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The burden of influenza in England by age and clinical risk group: A statistical analysis to inform vaccine policy

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Summary *Objectives:* To assess the burden of influenza by age and clinical status and use this to inform evaluations of the age and risk-based influenza vaccination policy in the United Kingdom.
Methods: Weekly laboratory reports for influenza and 7 other respiratory pathogens were extracted from the national database and used in a regression model to estimate the proportion of acute respiratory illness outcomes attributable to each pathogen.
Results: Influenza accounted for ~10% of the attributed respiratory admissions and deaths in hospital. Healthy children under five had the highest influenza admission rate (1.9/1000). The presence of co-morbidities increased the admission rate by 5.7 fold for 5–14 year olds (from 0.1 to 0.56/1000), the relative risk declining to 1.8 fold in 65+ year olds (from 0.46 to 0.84/1000). The majority (72%) of influenza-attributable deaths in hospital occurred in 65+ year olds with co-morbidities. Mortality in children under 15 years was low with around 12 influenza-attributable deaths in hospital per year in England; the case fatality rate was substantially higher in risk than non-risk children. Infants under 6 months had the highest consultation and admission rates, around 70/1000 and 3/1000 respectively.
Conclusions: Additional strategies are needed to reduce the remaining morbidity and mortality in the high-risk and elderly populations, and to protect healthy children currently not offered the benefits of vaccination.

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Introduction

Interest in prevention and control of seasonal influenza has heightened in the wake of the recent influenza A(H1N1)v pandemic. The World Health Organisation through its Global Action Plan for Influenza Vaccines has spearheaded a major initiative to increase influenza vaccine use and production capacity,[1] and additionally has recently revised its global recommendations on vaccination policy.[2] The United Kingdom has a long-established influenza vaccination programme that targets all those aged 65 years and over or in high-risk clinical groups. A major review of the national programme was recently undertaken in the United Kingdom that resulted in the recommendation for annual influenza vaccination of all children aged 2—16 years.[3] This recommendation was based on estimates of the burden of disease by age under the existing programme in those with and without high-risk clinical conditions, and modelling the likely impact of different vaccination strategies on the transmission dynamics of seasonal influenza[4] and the cost effectiveness of these strategies.[3]

Estimating influenza disease burden is challenging as symptoms are non-specific and few patients presenting with an acute respiratory illness are routinely investigated for virological evidence of influenza infection. Studies in which all patients with acute respiratory illness are tested for evidence of influenza are labour intensive and are usually focused on a particular age range and conducted over a limited number of seasons. This makes disease burden comparisons between age groups difficult. Furthermore, they may not capture differences between seasons in prevalent influenza strains, each of which may have its own morbidity profile. Also, while risk factors in virologically confirmed cases may be ascertained, it is difficult to translate these into relative risks in those with and without underlying chronic conditions in the absence of comparable information on the prevalence of such conditions in the population.

An alternative approach is to use regression models to estimate the burden of influenza by comparing the seasonal pattern of influenza and other respiratory pathogens with seasonal variations in acute respiratory illness. Several studies have used this method to assess influenza burden but none has taken account of the effect of underlying clinical risk on disease outcome. Furthermore, they have been limited by failure to include non-viral respiratory pathogens[5—9] such a *Streptococcus pneumoniae* which has been shown to be an important contributor to acute respiratory illness.[10] Existing analyses have also been criticised for failing to incorporate relevant epidemiological features, such as potential interactions between co-circulating respiratory pathogens.[11,12] We have developed a range of statistical models that address these limitations. Our analysis provide estimates of the number of influenza-associated health care outcomes in different age groups in those with and without high-risk conditions in England under the existing influenza vaccination programme. Measuring the effect of being in a high-risk group on the age-related burden of influenza was essential for the modelling and cost effectiveness analyses that underpinned the recent decision in the United Kingdom to extend the existing age and risk-based vaccination policy to healthy children.[3]

Materials and methods

Data sources

Data were obtained for the eight years immediately preceding the A(H1N1)v pandemic (2000/1 to 2007/8) and arranged into epidemiological years April to March to encompass the annual influenza season.

Laboratory reports: Public Health England receives weekly computerised reports of clinically significant infections confirmed by microbiology laboratories in England and Wales. The United Kingdom Standards for Microbiology Investigations recommend the diagnostic algorithms that should be applied to patients presenting with different clinical syndromes in order to promote consistency in testing over time and between laboratories.[13] Weekly numbers of reports by date of test and age group were obtained from the national database for the following pathogens: influenza A, influenza B, respiratory syncytial virus, parainfluenza, adenovirus, rhinovirus, *S. pneumoniae*, *Mycoplasma pneumoniae* and *Haemophilus influenzae*. Only invasive specimens of *S. pneumoniae*, *M. pneumoniae* and *H. influenzae* were included due to lack of consistency in reporting non-invasive isolates. The increasing use of genomic detection methods for rhinovirus and parainfluenza resulted in a spurious temporal increase in these respiratory viruses. Reports for these pathogens where the method of detection was either "genomic detection" or "antibody detection" were therefore omitted from the analysis. The proportion of influenza A cases that are either H1 or H3 subtypes was obtained from the results of routine surveillance specimens taken by general practices in the United Kingdom participating in the Royal College of General Practitioners Weekly Returns Service.[14]

Inpatient admissions: Weekly inpatient admissions to National Health Service hospitals in England were obtained from the Hospital Episode Statistics database.[15] Patients were included in the analysis if they had an acute respiratory illness code (ICD-10 codes J0*, J1*, J2*, J3*, J40*, J41*, J42*, J43*, J44*, J47*) in any diagnosis field.

Identifying Clinical Risk Groups: Patients with an acute respiratory illness code and with ICD-10 codes in other diagnostic fields for conditions indicated for seasonal influenza vaccination were flagged as being in a clinical risk group; see Supporting Text (Table S10) for a list of the ICD-10 codes which were used to identify patients in a risk group.

Deaths in hospital: The number of deaths in hospital by age and clinical risk group was estimated by counting inpatient admissions with an acute respiratory illness code extracted from the Hospital Episode Statistics database with death recorded as the discharge method. Only deaths within 30 days of admission were included in the analysis.

General practitioner consultations: The age-stratified weekly numbers of consultations in general practice for acute respiratory illness were obtained from the Royal College of General Practitioners Weekly Returns Service. The population monitored by the Royal College of General Practitioners is closely matched to the national population in terms of age, gender, deprivation index and prescribing patterns.[16] Consultation numbers were scaled by the size of the population covered by the Royal College of General

Practitioners practices (1.44% of population of England and Wales) in 2010[16] to give weekly consultation rates per 100,000 people. These rates were then multiplied by the population of England during the corresponding season to give estimated weekly numbers of episodes. The data were not available by clinical risk group.

Population by age and clinical risk group: The population of England in clinical risk groups indicated for seasonal influenza vaccination was estimated using the proportion of patients identified in the Royal College of General Practitioners practices as having a READ code indicating an influenza high-risk condition, averaged between 2003 and 2010.

Statistical modelling

Weekly counts in the laboratory reports for pathogens potentially responsible for acute respiratory illness were used as explanatory variables to estimate the proportion of health care outcomes (acute respiratory illness episodes leading to GP consultations, hospital admissions and deaths in hospital) attributable to influenza. We used an adaptation of a generalised linear model for negative binomial outcome distributions with an identity link function. The negative binomial distribution was used to account for overdispersion in many of the outcome variables and the identity link function to ensure contributions from different pathogens were additive (see Supporting Text Section 1 for model equations). The models were constructed by allowing for the incorporation of i) a moving average to smooth fluctuations in laboratory reports; ii) a secular trend in outcomes iii) the separation of influenza A into its subtypes; iv) the effects of interactions between co-circulating pathogens and v) a temporal offset between pathogen testing and the onset of clinical effect. Details are provided in Sections 1 and 2 of the Supporting Text. The best fitting model was selected using the Akaike Information Criterion. We observed that all model variations with an Akaike Information Criterion value close to that of the selected model produced a similar estimate for the proportion of influenza-attributable hospitalisations, indicating that the exact choice of model construction did not dramatically influence our estimates (see Supporting Text, Section 2). Model outcomes were stratified by age (<6 months, 6 months to 4 years, 5–14 years, 15–44 years, 45–64 years and 65+) and clinical risk group. Due to the small number of deaths in hospital in patients under 65 years patients were grouped into <15 years and 15–64 years to estimate influenza-attributable deaths in hospital.

Results

Laboratory reports and acute respiratory illness admissions

Seasonal variations in the numbers of laboratory reports for the 8 pathogens likely to cause acute respiratory illness are shown in Fig. 1 for two key age groups: 6 months–4 years (panel A) and 65 years and over (panel B). Respiratory syncytial virus dominates reports in young children during winter, while *S. pneumoniae* dominates reports in older people throughout the year, but especially during winter.

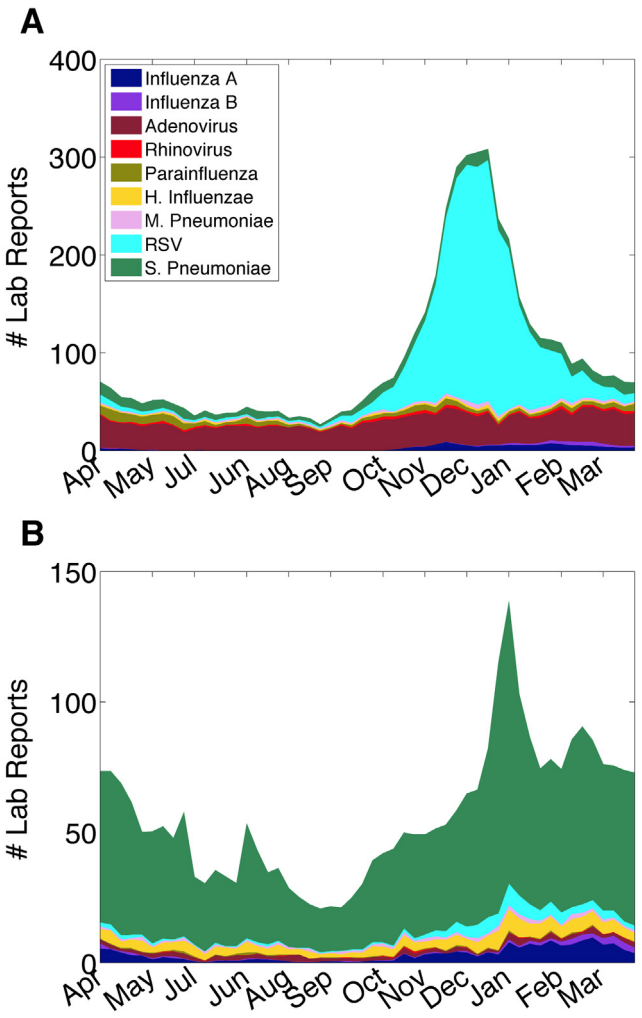

Figure 1 Seasonal trends in numbers of laboratory reports in England and Wales in two key age groups: 6 months–4 years (A) and 65 years and over (B). Data are presented as weekly results averaged over eight epidemiological years (2000/1 to 2007/8).

For influenza, there is substantial variation between seasons in the number of laboratory-confirmed cases by age group and strain (Fig. 2)

There was an annual average of over 300,000 admissions for acute respiratory illness among those without co-morbidities and almost 520,000 among those in a clinical risk group; the majority of the admissions and the highest case fatality rates were in 65+ year olds (Table 1). In all age groups, the incidence per 1000 population of admission for acute respiratory illness was higher in those with a clinical risk. For those under 65 years of age, the risk of dying in hospital was much higher for those in a clinical risk group, declining from 35.1 times higher in <6 month olds to 5.9 times higher in 45–64 year olds. In 65+ year olds the case fatality rate was similar in those with and without a clinical risk.

Model fitting and attribution of health outcomes to different pathogens

The best fitting model to the weekly number of episodes leading to hospital admissions, consultations in general

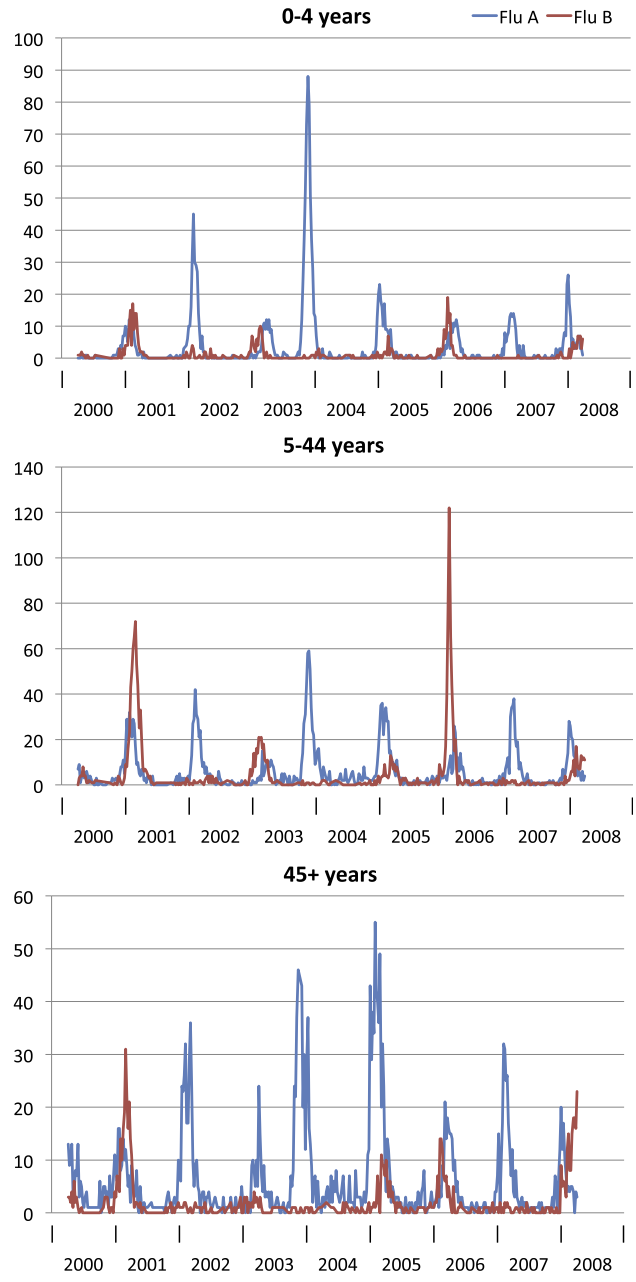

Figure 2 Number of influenza A and B reports in England and Wales by season and age group 2000/1 to 2007/8.

practice and deaths reproduces the observed annual averages to within 1% (Supporting Text — Section 4). This model was one that incorporated a moving average to smooth out laboratory reports, and a linear increase in the number of hospitalisations not attributable to specific respiratory pathogens. Separation of influenza A into subtypes, allowing for interactions between co-circulating pathogens and incorporating a temporal offset did not improve model fit. Detailed results of the fitting process, and examples comparing the best fitting model results with data on the weekly number of hospital admissions, GP consultations and deaths for various age and risk groups are presented in the Supporting Text (Sections 1—3). The contributions of the various pathogens to the attributed disease burden are shown in the Supporting Text — Section 4. In both risk and non-risk groups, *S. pneumoniae* and respiratory syncytial virus consistently account for the largest numbers of hospital admissions and deaths across all ages groups with influenza is usually the third most common pathogen accounting for an overall 9% and 11% respectively of the attributed acute respiratory illness admissions and deaths in hospital (and 2% and 3% respectively of the total number of acute respiratory illness admissions and deaths in hospital). There were some differences between risk and non-risk groups in the proportion of disease burden attributed to specific pathogens; for example *H. influenzae* is an important pathogen among risk group patients aged 65+ years of age but not in the non-risk elderly. Parainfluenza was responsible for 7% of deaths in hospital among risk groups but was not identified as a cause of mortality among non-risk groups.

Influenza-attributable burden of disease

Table 2 shows the average annual influenza-attributable hospital admission rate per 100,000 by strain, age and risk status. The highest admission rates for both influenza A and B are in children under five years of age, for whom the overall admission rate is 1.9/1000 (95%CI ± 0.023/1000); with no evidence of a higher overall rate in those with clinical risk factors. Overall, children under 15 years of age accounted for 37% of all annual influenza-attributable hospital admissions and 52% of admissions among those in non-risk groups (Fig. 3). Among older age groups the effect of being in a risk group increased the hospital admission rate between 5.7 fold for 5—14 year olds (from 0.1 to 0.56/1000) and 1.8 fold for 65+ year olds (from 0.46 to 0.84/1000). Among those aged 15 years and over there was little contribution from influenza B to admissions.

The estimated annual number of deaths in hospital from influenza for the three age groups <15, 15—64 and 65+ year olds are shown in Table 3 by risk status. Few deaths in hospital were estimated in children under 15 years of age, the annual average of 12 in England giving an estimated mortality rate of 1.3 per million overall for this age group. The vast majority of the annual deaths occurred in the 65+ age group (1676 of 1806, 93%), particularly those with underlying co-morbidities (1298, 72% of the total). The case fatality rate in risk group patients was between 38.6 and 2.3 fold higher than among non-risk group patients, the relative risk decreasing with age.

Children under 15 years of age have the highest rate of influenza-attributable episodes leading to consultations in general practice and bear the largest burden of disease due to influenza B (Table 4). Of the estimated 1,084,283 annual total consultations for influenza, 420,831 (39%) were in this age group (Supporting Table S5). For both consultations and admissions, the rates in infants under 6 months of age are particularly high, around 70 per 1000 and 3 per 1000 respectively. Unlike hospitalisations, the consultation rate for influenza does not increase in the elderly. In consequence, the ratio between consultation and admission rates varies with age and influenza strain and was lowest for the 65+ age group (9.2) and highest for 5—14 year olds (270) for both strains combined.

Table 1 Average annual admissions and death and the case fatality rate (CFR) in hospital for acute respiratory illness (ARI) by age and clinical risk group for the epidemiological years 2000/1 to 2007/8.

Age	Not at clinical risk				Clinical risk				CFR ratio Clinical risk/not clinical risk (95% CI)
	Admissions	Incidence per 1000	Deaths	Case fatality rate (Deaths/ 1000 admissions)	Admissions	Incidence per 1000	Deaths	Case fatality rate (Deaths/ 1000 admissions)	
<6 m	24,743	84.5	11	0.4	1408	161.1	22	15	35.1 (26.8–46.2)
6 m–4 y	83,977	33.6	17	0.2	12,008	84.8	55	5	22.6 (18.4–27.8)
5–14 y	42,649	7.7	10	0.2	9874	16.3	51	5	22.0 (17.1–28.5)
15–44 y	87,985	4.6	112	1.3	29,337	15.4	674	23	18.0 (16.7–19.5)
45–64 y	39,353	3.9	364	9.3	99,337	44.1	5458	56	5.9 (5.7–6.2)
65+ y	53,254	12.1	7729	144.8	368,489	101.6	54,933	151	1.03 (1.02–1.04)
All ages	331,960	7.9	8244	24.9	520,453	61.0	61,192	119	4.73 (4.69–4.77)

The annual variations in influenza-attributable hospital admissions, deaths in hospital and GP consultation rates by age and risk group status are shown in the Supporting Text, Section 5.

Discussion

Principal findings

We used microbiological and epidemiological surveillance data for England and Wales to estimate health outcomes attributable to influenza and other respiratory pathogens under the existing age- and risk-based national influenza vaccination programme. Our study shows that despite targeting vaccination at these vulnerable groups their disease burden is still disproportionately high compared with individuals in the same age group without co-morbidities, particularly in those under 65 years of age. Among 65+ year olds, the effect of underlying co-morbidities on hospitalisation and case fatality rates was less marked. Overall this age group contributed 93% all influenza-attributable deaths in hospital though only 29% of all admissions due to influenza (Table 3). Healthy children under 5 years of age had the highest influenza-attributable hospital admission rates, over 5 fold higher than 65+ year olds. Nearly 40% of the hospital admissions and consultations for influenza were in children under 15 years of age though annual mortality in this age group was low at around 1.3/million population.

Our study provides evidence to support the approach adopted in many developed countries of targeting influenza vaccination at high-risk individuals and the elderly. However, it also shows the limitation of such selective approaches in mitigating the consequences of disease in these vulnerable groups and suggests the need for additional prevention strategies. Vaccine coverage in England among those aged 65 years and over has been around 75% since 2005/6,[17] meeting the target uptake recommended by the European Union Council for this age group.[18] However, the relatively low vaccine efficacy in those aged 65 years and over[19] limits its impact on morbidity and mortality in this age group. Vaccine coverage in high-risk individuals under 65 years of age, such as those with cardiac, pulmonary or metabolic disorders, is low and has remained at around 50% since 2008/9 in England[20] despite the recent experience with AH1N1 (2009) pandemic influenza which demonstrated the substantially higher morbidity and mortality in these groups.[21,22] While vaccine uptake in these high-risk individuals needs to be improved, it is unlikely that this would be sufficient to abolish their morbidity and mortality differential given that vaccine efficacy against confirmed infection is only around 70% in a matched year in healthy adults[23] and, if hospitalised with influenza,

Table 2 Mean estimated annual incidence (95% Confidence Interval) of influenza attributable hospital admissions by strain, age and clinical risk group (epidemiological years 2000/1 to 2007/8) and relative risk of hospitalisation if in a risk group.

Hospitalisations annual rate per 100,000 (±95% CI)							
Age	Not at clinical risk			Clinical risk			Relative risk of hospitalisation if in a risk group
	Flu A	Flu B	All Flu	Flu A	Flu B	All Flu	All flu
<6 m	198 (10)	135 (8)	333 (12)	0 (0)	227 (21)	227 (21)	0.7 (0.6–0.8)
6 m–4 y	149 (4)	27 (3)	176 (5)	153 (11)	0 (0)	153 (11)	0.9 (0.8–0.9)
5 y–14 y	10 (0.8)	0 (0)	10 (0.8)	36 (2)	20 (2)	56 (3)	5.7 (5.2–6.3)
15–44 y	9 (0.3)	0 (0)	9 (0.3)	42 (1)	0 (0)	42 (1)	4.9 (4.7–5.1)
45–64 y	11 (0.3)	6 (0.2)	16 (0.3)	74 (3)	0 (0)	74 (3)	4.5 (4.3–4.7)
65+ y	46 (1)	0 (0)	46 (1)	84 (7)	0 (0)	84 (7)	1.8 (1.7–2)
All Ages	23 (0.3)	4 (0.2)	27 (0.4)	70 (3)	2 (0.1)	71 (3)	2.7 (2.5–2.8)

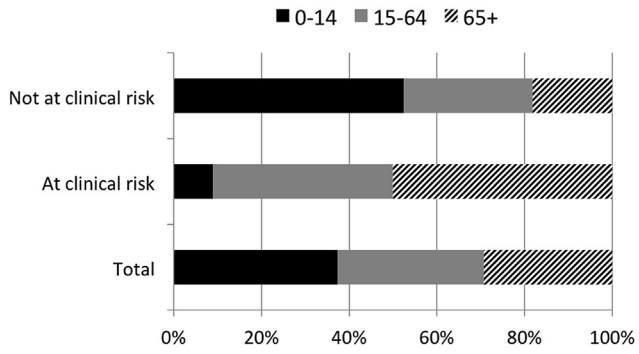

Figure 3 Percentage of total annual hospital admissions for influenza by age group and risk status.

high-risk individuals have substantially higher case fatality rates (Table 3).

The highest annual influenza-attributable admission and consultation rates were in infants under 6 months of age who, although too young to be vaccinated themselves, could benefit from maternal immunisation in pregnancy which has been shown to be 63% effective in reducing laboratory confirmed influenza in infants in the first 6 months of life.[24] The importance of offering influenza vaccination in pregnancy was recently emphasised by the World Health Organisation who identified pregnant women as the highest priority group for vaccination.[2] However coverage in pregnant women in England is poor only reaching 25.5% in those without co-morbidities in 2011/12.[20] There were marked differences between age groups in the ratio of consultation rates in general practice to hospital admission rates for influenza (Table 4). Consultation rates will not only reflect the underlying infection rate in that age group but also the propensity to consult for an influenza-like-illness if symptomatically infected. Similarly, hospital admission rates will reflect the age-specific severity profile as well as the age-specific incidence of infection. Quantifying the relationship between health care outcomes and the underlying infection rate in each age group is essential for building influenza transmission models that can assess the overall population impact of different vaccination polices. Estimation of age-specific influenza infection rates requires data from serological studies conducted before and after the influenza season. The value of seroepidemiology was recognised as a result of the H1N1 (2009) pandemic[25] but has not been systematically applied to seasonal influenza.

Strengths and weaknesses of our study

The strength of our study is that it enables a comparison of the influenza-attributable morbidity between age groups and the effect of underlying co-morbidities within an age

Table 3 Estimated annual number of influenza admissions and deaths in hospital and case fatality rate (CFR) with 95% confidence interval by age group and risk status, and relative risk of dying in hospital if in a clinical risk group for influenza.

Age group	Not at clinical risk			Clinical risk			CFR ratio Clinical risk/ not clinical risk (±95% CI)
	Estimated number of influenza admissions (±95% CI)	Estimated number of influenza deaths in hospital (±95% CI)	Deaths/1000 influenza admissions (±95% CI)	Estimated # influenza admissions (±95% CI)	Estimated number of influenza deaths in hospital (±95% CI)	Deaths/1000 influenza admissions (±95% CI)	
0—14 y	5862 (137)	2.5 (0.3)	0.43 (0.38—0.49)	573 (22)	10 (0.6)	17 (15—18)	38.6 (33.4—44.8)
15—64 y	3297 (61)	20 (1.2)	6.1 (5.7—6.4)	2452 (70)	98 (7)	40 (37—43)	6.6 (6.0—7.3)
65+	2040 (46)	378 (11)	185 (179—192)	3029 (255)	1298 (56)	428 (391—473)	2.3 (2.1—2.6)
All Ages	11,199 (157)	400 (11)	36 (35—37)	6054 (266)	1406 (56)	232 (219—246)	6.5 (6.1—6.9)

Table 4 Influenza-attributable GP consultations and hospitalisation rates by age, entire population and ratio of consultations to admissions (95% confidence intervals).

Age	GP consultations annual rate per 100,000 (±95% CI)			Hospitalisations annual rate per 100,000 (±95% CI)			Ratio GP consultations: hospital admissions (±95% CI)
	Flu A	Flu B	All Flu	Flu A	Flu B	All Flu	All Flu
<6 m	4829 (233)	2532 (195)	7361 (304)	192 (9)	138 (8)	330 (12)	22.3 (22.1—23.6)
6 m—4 y	3916 (137)	2174 (101)	6090 (170)	149 (4)	26 (3)	175 (5)	34.9 (33.5—36.3)
5 y—14 y	2131 (62)	1744 (88)	3875 (107)	12 (0.8)	2 (0.2)	14 (0.8)	270 (254—288)
15—44 y	1327 (25)	552 (24)	1878 (35)	12 (0.3)	0 (0)	12 (0.3)	160 (155—164)
45—64 y	1468 (26)	361 (21)	1829 (34)	22 (0.6)	5 (0.2)	27 (0.6)	68.1 (66.1—70.0)
65+ y	582 (26)	0 (0)	582 (26)	63 (3)	0 (0)	63 (3)	9.2 (8.6—9.8)
All Ages	1496 (17)	660 (16)	2156 (23)	31 (0.6)	4 (0.2)	34 (0.6)	62.9 (61.6—64.2)

group. Also, by using data from eight consecutive years, our estimates will reflect the variation in influenza incidence and severity between seasons. Our regression method uses the year-to-year changes in the timing of the influenza season as well as in the other respiratory pathogens that are more prevalent in winter. Thus it also allows the burden of disease attributable to influenza to be compared with other respiratory pathogens such as respiratory syncytial virus and *S. pneumoniae*. It shows that together these latter two pathogens are responsible for around 60% all attributed hospital admitted acute respiratory illness in both risk and non-risk individuals. Our analysis also identified *H. influenzae* and parainfluenza as important pathogens in individuals with underlying co-morbidities.

A potential limitation of this work is that we restricted our mortality analyses to patients with acute respiratory illness who die in hospital to allow derivation of case fatality rates for those in high-risk groups compared with non-risk individuals. This was essential for the cost-effectiveness analysis that was undertaken to evaluate the effect of different extensions to the current risk-based influenza vaccination programme[3] and will ensure that the results are conservative. For example, the annual number of influenza-attributable deaths in those aged 75 years and over obtained by regression methods using all-cause mortality as the outcome was around 10,000[6] compared with our estimate of under 1700 influenza-attributable deaths in hospital in those aged 65 years and over, Another limitation is that we also restricted our analysis to hospitalisations for acute respiratory illness and did not consider the association between influenza and cardiovascular-related morbidity (specifically myocardial infarction and stroke[26]). However, a recent study in England and Wales only found a significant association between influenza and myocardial infarction in patients 80 years old and over.[27] Furthermore, only 0.7%–1.2% of myocardial infarction-associated hospitalisations were estimated to be influenza-attributable. This would amount to around 1000 additional hospitalisations a year, compared to the 17,000 (all ages) we estimated in our model to be associated with influenza. Since, the increased risk of myocardial infarction and stroke lasts up to three months following the influenza episode,[26] it is unclear how such potentially long time lags can be robustly incorporated in these types of time-series models. Where possible we used data sources covering the entire United Kingdom, however in some cases data was only available for either England (hospital admissions and deaths) or England and Wales (laboratory reports). Due to the restriction on available hospitalisation data, where absolute numbers are presented, they relate to absolute numbers in England only.

The strength of our regression method is that we incorporated adjustments suggested by others[11,12] by fitting 9 different models. We observed that some of these adjustments, namely allowing for interactions between co-circulating pathogens and incorporating a temporal offset did not improve model fit and are therefore perhaps less important in practice. The regression method relies on the assumption that the temporal variation in reports of the different causative pathogens accurately reflects their relative incidence over time in the study populations. It is possible that there may be some seasonal variation in patterns of laboratory testing, but the recommended Standards for Microbiology Investigations [12] should minimise this. Interestingly, we found an increasing trend in hospitalisations that was not matched by increases in laboratory reports. This necessitated the incorporation of a trend term in the regression model in order to focus on the seasonal fluctuations in acute respiratory illness. A similar increase in pneumonia hospitalisations has been previously noted and remains unexplained.[28]

It is reassuring that where our estimates could be compared with those from virological studies, the results were similar. For example our estimated annual influenza-related hospitalisation was 1.9 per 1000 children under 5 years, similar to an estimate for severe influenza-attributable acute lower respiratory infection of 1 per 1000 children under 5 years (95% CI 1–2) in a meta-analysis of virological studies in developed countries.[29] It is also similar to estimates of the incidence of influenza-related hospitalisations in two English studies in which children admitted with a respiratory illness were virologically investigated: 1.44 per 1000 (95% CI 1.17–1.75) in children under 6 years in Leicester in 2001–2002,[30] and 1.57 per 1000 in children under 5 years in East London in 2002–2004.[31] Like us, the authors of the meta-analysis found that the highest rate of severe influenza in children in developed countries was in infants under 6 months of age, 340 per 100,00 (95% CI 230–500) (personal communication Dr. H. Nair) which is very similar to our estimate of 330 (95% CI 318–342).

Policy implications and future research

Our analyses indicate that additional strategies are needed to reduce the remaining morbidity and mortality in the high-risk and elderly populations, and to protect healthy children who are currently not offered the benefits of vaccination. Children play a key role in transmission of influenza and their vaccination is likely to bring additional herd immunity benefits.[4] Vaccine coverage among pregnant women needs to improve both for their own protection and that of their infants during the first 6 months of life when influenza morbidity is highest. Annual age-stratified serological studies are needed to help understand the transmission dynamics of seasonal influenza and to document the impact on transmission of the annual vaccination of children aged 2–16 years which is now recommended in the United Kingdom to complement the age and risk-based policy in place since 2000.[3] The same features in influenza burden may be present in other developed countries with a similar age and risk-based influenza vaccination programme; hence there may be value in considering similar policies in such settings.

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Author contributions

DC, EM, WJE and MJ conceived and designed the study; DF extracted and analysed data on consultations in general practice and proportion of patient in clinical risk groups; AJVH analysed Hospital Episode Statistics data; DC carried out the statistical modelling; DC, EM, AJVH and MJ wrote the manuscript with input from DF and WJE. All authors meet ICMJE criteria for authorship, and agree with manuscript results and conclusions.

Competing interests

WJE's partner works for GlaxoSmithKline. DMF has served as an advisor to several pharmaceutical companies (including GlaxoSmithKline) on matters relating to the epidemiology of influenza and the effectiveness of influenza vaccination, and has received support to attend international meetings relating to influenza.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jinf.2013.11.013.

References

1. WHO. *Report of the second WHO consultation on the Global Action Plan for influenza vaccines (GAP)*. Geneva: Switzerland; 2011.
2. Vaccines against influenza WHO position paper — November 2012. *Relevé épidémiologique hebdomadaire/Section d'hygiène du Secrétariat de la Société des Nations = Weekly epidemiological record/Health Section of the Secretariat of the League of Nations* 2012;**87**(47):461—76.
3. *JCVI statement on the annual influenza vaccination programme — extension of the programme to children*; 2012 Jul 25. Report No.
4. Baguelin M, Flasche S, Camacho A, Demiris N, Miller E, Edmunds WJ. Assessing optimal target populations for influenza vaccination programmes: an evidence synthesis and modelling study. *PLoS Med* 2013;**10**(10):e1001527.
5. Zhou H, Thompson WW, Viboud CG, Ringholz CM, Cheng P-Y, Steiner C, et al. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993—2008. *Clin Infect Dis: an Official Publication of the Infectious Diseases Society of America* 2012;**54**(10):1427—36.
6. Hardelid P, Pebody R, Andrews N. Mortality caused by influenza and respiratory syncytial virus by age group in England and Wales 1999—2010. *Influenza Other Respir Viruses* 2013;**7**(1):35—45.
7. Yang L, Chiu SS, Chan K-P, Chan K-H, Wong WH-S, Peiris JSM, et al. Validation of statistical models for estimating hospitalization associated with influenza and other respiratory viruses. *PLoS One* 2011;**6**(3):e17882.
8. Mangtani P, Hajat S, Kovats S, Wilkinson P, Armstrong B. The association of respiratory syncytial virus infection and influenza with emergency admissions for respiratory disease in London: an analysis of routine surveillance data. *Clin Infect Dis* 2006;**42**(5):640—6.
9. Newall AT, Wood JG, Macintyre CR. Influenza-related hospitalisation and death in Australians aged 50 years and older. *Vaccine* 2008;**26**(17):2135—41.
10. Melegaro A, Edmunds WJ, Pebody R, Miller E, George R. The current burden of pneumococcal disease in England and Wales. *J Infect* 2006;**52**(1):37—48.
11. Gilca R, De Serres G, Skowronski D, Boivin G, Buckeridge DL. The need for validation of statistical methods for estimating respiratory virus-attributable hospitalization. *Am J Epidemiol* 2009;**170**(7):925—36.
12. Jackson ML. Confounding by season in ecologic studies of seasonal exposures and outcomes: examples from estimates of mortality due to influenza. *Ann Epidemiol* 2009;**19**(10):681—91.
13. *UK Standards for Microbiology Investigations (SMI)* [updated Jul 18; cited 2013 Jul 18, 2013]. Available from: http://www.hpa.org.uk/ProductsServices/MicrobiologyPathology/UKStandardsForMicrobiologyInvestigations/; 2013.
14. Fleming DM, Andrews NJ, Ellis JS, Bermingham A, Sebastianpillai P, Elliot AJ, et al. Estimating influenza vaccine effectiveness using routinely collected laboratory data. *J Epidemiol Community Health* 2010;**64**(12):1062—7.
15. The Health and Social Care Information Centre. *HES online* [updated Jul 18, 2013]. Available from: http://www.hscic.gov.uk/hes; 2013.
16. Fleming DM, Miles J. The representativeness of sentinel practice networks. *J Public Health (Oxf, Engl)* 2010;**32**(1):90—6.
17. *Influenza vaccination uptake monitoring on behalf of the Department of Health* [cited 2013 Jul 18, 2013]. Available from: http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1195733756886; 2013.
18. Union CotE. Council recommendation of 22 December 2009 on seasonal influenza vaccination. *Off J Eur Union* 2009;**L**(348):71.
19. Rivetti D, Jefferson T, Thomas R, Rudin M, Rivetti A, Di Pietrantonj C, et al. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev* 2006;(3). CD004876.
20. Begum RPF. *Seasonal influenza vaccine uptake amongst GP patient groups in England*. Winter season 2011/12. London, UK: HPA; 2012 14 Jun. 2012. Report No.
21. Mytton OT, Rutter PD, Mak M, Stanton EAI, Sachedina N, Donaldson LJ. Mortality due to pandemic (H1N1) 2009 influenza in England: a comparison of the first and second waves. *Epidemiol Infect* 2012;**140**(9):1533—41.
22. Campbell CNJ, Mytton OT, McLean EM, Rutter PD, Pebody RG, Sachedina N, et al. Hospitalization in two waves of pandemic influenza A(H1N1) in England. *Epidemiol Infect* 2011;**139**(10):1560—9.
23. Jefferson TO, Rivetti D, Di Pietrantonj C, Rivetti A, Demicheli V. Vaccines for preventing influenza in healthy adults. *Cochrane Database Syst Rev* 2007;(2). CD001269.
24. Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med* 2008;**359**(15):1555—64.
25. Van Kerkhove MD, Hirve S, Koukounari A, Mounts AWGroup HNpsw. Estimating age-specific cumulative incidence for the 2009 influenza pandemic: a meta-analysis of A(H1N1)pdm09 serological studies from 19 countries. *Influenza Other Respir Viruses* 2013;**7**(5):872—86.
26. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med* 2004;**351**(25):2611—8.

27. Warren-Gash C, Bhaskaran K, Hayward A, Leung GM, Lo S-V, Wong C-M, et al. Circulating influenza virus, climatic factors, and acute myocardial infarction: a time series study in England and Wales and Hong Kong. *J Infect Dis* 2011;**203**(12):1710—8.
28. Trotter CL, Stuart JM, George R, Miller E. Increasing hospital admissions for pneumonia, England. *Emerg Infect Dis* 2008;**14**(5):727—33.
29. Nair H, Brooks WA, Katz M, Roca A, Berkley JA, Madhi SA, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet* 2011;**378**(9807):1917—30.
30. Nicholson KG, McNally T, Silverman M, Simons P, Stockton JD, Zambon MC. Rates of hospitalisation for influenza, respiratory syncytial virus and human metapneumovirus among infants and young children. *Vaccine* 2006;**24**(1):102—8.
31. Ajayi-Obe EK, Coen PG, Handa R, Hawrami K, Aitken C, McIntosh EDG, et al. Influenza A and respiratory syncytial virus hospital burden in young children in East London. *Epidemiol Infect* 2008;**136**(8):1046—58.