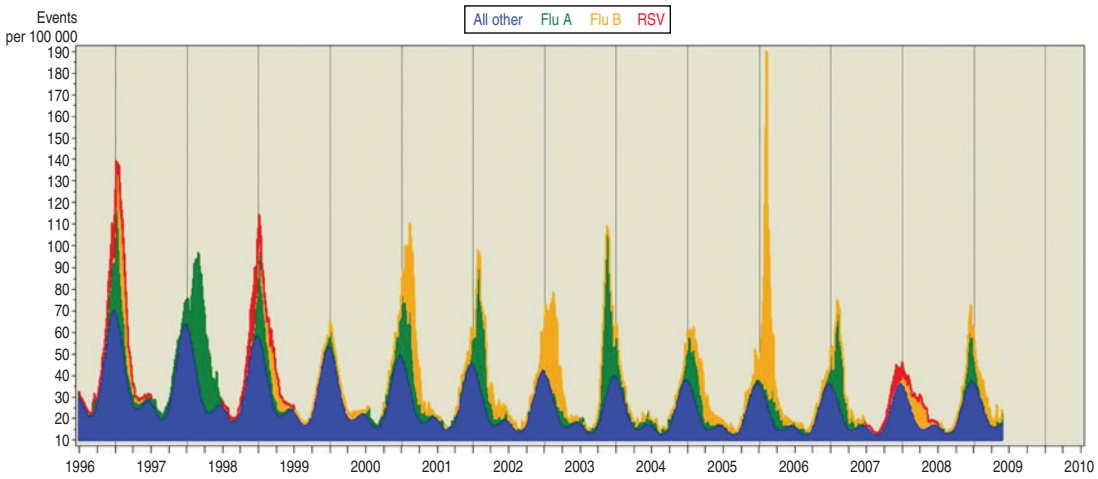

Fig. 1. Attribution modelling showing excess GP episodes attributable to influenza A and B and respiratory syncytial virus (RSV) in children aged 5–17 years. The pattern was observed to be the same for other age groups. 'All other' refers to GP episodes not attributable to influenza or RSV. The denominator is the UK population.

β_{p1a}Influenza A(pre-July 2001) + β_{p1b}Influenza A (post-July 2001) are influenza terms pre- and post-July, 2001. The RSV terms control for RSV epidemics. Influenza A, Influenza B and RSV are observed counts of positive tests from the PHE LabBase dataset.

Outcome and pathogen series were tri-mean-smoothed, i.e. the smoothed value of X at week t is $(X_{t-1} + X_t + X_{t+1})/3$. The week numbers ($t$) were calculated as ISO 8601 V-weeks. The weekly attribution to each virus was computed as the product of the observed value of the explanatory variable (i.e. number of positive virology samples) and the corresponding regression coefficient (β_{p1a}–β_{p2b}), and the weekly estimates summed to produce the seasonal estimates. The variability of seasonal estimates was assessed using standard deviations but limited to all-age estimates. This standard deviation represents the variability of the attributable burden between seasons and not the uncertainty of the individual seasonal estimates. Results were expressed as numbers of persons consulting a GP (GP episodes) and as the mean seasonal (from September to mid-May) rates of persons consulting a GP per 100 000 population.

Outside pandemics, influenza is exclusively a winter illness and thus summertime data were excluded from the analysis. Previous evidence suggests that winter increases in the incidence of RSV-associated outcomes (e.g. acute bronchitis) in adults follow those in children by 2–3 weeks [1]. Therefore, for age groups aged $\geqslant$18 years, we lagged the RSV time-series by 2 weeks and achieved an improved model fit; we did not lag the influenza time-series as doing so did not substantially alter model fit or influenza burden attributions. The time-series of prescriptions of antibiotics was modelled in the same way as the health outcome time-series to estimate antibiotic prescribing attributable to influenza. The model did not attribute any positive influenza burden to the control outcome (urinary tract infection).

The protocol was approved by the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink (CPRD, formerly the General Practice Research Database). Informed consent was not required.

RESULTS

Time trends

The onset of the influenza epidemic period usually followed RSV, and influenza A usually preceded influenza B (illustrated for the 5–17 years age group in Fig. 1).

Model fit

The goodness-of-fit was assessed using adjusted R^2. The model fit in most strata was very good, with adjusted R^2 between 0·75 and 0·86 for the respiratory broad outcome (Supplementary Table S1). Moreover, we found a substantial 'lift' in the adjusted R^2 value when introducing the virology terms into the base secular model. We did not adjust the model form (by including or excluding terms) individually for

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Table 2. *Persons consulting a general practitioner in a mean season (number and rate/100 000 population) attributable to influenza in the UK, by age (1995–2009)*

		Influenza A		Influenza B	
Outcome	Age, yr	*n* (S.D.)	Rate (S.D.)	*n* (S.D.)	Rate (S.D.)
Respiratory disease broadly defined	0–4	84 806	2436	18 781	539
	5–17	120 151	1217	98 380	996
	18–49	234 476	899	75 160	288
	50–64	110 768	1076	18 386	179
	⩾65	102 513	1140	6810	76
	All ages	649 219 (366 681)	1105 (624)	208 777 (218 110)	355 (371)
Bronchitis and bronchiolitis	0–4	10 027	288	0	0
	5–17	17 078	173	10 058	102
	18–49	64 179	246	18 774	72
	50–64	50 640	492	6603	64
	⩾65	63 621	707	3735	42
	All ages	210 607 (137 270)	359 (234)	38 120 (46 417)	65 (79)
Influenza-like illness	0–4	21 955	631	4260	122
	5–17	33 153	336	19 103	193
	18–49	91 202	350	25 954	99
	50–64	38 045	369	6100	59
	⩾65	25 589	284	2110	23
	All ages	209 154 (146 553)	356 (250)	55 969 (61 902)	95 (105)
Pneumonia and influenza	0–4	8923	256	1247	36
	5–17	19 991	202	8978	91
	18–49	73 273	281	20 181	77
	50–64	32 394	315	4521	44
	⩾65	25 722	286	2158	24
	All ages	161 228 (123 129)	274 (210)	36 541 (43 993)	62 (75)
Otitis media	0–4	18 202	523	6589	189
	5–17	19 093	193	15 041	152
	18–49	8816	34	2924	11
	50–64	878	9	1052	10
	⩾65	158	2	315	3
	All ages	44 534 (25 065)	76 (43)	24 243 (28 284)	41 (48)
Antibiotic prescriptions	0–4	49 759	1429	12 130	348
	5–17	69 008	699	59 427	602
	18–49	159 650	612	54 858	210
	50–64	93 806	911	15 286	148
	⩾65	88 172	980	5547	62
	All ages	461 839 (262 785)	786 (447)	142 203 (162 168)	242 (276)

n, Number of episodes; S.D., standard deviation.

each outcome, age, and risk stratum, but applied the given form across all strata.

Overall disease burden

In a mean season there were an estimated 857 996 GP episodes in persons of all ages (1·5% of the population) for influenza-attributable respiratory disease (broadly defined), of which around 75% (649 219) were for influenza A (Table 2). There was wide inter-seasonal variability in influenza A- and B-attributable GP episodes, compared to a more stable consulting rate for RSV (Fig. 2). In the seasons studied the number of GP episodes for an influenza-attributable respiratory disease ranged between 174 305 (2002–2003) and 1 340 937 (1995–1996) for influenza A, and between 2075 (1997–1998) and 646 457 (1996–1997) for influenza B. The highest rates of GP episodes for influenza A-attributable respiratory disease were observed in children aged <5 years (Table 2). The highest seasonal incidence rates for influenza B were observed in those aged 5–17 years.

The rate of GP episodes for influenza A-attributable respiratory disease tended to increase after age 50 years,

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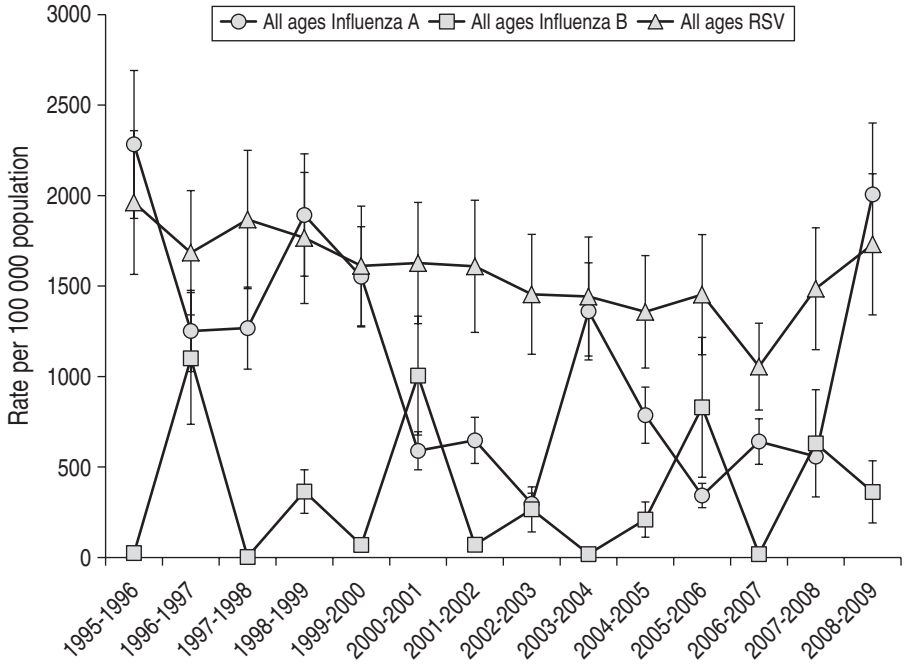

Fig. 2. Seasonal rates (with 95% confidence intervals) of GP episodes for respiratory disease (broadly defined) attributable to influenza A, influenza B and respiratory syncytial virus (RSV).

whereas GP episodes for influenza B-attributable respiratory disease decreased with age (Table 2). In the ⩾75 years age group, the rate of GP episodes for respiratory disease was 1255/100 000 for influenza A and 93/100 000 for influenza B.

In a mean season, the rate of GP episodes for influenza A-attributable bronchitis was higher in adults than in children, whereas the rate of GP episodes for influenza-like illness was higher in children than adults (Table 2). The rates of influenza A-attributable GP episodes for 'pneumonia and influenza' were higher in adults than in children. In those aged ⩾75 years, the mean seasonal rate of GP episodes for 'pneumonia and influenza' was 309/100 000 for influenza A, and 24/100 000 for influenza B.

Otitis media and antibiotic use

Influenza A and B contributed to 68 777 GP episodes for otitis media per season, with the highest number in children (Table 2). Around one third of the GP episodes for otitis media were attributed to influenza B.

There were 604 042 prescriptions for antibiotics attributed to influenza-associated respiratory disease (as measured in the broad respiratory outcome) per season across all age groups (Table 2).

Comorbid risk status and vaccination

Individuals with comorbid conditions that put them at high risk of severe influenza infection were more likely to consult a GP for an influenza-attributable respiratory disease than individuals at low risk (Table 3). The exceptions were children aged <5 years for influenza A, and adults aged 50–64 years for influenza B. The average seasonal rates of influenza A-attributable GP episodes in the unvaccinated high comorbid risk group were 1·79-, 1·56- and 1·83-fold higher than in the low comorbid risk group for older adults aged 50–64, 65–74 and ⩾75 years, respectively. Trends for influenza B were similar for the 65–74 and ⩾75 years age groups (1·74- and 2·97-fold higher rates in high comorbid risk group, respectively).

Higher rates of GP episodes were observed in all age groups when comorbid risk factors were present than when they were absent for the other outcomes studied.

Between 2000 and 2008 influenza vaccine coverage in the CPRD population aged ⩾65 years ranged between 64% and 76%, which was similar to coverage estimated by PHE [17]. In each season studied the rate of influenza A-attributable GP episodes in the high comorbid risk group aged 18–49 years was 0·6- to 0·89-fold lower in vaccinated compared to unvaccinated individuals. The rate ratio of influenza

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Table 3. *Persons consulting a general practitioner in a mean season (rate/100 000 population) for outcomes attributed to influenza A and B by comorbid risk status*

		Influenza A		Influenza B	
Outcome	Age, yr	Low risk (S.D.)	High risk (S.D.)	Low risk (S.D.)	High risk (S.D.)
Respiratory broadly defined	0–4	2482	1713	528	745
	5–17	1166	1562	953	1315
	18–49	831	1454	286	309
	50–64	948	1534	192	141
	⩾65	889	1439	67	98
	All ages	1024 (569)	1464 (920)	374 (390)	289 (299)
Bronchitis and bronchiolitis	0–4	279	417	0	95
	5–17	148	335	91	181
	18–49	212	523	69	98
	50–64	411	778	65	65
	⩾65	516	934	31	60
	All ages	275 (179)	718 (496)	62 (74)	82 (103)
Influenza-like illness	0–4	615	828	121	149
	5–17	316	465	186	252
	18–49	330	515	97	121
	50–64	339	482	60	55
	⩾65	242	337	21	26
	All ages	339 (231)	435 (341)	99 (109)	81 (91)
Pneumonia and influenza	0–4	248	362	35	44
	5–17	189	295	88	110
	18–49	264	425	75	97
	50–64	285	425	45	41
	⩾65	226	362	18	32
	All ages	251 (187)	383 (316)	63 (76)	58 (72)

S.D., Standard deviation.

A-attributable GP episodes in the high comorbid risk group in vaccinated over unvaccinated individuals was between 0·74 and 0·76 in those aged 50–64 years, and 0·81–0·85 in those aged ⩾65 years.

Similarly, in these age groups the rate of GP episodes was lower in vaccinated *vs.* unvaccinated persons at low risk: the rate ratio of influenza-A attributable GP episodes in the low comorbid risk group in vaccinated over unvaccinated was 0·78–1 in those aged 18–49 years, 0·79–0·92 in those aged 50–64 years, and 0·76–0·98 in those aged ⩾65 years.

Clinical syndromes

A wide spectrum of diseases that resulted in a GP episode was attributable to influenza A and B (Fig. 3). The relative proportions attributable to influenza A and B varied with the GP-reported diagnoses, highlighting the importance of influenza B in the 5–17 years age group; especially so since influenza B seasons are less frequent than influenza A.

DISCUSSION

We used the CPRD in the UK, a promising but as yet underutilized nationally representative database for influenza burden assessment, to estimate the age-specific influenza burden in primary care [16]. We employed traditional methods used for hospitalization and mortality studies, and applied them to time-series of GP episodes for a diverse range of outcomes forming part of the burden of influenza, such as comorbidity risk status and antibiotic prescriptions, after taking account of the potentially confounding effects of RSV. In a mean season, around 1·5% of the UK population were estimated to present to GPs with diverse respiratory syndromes attributable to influenza A or B. The estimated mean seasonal burden of influenza A was much larger than influenza B in all age groups and for most respiratory outcomes. Approximately 0·7% of children aged <5 years were estimated to consult a GP for influenza-related otitis media in a mean season, and nearly 2% of all children received antibiotic prescriptions which were attributable to influenza.

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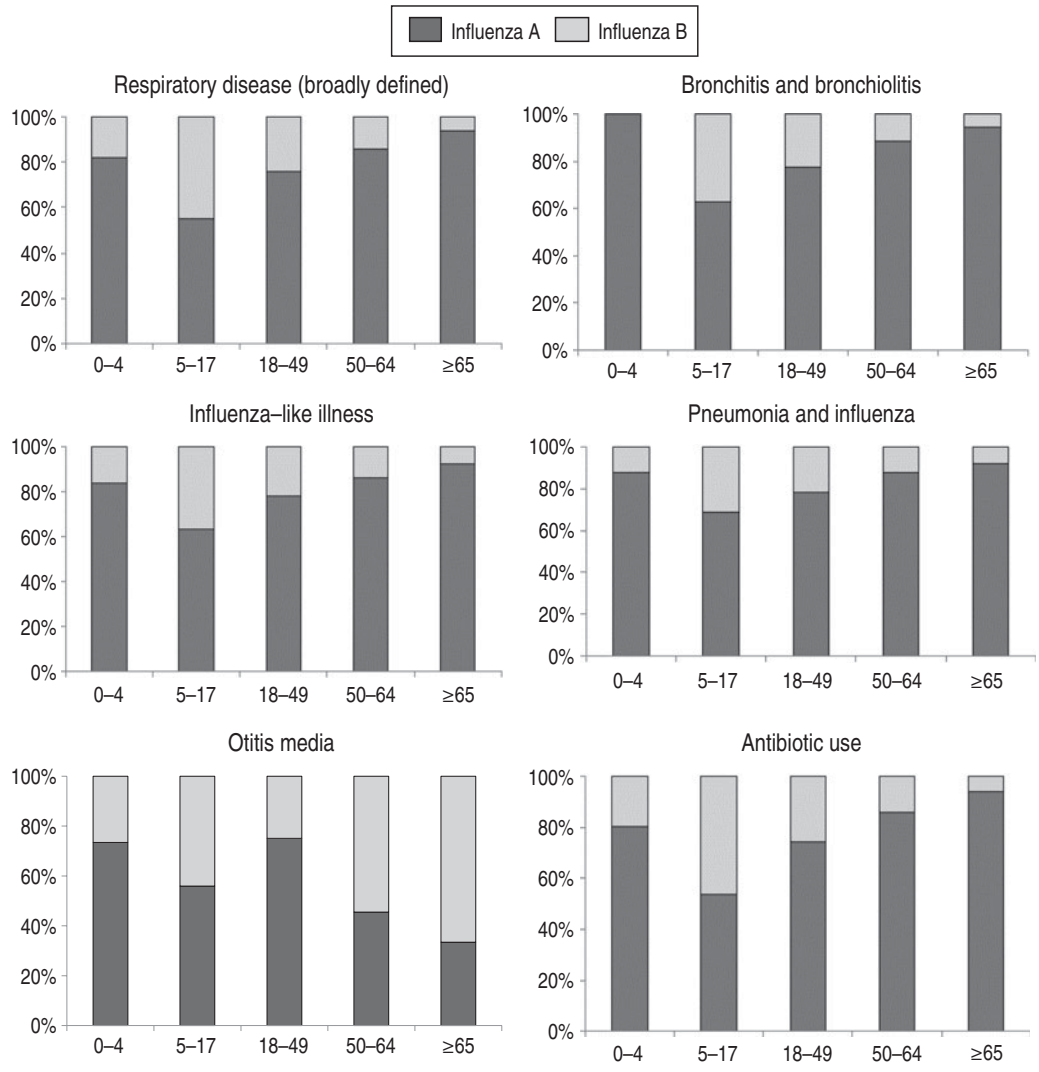

Fig. 3. The percentage of the estimated burdens for several outcomes attributed to influenza A and influenza B by five age groups (mean across seasons). The total number of GP episodes for each outcome was: respiratory disease (broadly defined) ($n = 857\,996$), bronchitis and bronchiolitis ($n = 248\,727$), influenza-like illness ($n = 265\,123$), pneumonia and influenza ($n = 197\,769$), otitis media ($n = 68\,777$), antibiotic use ($n = 604\,042$).

Compared to the relatively stable disease burden attributable to RSV in each season, the influenza burden was characterized by marked inter-seasonal variability according to epidemic activity.

The single previous UK study by Pitman *et al*. that used the CPRD data source to study GP office visits examined only a single season (2002–2003) [13]. In that study, Pitman *et al*. estimated approximately one million influenza-attributable consultations. This is higher than our estimate for that season of 330 763 GP episodes, but closer to our mean seasonal estimate encompassing 14 seasons. As well as the inherent instability of estimates produced using a single season, the model used by Pitman *et al.* [13] reported two alternative estimates obtained by models with and without a bacterial pathogen series included in the explanatory variables. The inclusion in the model of Pitman *et al.* of the bacterial series, characterized by a dominant sinusoidal pattern, likely affected the influenza burden estimate similarly to our use of cyclic components.

Estimates of the number of persons infected with influenza in an average season vary widely, but when measured as persons consulting with clinical illness they are mostly less than 5% of the population, depending on the diagnostic outcomes measured [8, 9, 21, 22]. Our findings are consistent with a simpler analysis conducted in a database of the Royal

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College of General Practitioners, which estimated an influenza burden affecting 2·1% of the population of England and Wales in seasons 1989–1999 [5].

We observed that in persons with comorbid conditions that placed them in a high risk group and in all persons aged <65 years, there were fewer GP episodes for influenza-attributable respiratory disease in vaccinated than non-vaccinated persons. This finding is difficult to interpret because our study was not designed to measure vaccine effectiveness, which would require a different study design. Such studies would require an analysis of the propensity to consult, which differs between vaccinated and non-vaccinated persons, and between those with high and those with low comorbidity risk.

Population-based studies of the influenza burden relying on individual laboratory-confirmed cases alone are not practical, due to the lack of standard testing, the expense of large-scale testing using sensitive PCR-based assays, and the fact that infections are often resolved by the time patients seek medical care (if they seek such care at all). Instead, indirect modelling approaches have been used for many years to estimate the burden of influenza [12, 23]. We used a previously described linear regression model [24], which adopted a recent refinement of regression techniques guided by virus surveillance data as described in studies by Pitman *et al.* [13] and Zhou *et al.* [25]. Other models used to estimate the burden of respiratory infections, such as Poisson regression with a natural logarithm for the link function [11, 26], imply multiplicative effects of respiratory viruses (i.e. the effect of multiple simultaneously circulating respiratory viruses is different from the sum of their individual effects). This is likely an unrealistic assumption for influenza strains [27, 28]. The linear regression model has the advantage over other methods of being an additive model, which corresponds to the view that the total burden in the population is due to the sum of outcomes due to different causes, including viral infections [27, 29].

The strengths of our model include the use of large nationally representative databases, which limited the potential for sampling error; inclusion of data over a long period that covered 14 seasons; and the use of control outcomes with no inherent seasonality and no association to influenza. By defining a new outcome category ('respiratory disease broadly defined'), we aimed to improve the sensitivity in capturing the full burden of influenza-attributable disease, while retaining sufficient specificity; for example, the additional codes in the 'respiratory broad' outcome increased the average seasonal all-age estimate by 14% over the stricter 'respiratory' outcome, but left the confidence intervals and the model fit virtually unchanged (data not shown). Age stratification allowed detailed estimation of the age-specific burden, controlled for the observed age effect on consultation rates and overcame possible confounding due to higher frequency of viral testing in some age groups. Finally, weekly occurrences of outcomes were assumed to be determined by the circulation of influenza, RSV, and other causes which follow a seasonality that was estimated using a combination of sine and cosine terms. The inclusion of both cyclical terms (sine and cosine functions) controlled for confounders for which data are not available. Tri-mean smoothing of pathogens and outcomes series mitigated short-term effects such as national holidays and extreme weather conditions on viral testing and GP consultations.

A potential limitation of the study is the exclusive analysis of influenza and RSV virus time-series with no consideration of other respiratory pathogens; if such pathogens consistently circulate at the same time as influenza, the influenza burden could be overestimated. We did not generate time-series for influenza subtypes as we did not have access to subtyped data. We did not evaluate the effect of pneumococcal vaccination in children or older age groups [30], or consider changes in herd immunity during the period of study, nor did we consider the effects of obesity [31, 32]. The study is also dependent on the quality and consistency of routine recording in the practice network. The burden of illness as encountered in primary care, which is the primary objective of this study, includes all consulting persons regardless of their propensity to consult. We did not study the indirect burden of illness in individuals with influenza who did not consult. While our study provides up-to-date and detailed information on health service utilization, the study does not provide information for evaluation of indirect medical costs associated with influenza. None of the potential limitations of the study are likely to have influenced the model estimates in any major way.

In addition to influenza-attributable respiratory disease, we estimated the burden of influenza-attributable otitis media, which has often been regarded as a common complication of influenza [33]. Our study found almost as many children (aged <5 years) were diagnosed at presentation with influenza-attributable otitis media as with influenza-like illness, suggesting that otitis

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media is part of the primary symptomatology of influenza. The diverse range of presenting illnesses identified as attributable to influenza in our study questions the relevance of diagnostic criteria by which influenza is defined clinically. Like other studies that have tried unsuccessfully to correlate specific symptoms with a diagnosis of influenza [34, 35], our study suggests that collections of symptoms with/without fever are largely inadequate for measuring the burden of illness.

Finally, the model estimated that more than 600 000 antibiotic courses were prescribed for influenza-associated respiratory disease per season. The potential misuse of antibiotics is a well-recognized cause for concern, particularly in relation to common respiratory infections [36]. A simple test that is able to discriminate between bacterial and viral infection would be a great step forward, as would timely local influenza surveillance data that would allow physicians to assess the probability that an acute respiratory infection is caused by influenza.

Health economic models can inform policy choices, but they depend on accurate and age-specific parameter estimates of the disease burden. Furthermore, it is critical to use estimates based on recent assessments of the burden: earlier publications could overestimate the current burden. Because the effectiveness of influenza vaccination in preventing otitis media appears similar to that of pneumococcal conjugate vaccines [37], it is important that estimates of the otitis media burden and the potentially preventable fraction be included in cost-benefit estimates of influenza interventions in this age group. Our study provides a source for understanding the national influenza burden and undertaking cost evaluations.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268815001119.

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DECLARATION OF INTEREST

Gonçalo Matias, Dave J. Webb, John Logie, and François Haguinet are employed by the GSK Group of Companies. Dave J. Webb and John Logie report ownership of stock options and/or restricted shares. Robert J. Taylor, Roger L. Lustig, and Cynthia Schuck-Paim report having received consulting fees from Sage Analytica LLC to perform this study, paid for by the GSK Group of Companies. Douglas M. Fleming reports personal fees from Sage Analytica, personal fees and non-financial support from the GSK Group of Companies during the conduct of the study.

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