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

Deborah Cromer [a,*], **Albert Jan van Hoek** [b], **Mark Jit** [b,c], **W. John Edmunds** [c], **Douglas Fleming** [d], **Elizabeth Miller** [b]

[a] *Complex Systems in Biology Group, Centre for Vascular Research, University of New South Wales, Sydney, Australia*
[b] *Public Health England, London, United Kingdom*
[c] *Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom*
[d] *Research and Surveillance Unit, Royal College of General Practitioners, Birmingham, United Kingdom*

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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.

* Corresponding author.
E-mail address: d.cromer@unsw.edu.au (D. Cromer).

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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