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Original Research

The impact of targeting all elderly persons in England & Wales for yearly influenza vaccination: excess mortality and time trend study

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Article Summary

1) Article focus:

> There has been no assessment of the impact on mortality of the switch from risk-based to age group-based targeting of yearly influenza vaccination of the elderly in England & Wales which was phased in from 1998/99 and which resulted in a marked increase in yearly vaccine coverage.

> Our aim was to investigate the impact on mortality of the change from risk-based to age group-based targeting of the elderly for yearly influenza vaccination in England & Wales.

2) Key messages:

> Our study provides weak evidence for lower influenza-related mortality under age group-based targeting compared with risk based targeting of yearly influenza vaccination of the elderly.

3) Strengths and limitations:

> Strengths are that we analysed a long-time series of data, carefully controlling for changes to coding and laboratory practices and using the most specific mortality outcome available

> Limitations include potential underestimation of mortality and residual confounding

Abstract

Objective

To investigate the impact on mortality of the change from risk-based to age group-based targeting of the elderly for yearly influenza vaccination in England & Wales.

Design

Excess mortality estimated using time series of deaths registered to pneumonia or influenza, accounting for seasonality, trend and artefacts. Non-excess mortality plotted as proxy for long-term trend in mortality.

Setting

England & Wales

Participants

Persons aged 65-74 and 75+ whose deaths were registered to underlying pneumonia or influenza between 1975/76 and 2004/05

Outcome measures

Average difference in excess pneumonia and influenza deaths each winter in the 4-6 winters since age group-based targeting of vaccination was introduced (in persons aged 75+ from 1998/99; in persons aged 65+ from 2000/01), compared to before, estimated using linear regression adjusted for temperature, antigenic drift, and vaccine mismatch, and stratified by dominant circulating influenza subtype. Trend in baseline weekly pneumonia and influenza death rates.

Results

There is a suggestion of lower average excess mortality in the 6 winters after age group-based targeting began compared to before but confidence intervals include no difference. Trend in baseline pneumonia and influenza mortality shows an apparent downwards turning point around 2000 for the 65-74 age group and from the mid-1990s in the 75+ age group.

Conclusions

There is weakly supportive evidence that the marked increases in vaccine coverage accompanying the switch from risk-based to age group-based targeting of the elderly for yearly influenza vaccination in

England & Wales was associated with lower levels of pneumonia and influenza mortality in older people in the first 6 years after age group-based targeting began. The possible impact of these policy changes is observed both as weak evidence for lower average excess mortality and as a turning point in baseline mortality coincident with the changes. Further work is required to exclude residual confounding.

Introduction

There has been no assessment of the impact on mortality of the switch from risk-based to age group-based targeting of yearly influenza vaccination of the elderly in England & Wales. The policy of targeting people for yearly influenza vaccination based on risk alone, in place until 1998/99, meant that only people with certain medical conditions (chronic heart, respiratory or renal disease, diabetes mellitus or immunosuppression) were offered free yearly influenza vaccination.(1) The age group-based targeting policies adopted in 1998-2000 meant that from then on, all those people aged 75 and over (from 1998) and aged 65 and over (from 2000) would be offered free yearly influenza vaccination. These policy changes were followed by a marked increase in vaccination coverage of those 65 years of age and over, from 46% in the winter of 1999/00 to 66% in 2000/01 (calculated based on reported coverage in high risk and low risk people 65+ in (2)). Vaccine coverage has continued to rise or stay above this level ever since.(2-4) Evidence for lower excess mortality in the elderly in the years shortly following the move to age group-based targeting, or for a fall in baseline respiratory mortality in the elderly coincident with these policy changes, would be evidence that these changes have prevented more elderly deaths than the former risk-based approach to vaccine targeting.

Debate surrounds the question of the efficacy and effectiveness of influenza vaccine in the elderly.(5-8) Two systematic reviews concluded that there is insufficient good quality evidence,(9, 10) though one of these reviews did include a randomised controlled trial showing efficacy against influenza disease of 58% (95% CI 26 to 77%) in adults aged 60 and over.(11) Observational studies controlling for positive confounding by healthier people seeking vaccination have also demonstrated effectiveness against mortality.(12, 13) There has been much interest in measuring the mortality impact of influenza vaccination of the elderly in other settings and results have been mixed. In

Holland, all-cause excess mortality during influenza epidemics declined after the introduction of universal yearly vaccination of those aged 65 and over.(14) In contrast, three other studies, in the US, Italy and in Catalonia, did not detect an impact of rising vaccine coverage of the elderly on all-cause excess mortality.(15-17) Previous studies of influenza attributable or excess mortality in the UK have not related this to vaccination.(18-20)

While the level of mortality observed when influenza is circulating in the community (often quantified using excess mortality) varies from winter to winter, baseline respiratory mortality (i.e. excluding excess) has a seasonal pattern which is more or less constant from winter to winter, though it may change over the long-term.(21) Previous studies of the long-term trends in influenza-related mortality in England & Wales have covered earlier, and usually shorter, time periods. One study examined trends in pneumonia or influenza (P&I) mortality in England & Wales from 1994/95 to 2000/01 and showed a plot of rates of P&I mortality in the 65-74 age group in this period which appears to have little secular trend.(18) The shape of the trend in baseline respiratory mortality in England & Wales since 2000/01 is unclear.

This work evaluates a public health initiative, to specifically target all people 65 years of age and older for yearly influenza vaccination regardless of risk group, which has been in place since 2000. Studying patterns in excess mortality and trends in baseline mortality in the years shortly following the introduction of this initiative allows us to provide evidence for the impact of this policy.

Methods

Daily counts of deaths registered to underlying pneumonia or influenza (P&I) in England & Wales between 1975 and 2005, by date of death, sex and age group, were provided by the Office for National Statistics (ONS). Deaths registered to underlying P&I, not just confirmed influenza deaths, were analysed because deaths from influenza are rarely laboratory confirmed and because deaths in

the elderly which occur secondary to influenza often result from pneumonia.(22, 23) P&I mortality rates are a more specific measure of influenza activity than rates of all-cause mortality.(24)

The mortality data were adjusted to account for the following historical modifications to how the data are coded so that our assessment of trends would not be influenced by these artefactual step changes. The ICD changed from version 8 to 9 in 1979, leading to a small decline in deaths coded to underlying P&I.(25) In 1984, ONS introduced a broader interpretation of rule 3 for coding underlying cause of death, which led to an abrupt fall in deaths registered to underlying pneumonia, and to a rise in deaths registered to underlying cancer and ischemic heart disease.(26) In 1993, ONS adopted an automated system for coding underlying cause of death which narrowed the interpretation of rule 3 and approximately reversed the change adopted in 1984 (i.e. rates of deaths being registered to underlying pneumonia rose back to a level approximately equal to that pre-1984).(27) With the change from ICD 9 to 10 in 2000, deaths coded to underlying respiratory disease fell by approximately 22%, and deaths coded specifically to underlying pneumonia fell by 38%.(28)

The Health Protection Agency Centre for Infections (HPA CfI) provided an extract of all individual reports of laboratory-confirmed influenza A infections between 1975 to 2005 from their LabBase2 database. These reports, based on virus isolation and PCR, were reported voluntarily by National Health Service (NHS) and HPA laboratories in England & Wales. Records included individuals' age, sex and the earliest specimen date.

The statistical methods used are summarized below, with full details provided in the supplementary material. Vaccine coverage estimates for 1989/90 to 2004/05 were adapted from published sources. Published estimates of vaccine coverage were available by age group and separately for persons considered at high or low risk of influenza complications.(2, 3) Separate estimates by risk group were combined proportionately according to the number of each group

vaccinated to give coverage for that age group regardless of risk group.

There are numerous approaches in the literature to quantifying excess mortality as a measure of influenza severity and no gold standard approach. We elected to modify the method of Simonsen and colleagues,(15) used in their paper analysing influenza vaccine impact in the US, to examine both excess mortality and the long-term trend in non-excess mortality in relation to changes in vaccine policy and coverage. The Simonsen method is a modification of Serfling's cyclical regression approach,(21) where non-epidemic data are modeled to estimate expected mortality and mortality greater than expected is labelled as excess, but improves on the specificity of Serfling's model in that epidemic periods in the data are informed by a specific measure of influenza.

An influenza year was defined as week 26 of one year to week 25 of the next because the timing of influenza circulation during a given winter usually spans two calendar years (i.e. extends from October of one year to March of the next year). Mortality and laboratory data were collapsed into weekly counts for analysis. In order to differentiate excess from baseline mortality we used laboratory data to estimate which were the epidemic weeks in the time series. We then fitted models to the mortality time series to determine both excess and baseline mortality with reference to these epidemic weeks. Excess mortality was the sum of observed minus predicted deaths in weeks when laboratory data breached their epidemic threshold, by influenza year. Baseline trend in mortality incidence was approximated by fitting the mortality model to the death counts not labelled as excess. This model fit was then deconstructed and just the spline (i.e. trend) component was plotted in order to graphically assess its shape for changes, or turning points, in the direction of the trend coincident with policy changes. In the same way, estimates of excess mortality were plotted over time to look for evidence of turning points in the trend. Estimates of excess mortality and plots of baseline trends were determined separately for the age groups 65-74, 75+ and 45-64 (the latter age group being

"unexposed" to a change in vaccine policy or coverage over the period). Any estimates of negative excess mortality were recoded to 0. No model was stratified by sex because an initial exploration of the data suggested similar trends by sex in the study period. A sensitivity analysis was carried out defining epidemic periods based on counts of combined laboratory-confirmed influenza A and influenza B virus infections (as opposed to the main analysis where this was done using counts of influenza A infections only).

To quantify vaccine impact on excess mortality, we fitted age group-specific linear regression models of excess mortality for each influenza year against a) a dummy variable having a value of 0 for 1989/90 to 1999/00 and 1 for 2000/01 to 2004/05 to capture the start of the policy targeting all those 65+ for yearly influenza vaccination (exposure of interest), b) the minimum monthly temperature observed in each influenza year,(29) c) whether the influenza season experienced a large antigenic drift event or not,(30) and d) whether the influenza season was characterised by a mismatch between vaccine and circulating H3N2 viruses or not (references in Table). Models were fitted separately for influenza A/H3N2 virus-dominated influenza seasons and for influenza seasons dominated by other influenza virus subtypes. This was done to allow for greater mortality, and thus potentially greater vaccine impact, in influenza seasons dominated by influenza A/H3N2 viruses than those dominated by influenza A/H1N1 or B viruses.(31) Vaccine mismatch was not included in models where the outcome was excess mortality in non-influenza A/H3N2 virus-dominated seasons because both mismatch seasons were seasons when influenza A/H3N2 viruses dominated. Separate sensitivity analyses were carried out a) defining the vaccine coverage dummy variable with reference to 1998/99 rather than 2000/01 (because 1998/99 was the first influenza year of age group-based targeting of vaccination (to those 75+)) and b) modelling vaccination as a linear term, using derived estimates of coverage by age group in each influenza year, rather than as a dummy variable.

To establish the extent of circulation of influenza in the community over the influenza years studied, weekly rates of consultation for influenza-like illness (ILI), and for infectious and parasitic diseases (which excludes ILI), with sentinel general practices in England & Wales for 0-4 and 5-14 years olds were plotted over time (data provided by the Royal College of General Practitioners weekly returns service). We also plotted weekly, all-age rates of laboratory-reported influenza A and B infections over time.

Models were fitted in R (R version 2.12.1 (2010-12-16), Copyright 2010 The R Foundation for Statistical Computing).

Results

Weekly deaths registered to underlying P&I in those 65 years of age and older in England & Wales in the period from 1975/76 to 2004/05 ranged from 34 deaths per 1,000,000 person weeks (in week 36 of 1984) to 481 deaths per 1,000,000 person weeks (in week 7 of 1976).

Excess mortality

Excess mortality for the 65-74 age group ranged from 0 to just over 2000 deaths per influenza year in the study period (Table). For the 75+ age group, the range was from 0 to over 14,000 deaths per influenza year. Mortality attributable to epidemic influenza was highly variable year to year. For neither age group does there appear to have been a turning point in the trend in excess mortality coinciding with the 2000/01 season, when the policy of targeting all persons aged 65 and over for yearly influenza vaccination was enacted (Figure 1). Similarily, there was no turning point in the trend in excess mortality in the 75+ age group around 1998/99 when this age group became fully targeted for yearly influenza vaccination. The direction of the trend in excess mortality over the whole time period appears to be downwards or flat. Trend in excess mortality in the 45-64 age group is approximately flat in the same period (Supplementary Figure 1).

Vaccine impact from linear regression

Point estimates for the average difference between excess mortality after 2000 compared to before, adjusting for cold weather and antigenic drift in influenza A/H3N2 viruses and stratified by dominant circulating virus subtype, are in the direction of lower excess mortality after 2000 than before for both the 65-74 and 75+ age groups, except for mortality in seasons dominated by influenza A/H1N1 or B viruses for the 65-74 age group which was similar after 2000 to before (Figure 2). However, confidence intervals include no difference. Point estimates indicate greater impact in influenza A/H3N2 virus-dominated seasons than in influenza A/H1N1 or B virus-dominated seasons. These findings are robust to modelling the vaccine policy change as occuring in 1998/99 instead of 2000/01 (data not shown). For the 45-64 age group, point estimates suggest lower excess mortality after 2000 than before for seasons dominated by influenza A/H3N2 viruses, but the confidence interval again includes the null (Figure 2). For each of the three age groups, modelling the effect of change in vaccine coverage as a linear instead of binary (dummy) variable results in point estimates suggesting lower excess mortality per unit increase in vaccine coverage but with wide confidence intervals including the null (data not shown).

Trends in baseline mortality

Long-term trends in mortality not labelled as excess, analysed as a proxy for baseline P&I mortality, are complex, with three to four periods during which different trends were observed. For the 65-74 age group, rates in the study period were highest until the late 1970s, declined to approximately 1990, plateaud to 2000 and fell after 2000 (Figure 3). For the 75+ age group, rates increased to the late 1970s, declined to the mid-1980s, plateaud to the mid-1990s and then fell. The 45-64 age group showed a broadly similar baseline trend to that of the 65-74 age group, though the trend was more tortuous due to smaller numbers (Supplementary figure 2). Residuals from fitted

models were normally distributed with mean approximately 0 and standard deviation approximately 1 with some residual autocorrelation (data not shown). Findings are robust to defining epidemic periods using laboratory reports of influenza A infections alone or to using both influenza A and B infections for this purpose.

Secular trends in circulation of influenza in the community during the study period

During the period 2000-2005, ILI consultations for 0-4 and 5-14 year olds were lower than historically (supplementary fig 3). However, over the same time period consultations for infectious and parasitic diseases (which excludes ILI) also appeared to decline, especially in the 5-14 year age group (supplementary fig 4). Rates of laboratory reported influenza infections were lower in 2000-2005 than in the decade prior. (supplementary fig 5). Rates in 2000-2005 were similar to those observed around 1980 (figure 3).

Discussion

Statement of principal findings

There is weakly supportive evidence that the switch from risk-based to age group-based targeting of influenza vaccination for older people was associated with lower influenza-related mortality in the 4-6 years following this policy change. Results from our multivariable linear regression suggest that this policy change had a weak, positive impact on excess mortality in both the 65-74 and 75+ age groups. There is no indication of a downwards turning point in the trend in excess mortality around 2000/01 (when all those 65+ began to be targeted for vaccination) or 1998/99 (when those 75+ began to be targeted) which argues against a strong, specific impact of this policy change on excess mortality in either age group. Trends in baseline, as opposed to excess, mortality do show a suggestion of a downwards turning point in the mid-1990s for the 75+ age group and around 2000 for the 65-74 age group, coinciding approximately with the timing of the changes to specifically target

these age groups for vaccination. Results obtained by fitting the various models to data for the 45-64 age group, in whom vaccine coverage was largely static over the study period, are in a similar direction but are of a smaller magnitude than the apparent impact in the 65-74 and 75+ age groups, suggesting there may have been other factors acting to bring down P&I mortality at the time of the policy changes. Thus our analysis is consistent with a small mortality impact in the 65-74 and 75+ age groups during the six years after policies to wholly target these age groups for yearly influenza vaccination were enacted.

Strengths and weaknesses of the study

There are a number of strengths to the work undertaken, as well as several limitations. The key strengths are that we estimated excess mortality and long-term trend in mortality over a long period (30 years). We carefully controlled for changes to death coding and laboratory practices which occurred over this time period. The analytical approach we used, which is similar to one used by many others,(15, 16) of modelling seasonality and trend using splines in addition to sinuisoidal terms (full details provided in the supplementary material), is a highly flexible method of fitting complex patterns and trends that is especially helpful when modelling a long time series. The outcome we chose to model (deaths from underlying P&I) is the most specific option available which allows sufficient numbers of deaths for analysis. This choice maximised our ability to discern high mortality impact influenza years from those less so, and thus to detect vaccine impact. Analysing underlying P&I of course means our estimates of excess mortality underestimate the burden of mortality due to all respiratory disease (which includes bronchitis), cardiovascular disease and other causes of death which may be linked to influenza. (19, 20) However, it was not the aim of this work to estimate the total mortality burden due to influenza. Further adding to the specificity of our outcome was our designation of epidemic periods in the mortality data with reference to the time series of laboratory-

confirmed influenza A infections. Better still might have been to use influenza A/H3N2 infections, the subtype most often associated with influenza years when there is substantial mortality,(53) but the laboratory data available for this analysis were not broken down by subtype. The limitations of our work include that our estimate of the extent of variability in excess mortality across influenza years is likely to be an underestimate because our model failed to explain all variability in the mortality data (as evidenced by a small amount of autocorrelation in residuals, data not shown). This may be because we did not include temperature or other climatic variables in the models estimating excess mortality. We did adjust for temperature in linear regression models of vaccine impact on excess mortality and as such our analysis of vaccine impact should not be confounded by temperature. However, our results regarding long-term trends in non-excess mortality may be confounded by temperature as there is evidence that minimum winter temperatures have increased since the early 1960s.(54) In using laboratory data to inform epidemic periods in the mortality data, we made no allowance for a lag between the increase, or peak, in incidence of laboratory-reported infections and the timing of excess deaths associated with these infections. This is likely to have led us to underestimate excess mortality, assuming the peak in deaths rarely precedes and generally coincides or follows the peak in laboratory reports. However, the rise in influenza activity in the community in terms of GP consultations generally coincides with the rise in numbers of laboratory reports of influenza infections,(36) and, during influenza years dominated by circulation of influenza A viruses, peak weekly GP consultation rates for influenza-like illness in the 45–64, 65–74 and >=75 years age groups tend to coincide with same-age peaks in respiratory deaths, plus or minus 1 week (e.g. 1995/1996, 1996/1997, 1998/1999 and 1999/2000).(18) Hence the potential bias in our estimates of excess mortality is likely to be minimal because the weeks we might have missed by not allowing for a lag will be close to the start or end of the period of influenza circulation and thus will make up a small

proportion of the total influenza attributable P&I deaths in a given winter. Our estimates of long-term trends may be confounded by the trends in co-morbidities linked to smoking or by long-term patterns in other co-morbidities associated with respiratory mortality, which we have not accounted for. Finally, the separate vaccine coverage estimates we present for the 65-74 and 75+ age groups from 2000/01 onwards are sensitive to our assumption of a constant ratio of vaccine coverage in the 65-74 to 75+ age groups from 2000/01 onwards (described in the supplementary file). The assumption of a constant ratio is unlikely to be true and as such we have probably underestimated coverage in the 65-74 age group and overestimated it in the 75+ age group; the increase in coverage in 2000/01 was probably disproportionately accounted for by an increase in coverage in the 65-74 age group, newly targeted as fully "at risk" from the 2000/01 influenza season. Our main findings are unaffected by this because we focus on results from linear models of the effect of change in vaccination policy as a binary variable.

Strengths and weaknesses in relation to other studies, discussing important differences in results

Using as a reference the previous estimates which exist of excess respiratory mortality in England & Wales, our estimates appear to be a valid reflection of variability between years and between age groups in influenza-attributable mortality. Findings as to vaccine impact from other settings have been mixed, thus our observation of perhaps some limited impact is not inconsistent with reports from other settings which analysed the impact of similar levels of vaccine coverage to that achieved in the UK. Previous estimates of excess, all-age respiratory mortality for the influenza years 1975/76, 1976/77 and 1977/78 are higher than our excess P&I estimates for these years but the relative magnitude of the excess mortality between these years matches our estimates well. (supplementary table). The absolute value of the previous estimates is higher than ours because the authors included bronchitis deaths and analysed all-ages combined, not just the elderly. For the

influenza years 1994/95 to 1999/2000, published estimates of average influenza-attributable respiratory mortality by age group (45-64, 65-74 and 75+) are higher than our averages for the same age groups over the same period but ratios between different age groups are similar to our estimates. Differences in the magnitude of estimates from the two methods will be because they include bronchitis deaths and but also because the rate difference-type method used by Fleming and colleagues tends to produce higher estimates of excess than the Serfling-type method we used, due to a lower reference mortality and the mortality rate in the "influenza-active periods" being entirely attributed to influenza.(55) There has been much interest in measuring the impact of influenza vaccination campaigns in other settings.(14, 15, 17, 56) Excess all-cause mortality declined in Dutch elderly after the introduction of universal yearly vaccination of those aged 65 and over which saw yearly coverage reach 80%.(14) Excess all-cause mortality and influenza-related hospitalisations and GP visits declined more in Ontario than in other Canadian provinces after the introduction of universal yearly vaccination for all Ontario residents.(56) Analyses of the impact of rising vaccine coverage of the elderly on excess all-cause mortality in the US, Italy and in Catalonia did not detect impact perhaps because, in the case of the US and Italy, coverage did not reach high enough levels for long enough during the study period, or because, as in Catalonia, there were limited data available, prior to coverage exceeding 60%, to provide a baseline against which to estimate impact.(15-17) Because ratios of our estimates of excess P&I between adjacent seasons, and between age groups, are consistent with previous work using different models, we are confident that our impression of the relative magnitude of P&I mortality between age groups and from one influenza year to the next are a true reflection of patterns in influenza mortality during the study period. Our having observed some evidence for vaccine impact on excess mortality in the 6 years after implementation of age group-based influenza vaccination is consistent with findings from other temperate nothern hemisphere

settings which have attained similar levels of vaccine coverage in the elderly, where some studies have demonstrated impact and others have not.

Meaning of the study: possible explanations and implications for clinicians and policymakers

Our analysis suggests high yearly vaccination coverage of the elderly had a small impact on P&I deaths in the 4-6 years following implementation of age group-based targeting of the elderly for influenza vaccination. Alternative explanations are that there was less influenza around during the time of high vaccine coverage, making it look like vaccination produced an impact on mortality when it did not. The fact that we observed smaller magnitude but same direction associations between the timing of policy changes in the elderly and mortality in the 45-64 age group, in whom vaccination policy and coverage were approximately constant over the study period, support this alternative explanation. However, our analysis of to what extent influenza circulated in the community in the study period does not provide clear answers: consultations among children for both ILI and infectious and parasitic diseases (which excludes respiratory disease) were lower in the 2000-2005 period than earlier in the study period. It is difficult to interpret lower ILI rates as strong evidence for less influenza circulating in 2000-2005 than previously since the decline in rates of infectious and parasitic diseases rates then still needs explaining. It may in part be that there was progressively lower use of GP services in the 2000-2005 period. Rates of laboratory reported influenza infections for all-ages, reported to the HPA CfI, were certainly lower in 2000-2005 than in the decade prior, and were similar to rates observed around 1980 when excess mortality also appeared to be low for several consecutive years. It is difficult to interpret long-term trends in laboratory reports of influenza infections because of changing testing practices and changing volumes of test requisitions over the time period. For example, between 1975 and 1992, the number of laboratory reports of viral infections doubled (57); this is unlikely to reflect a doubling of viral infections over this period. If more tests were requisitioned

in 2000-2005 than in the years around 1980 similar rates of positive reports in the two periods would suggest less viral activity in 2000-2005 than around 1980. However, it is hard to see how less influenza in circulation later than earlier in the study period could explain a turning point in baseline mortality in the 65-74 and 75+ age groups approximately coincident with policy changes to specifically target these age groups for vaccination. We think the observation of a turning point in baseline mortality reflects partly a non-specific impact of influenza vaccination on respiratory mortality in the elderly that is not directly attributable to influenza as well as partly a specific impact of influenza vaccination given that analysing excess mortality necessarily means some truly influenza-attributable mortality (i.e. that which does not breach the epidemic threshold) contributes to baseline. A further possible alternative explanation for the apparent, small influenza vaccine impact we have observed is that this is really an impact of pneumococcal vaccination. This is unlikely to be true; to the end of the 2004/05 influenza year, less than 30% of people 65 years of age and over had received the recommended 23-valent pneumococcal polysaccharide vaccine.(58) Pneumococcal conjugate vaccination of infants and children, which might be expected to provide indirect protection to the elderly, has only been routinely recommended since 2006. It is possible that there is some other factor which also changed over the time period and which explains part of the mortality impact we observed (e.g. trends in co-morbidities linked to smoking).

Unanswered questions and future research

Influenza vaccine impact can be difficult to measure due to its reliance on surveillance data which are generally not collected in a consistent way over time, and because of the variable nature of influenza activity over time. One way of adding to the evidence base is to look at vaccine effectiveness. In order to strenghthen the evidence base for influenza vaccine effectiveness in the elderly, further good quality cohort and case-control studies across multiple influenza seasons with

varying degrees of match between vaccine and circulating variants, and adequate control for negative confounding by indication (sicker elderly being preferentially offered vaccination) and positive confounding by healthier older people putting themselves forward for vaccination, are required. It remains unclear to what extent our findings are due to there being less influenza around 2000-2005 than before this time or to confounding by factors such as trends in co-morbidities linked to smoking. Analyses including more recent influenza seasons will help to answer these questions and to monitor whether the modest mortality impact we observed in the 6 years after age group-based targeting of vaccination began has been sustained. This analysis will be complicated by the presence of pneumococcal vaccination of infants and the elderly, making teasing apart the effects of how much influenza circulated during the time period, the impact of influenza vaccination and the impact of pneumococcal vaccination a challenge.

Competing interest

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: that funding for the submitted work was provided by the National Institute of Health Research in the UK (fellowship to AGM) and that none was garnered from elsewhere; that JCW is currently employed by, and holds stock options with, GlaxoSmithKline but that the relationship of JCW to GSK had no influence on the work or on the decision to publish it; that there are no other relationships or activities that could appear to have influenced the submitted work.

Contributors

AGM, PM and JCW conceived of the study, AGM conducted the analysis, led on the interpretation and wrote the paper; JCW, PM and CAR contributed to interpretation and to

subsequent drafts of the paper. All authors approved the final version to be published. AGM is the guarantor for the study. P&I data were provided by Cleo Rooney and Emma Gordon from the Office for National Statistics. Laboratory data were provided by Carol Joseph and Joy Field of the Health Protection Agency Centre for Infections. GP consultation data were provided by Douglas Fleming and Alex Elliot of the Royal College of General Practitioners.

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Access

AGM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing

There are no additional data available.

Ethics

This study was approved by the ethics committee of the London School of Hygiene & Tropical Medicine (approval number 5109).

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Table title

Tab: Influenza seasons in England & Wales, 1974/75-2004/05: dominant variant, antigenic drift events in evoluation of influenza A/H3N2 viruses,vaccine mismatch, vaccine coverage and numbers of excess P&I deaths by age group. Bolding means H3N2 dominant and vaccine variants are from different antigenic clusters.

Figure legends

Fig 1: Excess mortality in the a) 65-74 and b) 75+ age groups in each influenza season in England & Wales, stratified by the dominant influenza virus in circulation (black 'x' = A/H3N2 viruses were dominant or co-dominant; grey '+' = A/H1N1 or B viruses were dominant). Best-fitting trend lines in excess mortality, with 95% CIs, are overlayed. Vaccine coverage in the respective age group from published data is also shown (dots and asterisks, right axis). Asterisks indicate that vaccine coverage in these years was inferred from observed vaccine coverage in the 65+ age group and the average ratio of coverage in the 65+ to 65-74 (or 75+) age group.

Fig 2: Summary of estimated vaccine impact from linear regression models of the binary effect of the switch to age group-based targeting of yearly influenza vaccination to all those 65 years of age and older (from 2000/01 onwards) compared to before 2000/01. Squares are the 65-74 age group, circles the 75+ age group and triangles the 45-64 age group. Filled symbols represent seasons dominated by influenza A/H3N2 viruses, open symbols seasons dominated by influenza A/H1N1 or B viruses.

Fig 3: Model fit: The observed time series of weekly P&I deaths in the a) 65-74 sand b) 75+ age group in England & Wales between 1975 and 2005 (light dotted line on each plot). The fitted curve from the log-linear Simonsen-like model fitted excluding December to April and accounting for seasonality, long-term trend and artefacts is overlayed (dark line). Vaccine coverage (in the 65-74 and 75+ age groups) adapted from published data is shown on the right axis of each plot (dots and asterisks). Asterisks indicate that vaccine coverage in these years was inferred from observed vaccine coverage in the 65+ age group and the average ratio of coverage in the 65-74 (or 75+) to 65+ age group. The fitted curve can be deconstructed into its constituent parts. Thus c) and d) show just the long-term trend (i.e. cubic spline) component of the fitted curve (dark lines), with its 95% confidence interval (light lines), for the 65-74 and 75+ age groups, respectively. Doing this allows a better visualisation of the shape of the long-term trend.

Table

Influenza season	Dominant influenza variant(s)	Antigenic drift events(30)	Vaccine cluster*	Minimum monthly temperature (°C)	Vaccine coverage, 65-74 yrs	Excess deaths (n), 65-74 yrs	Vaccine coverage, 75+ yrs	Excess deaths (n), 75+ yrs	Vaccine coverage, 45-64 yrs	Excess 45-64
1975/76	H3N2/B(32)	EN72-VI75		4.5	0%	1910	0%	9389	0%	863
1976/77	H3N2(33)			2	0%	456	0%	2986	0%	203
1977/78	H3N2/H1N1(32)	VI75-TX77		2.8	0%	419	0%	2563	0%	158
1978/79	B(32)			-0.4	0%	14	0%	25	0%	0
1979/80	H3N2(32)	TX77-BA79		2.3	0%	0	0%	95	0%	0
1980/81	H1N1/H3N2(32)			3	0%	89	0%	605	0%	73
1981/82	B/H3N2(34)			0.3	0%	174	0%	501	0%	4
1982/83	H3N2(34)			1.7	0%	264	0%	1947	0%	48
1983/84	H1N1/B(34)			3.3	0%	88	0%	742	0%	38
1984/85	H3N2/B(34)			0.8	0%	74	0%	395	0%	5
1985/86	B(35)			-1.1	0%	0	0%	0	0%	14
1986/87	H1N1(35)			0.8	0%	0	0%	0	0%	0
1987/88	H3N2/H1N1(36)	BA79-SI87		4.9	0%	0	0%	5	0%	4
1988/89	H1N1/H3N2(36)			5.2	0%	374	0%	2023	0%	119
1989/90	H3N2(36)	SI87-BE89	SI87(37)	4.9	22%	2007	27%	14115	9%	638
1990/91	B(36)		BE89(38)	1.5	24%	0	31%	178	9%	0
1991/92	H3N2(36)		BE89(39)	3.7	27%	413	33%	3302	10%	111
1992/93	B/H1N1(36)	BE89-BE92	BE89(40)	3.6	26%	0	33%	0	10%	0
1993/94	H3N2(36)		BE92(41)	3.2	32%	557	39%	4238	12%	137
1994/95	B(36)		BE92(42)	4.8	33%	0	40%	0	12%	0
1995/96	H3N2(36)	BE92-WU95	BE92(43)	2.3	33%	651	42%	5365	12%	226
1996/97	H3N2(36)		WU95(44)	2.5	33%	0	41%	15	12%	9
1997/98	H3N2/H1N1(45)	WU95-SY97	**WU95(45)**	5.2	38%	0	46%	9	14%	10
1998/99	H3N2/B(46)		SY97(46)	5.3	37%	628	49%	6802	13%	233
1999/00	H3N2(47)		SY97(47)	4.9	40%	1083	53%	10554	14%	560
2000/01	B/H1N1(48)		SY97(48)	3.2	59%**	0	74%**	109	16%	0
2001/02	H3N2/H1N2(49)		SY97(49)	3.6	61%**	21	76%**	0	17%	0
2002/03	B/H3N2(50)	SY97-FU02	SY97(50)	3.9	63%**	0	78%**	0	17%	10
2003/04	H3N2(51)		**SY97(51)**	4.8	65%**	338	82%**	2704	18%	152
2004/05	H3N2(52)		FU02(52)	4.3	64%**	1	81%**	27	NA	9

* Bolding indicates a mismatch between vaccine and dominant circulating A/H3N2-virus cluster

** Estimated from coverage 65+ and mean ratio of coverage in the 65-74 to 65+ age group and 75+ to 65+ age group for 1989/90-1999/00

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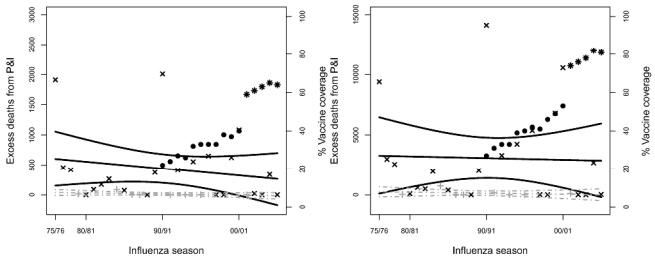

Excess mortality in the a) 65-74 and b) 75+ age groups in each influenza season in England & Wales, stratified by the dominant influenza virus in circulation (black 'x' = A/H3N2 viruses were dominant or co-dominant; grey '+' = A/H1N1 or B viruses were dominant). Best-fitting trend lines in excess mortality, with 95% CIs, are overlayed. Vaccine coverage in the respective age group from published data is also shown (dots and asterisks, right axis). Asterisks indicate that vaccine coverage in these years was inferred from observed vaccine coverage in the 65+ age group and the average ratio of coverage in the 65+ to 65-74 (or 75+) age group.
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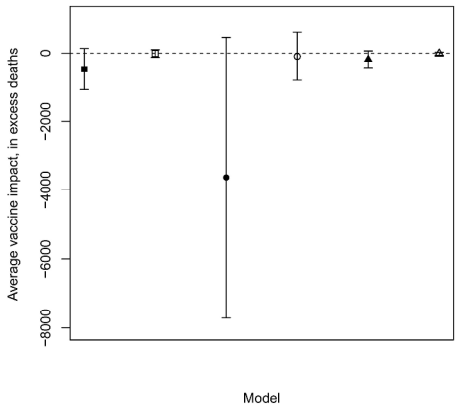

Summary of estimated vaccine impact from linear regression models of the binary effect of the switch to age group-based targeting of yearly influenza vaccination to all those 65 years of age and older (from 2000/01 onwards) compared to before 2000/01. Squares are the 65-74 age group, circles the 75+ age group and triangles the 45-64 age group. Filled symbols represent seasons dominated by influenza A/H3N2 viruses, open symbols seasons dominated by influenza A/H1N1 or B viruses.
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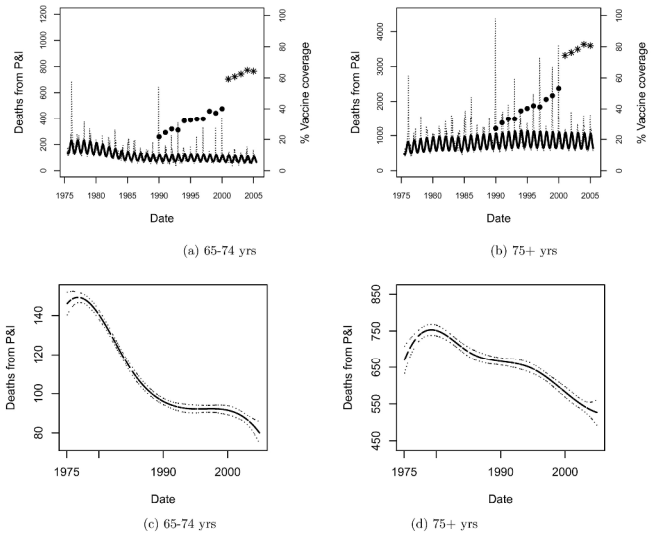

Model fit: The observed time series of weekly P&I deaths in the a) 65-74 sand b) 75+ age group in England & Wales between 1975 and 2005 (light dotted line on each plot). The fitted curve from the log-linear Simonsen-like model fitted excluding December to April and accounting for seasonality, long-term trend and artefacts is overlayed (dark line). Vaccine coverage (in the 65-74 and 75+ age groups) adapted from published data is shown on the right axis of each plot (dots and asterisks). Asterisks indicate that vaccine coverage in these years was inferred from observed vaccine coverage in the 65+ age group and the average ratio of coverage in the 65-74 (or 75+) to 65+ age group. The fitted curve can be deconstructed into its constituent parts. Thus c) and d) show just the long-term trend (i.e. cubic spline) component of the fitted curve (dark lines), with its 95% confidence interval (light lines), for the 65-74 and 75+ age groups, respectively. Doing this allows a better visualisation of the shape of the long-term trend.
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SUPPLEMENTARY FIGURES

Article title: "The impact of targeting all elderly persons in England & Wales for yearly influenza vaccination: excess mortality and time trend study"

Journal: BMJ Open

Authors: Andrea G. Mann, Punam Mangtani, Colin A. Russell, John C. Whittaker

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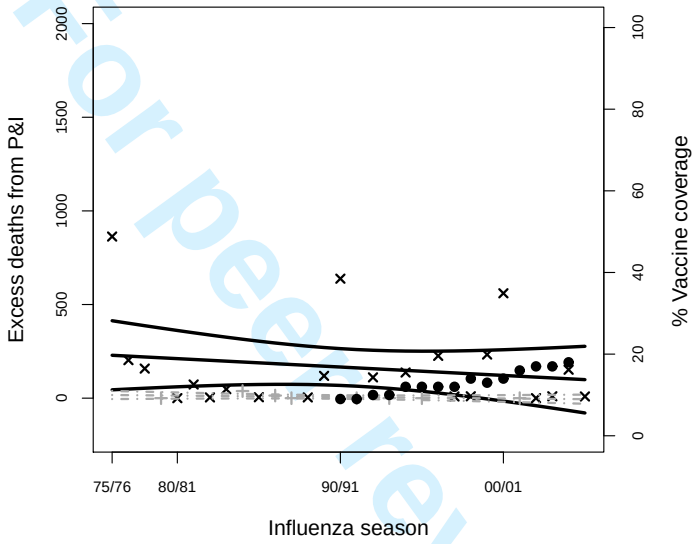
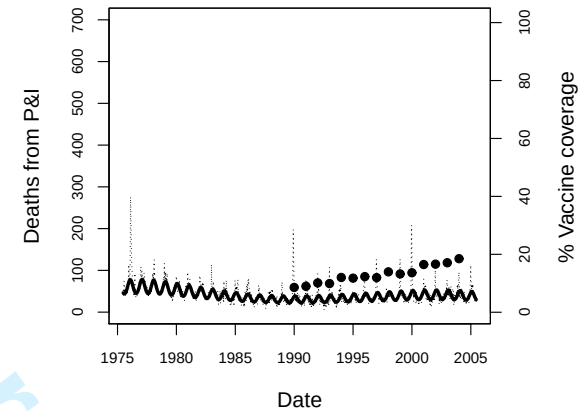
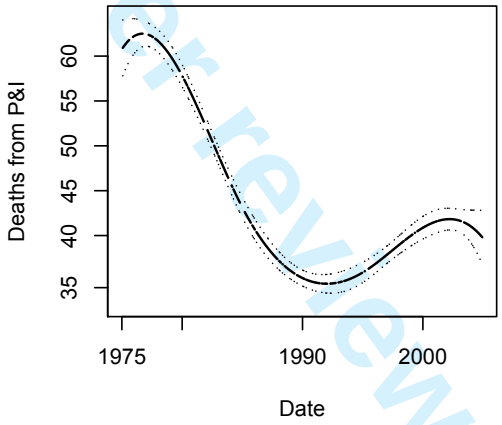


(a)

Figure 1: **Excess mortality in the 45-64 age group in each influenza season from 1975/76 to 2004/05, stratified by the dominant influenza virus in circulation (black 'x' = A/H3N2 viruses were dominant or co-dominant; grey '+' = A/H1N1 or B viruses were dominant). Best-fitting trend lines in excess mortality, with 95% confidence intervals, are overlayed. Vaccine coverage in the 45-64 age group from published data is also shown (dots, right axis).**

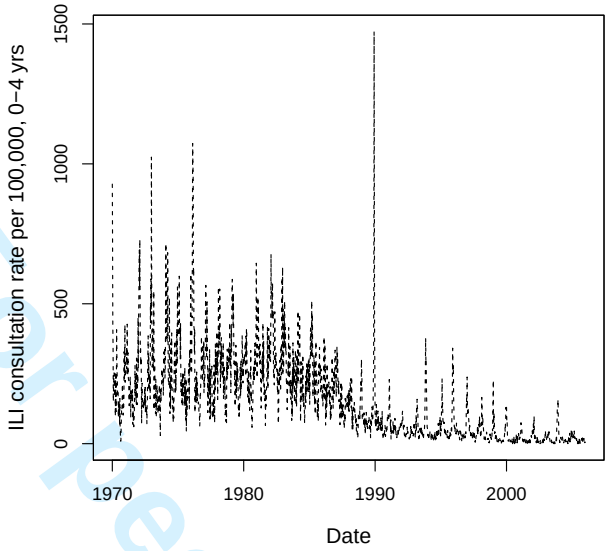


(a)

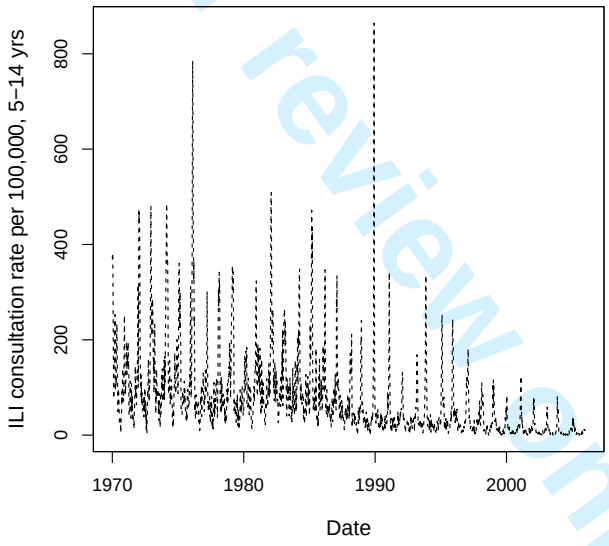


(b)

Figure 2: **Model fit: (a) The observed time series of weekly P&I deaths in the 45-64 age group in England & Wales between 1975 and 2005 (light dotted line). The fitted curve from the log-linear Simonsen-like model fitted excluding incidence from December to April and accounting for seasonality, long-term trend and artefacts is overlayed (dark line). Vaccine coverage in the 45-64 age group from published sources is also shown (dots, right axis). The fitted curve can be deconstructed into its constituent parts. Thus (b) shows just the long-term trend (i.e. cubic spline) component of the fitted curve (dark line), with its 95% confidence interval (light lines). Doing this allows a better visualisation of the shape of the long-term trend.**

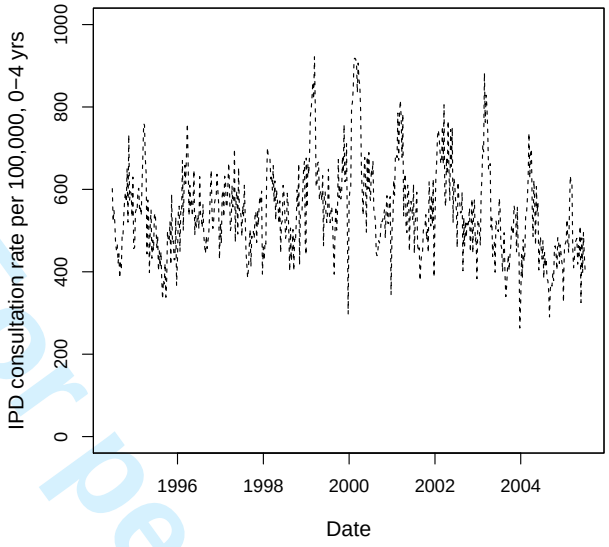


(a)

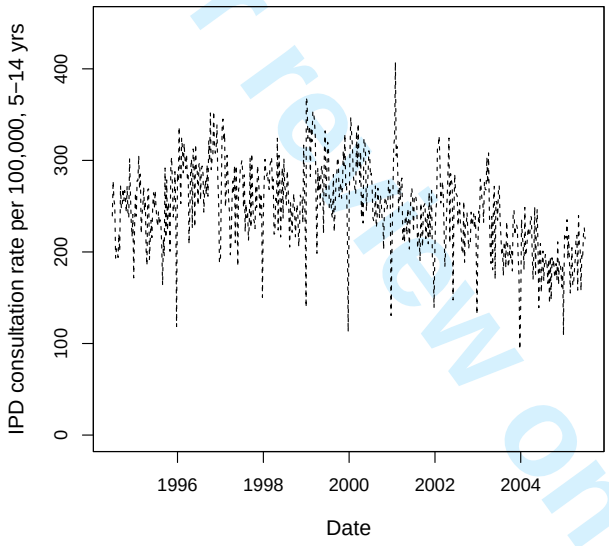


(b)

Figure 3: **The weekly rate of GP consultations for influenza-like illness in the (a) 0-4 and (b) 5-14 age groups, per 100,000 population, in sentinel general practices in England & Wales.**



(a)



(b)

Figure 4: **The weekly rate of GP consultations for infectious and parasitic diseases (which excludes respiratory diseases) in the (a) 0-4 and (b) 5-14 age groups, per 100,000 population, in sentinel general practices in England & Wales.**

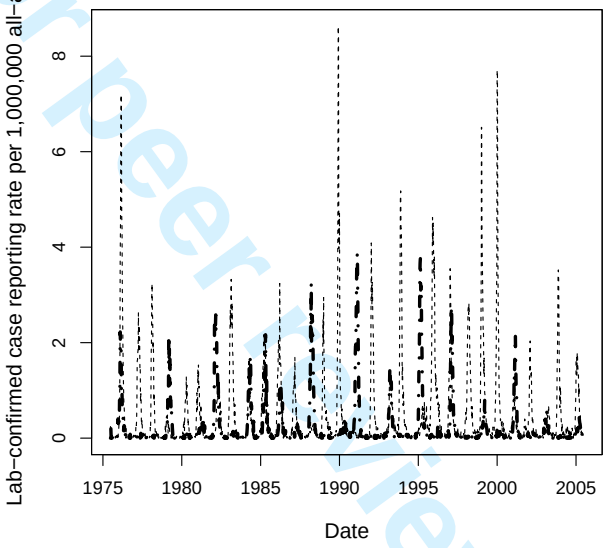


Figure 5: **The weekly rate of laboratory reports for influenza A (light dotted line) and influenza B (dark dotted line) per 1,000,000 population, voluntarily reported to the Health Protection Agency Centre for Infections, England & Wales.**

SUPPLEMENTARY TABLES

Article title: The impact of targeting all elderly persons in England & Wales for yearly influenza vaccination: excess mortality and time trend study

Journal: BMJ Open

Authors: Andrea G. Mann, Punam Mangtani, Colin A. Russell, John C. Whittaker

Corresponding author contact details: Andrea G. Mann, Department of Infectious Disease Epidemiology, Faculty of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, London, UK; andrea.mann@lshtm.ac.uk

Supplementary table. Comparison of estimates of excess mortality in previous work to our estimates.

Study	Estimates	Comparison with our estimates
Tillett, 1980 (1)	Number of all-age excess respiratory deaths for 1975/76 3.4 times that for 1976/77 and 3.8 times that for 1977/78	Summing our excess P&I estimates for the 65-74 and 75+ age groups gives combined 65+ excess P&I estimate for 1975/76 of 3.3 times 1976/77 and 3.8 times 1977/78
Fleming, 2005 (2)	For the influenza years 1994/95 to 1999/2000, average mortality in 65-74 age group 2.6 times that in 45-64 age group and 0.2 times that in 75+ age group	Equivalent ratios calculated from our estimates: 2.3 and 0.1.

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2. Fleming DM, Cross KW, Pannell RS. Influenza and its relationship to circulatory disorders. Epidemiol Infect. 2005;133(2):255-62.

STATISTICAL METHODS: FURTHER DETAIL

Article title: The impact of targeting all elderly persons in England & Wales for yearly influenza vaccination: excess mortality and time trend study

Journal: BMJ Open

Authors: Andrea G. Mann, Punam Mangtani, Colin A. Russell, John C. Whittaker

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Calculating vaccine coverage

Vaccine coverage estimates for 1989/90 to 2004/05 were adapted from published sources as follows. Published estimates of vaccine coverage were available by age group and separately for persons considered at high or low risk of influenza complications.(1, 2) Vaccine coverage for the 45-64 age group overall (i.e. regardless of risk group) was derived from the published estimates of coverage in those 45-64 at high risk and coverage in those 45-64 at low risk and the number of vaccinees in the two risk categories. The denominator (number of persons 45-64 eligible for vaccination) was calculated as the sum across risk groups of the number vaccinated divided by the percentage vaccinated. The sum of the number of vaccinees in the two risk categories was then divided by the total number eligible for vaccination, giving coverage in the 45-64 age group regardless of risk group. The same procedure was undertaken to derive coverage for the 65-74 and 75+ age groups regardless of risk group, with a necessary modification. In the published estimates from 2000/01 onwards, coverage was not broken down into 65-74 and 75+ years. Coverage for the 75+

age group from 2000/01-2004/05 was therefore derived by calculating the coverage for those 65+ (regardless of risk group), using the method described above for the 45-64 age group, for all years and determining the average ratio of coverage in the 75+ age group to 65+ age group for years when coverage in those 75+ was reported (1989/90-1999/00). Multiplying coverage in the 65+ age group for 2000/01 by this average ratio gave estimated coverage in the 75+ age group for 2000/01 (and so on for 2001/02-2004/05). The same procedure was followed to estimate coverage for the 65-74 age group.

Estimating excess and baseline mortality

There are numerous approaches in the literature to quantifying excess mortality as a measure of influenza severity and no gold standard approach. The different methods produce different estimates of excess mortality when fitted to the same data.(3) We elected to modify the method of Simonsen and colleagues,(4) used in their paper analysing influenza vaccine impact in the US, to examine both excess mortality and the long-term trend in non-excess mortality in relation to changes in vaccine policy and coverage. The Simonsen method is a modification of Serfling's cyclical regression approach,(5) where non-epidemic data are modeled to estimate expected mortality and mortality greater than expected is labelled as excess, but improves on the specificity of Serfling's model in that epidemic periods in the data are informed by a specific measure of influenza. We adapted Simonsen's approach to the specifics of our data in two ways. We fitted log-linear negative binomial, instead of Poisson, models to allow for overdispersion apparent in the P&I data from England & Wales. Also, we used all-age laboratory reports for influenza A to inform epidemic periods in the data instead of laboratory-confirmed influenza deaths because there are too few laboratory-confirmed influenza deaths in England & Wales to allow them to be modelled (a given year may have only 25 laboratory-confirmed influenza deaths

(Emma Gordon, personal communication)). Our modelling approach differed from Simonsen's in two additional ways. Firstly, we controlled for the changing size of the population at risk via the offset term rather than fitting models in fine age bands and calculating age-standardized sums of excess deaths. Second, we directly modelled long-term trend using cubic splines rather than first removing trend from the data with a smoothing spline. This was done so that we could pull out the long-term trend component of the fitted model to plot and visualise in its own right. Our approach to analysis is decribed in full below.

An influenza year was defined as week 26 of one year to week 25 of the next because the timing of influenza circulation during a given winter usually spans two calendar years (i.e. extends from October of one year to March of the next year). Mortality and laboratory data were collapsed into weekly counts for analysis. In order to differentiate excess from baseline mortality we used laboratory data to estimate which were the epidemic weeks in the time series. We then fitted models to the mortality time series to determine both excess and baseline mortality with reference to these epidemic weeks. Specifically, in the first instance we fitted a negative binomial model to all-age weekly counts of laboratory-confirmed influenza A infections excluding counts from the period when influenza is most likely to be circulating in the community (December to April, week numbers 48 of one calendar year to 18 of the next (4)). This negative binomial model included the following terms: as an offset the decennial census population of England & Wales from census years and an inter-census estimate from years between censuses,(6) cubic splines with 6 degrees of freedom to model trend, 1 Fourier term (ie. 1 sine and 1 cosine term) with period 52.2 weeks to model seasonality, and dummy variables to account for minor artefacts. (An initial exploration of options to model trend as linear, quadratic or

with a cubic spline with up to 20 degrees of freedom (df) was undertaken to determine how to fit trend (data not shown)). A time series of counts was predicted from this model when refitted to the full time series of influenza A counts (i.e. not excluding Dec – Apr). The epidemic threshold for each week was defined as the upper 95% confidence bound on the predicted laboratory count for that week. We then fitted the same negative binomial model (except with trend modeled using a cubic spline with 5 df, informed based on our earlier model selection exercise) to the time series of death counts with December to April deleted. We again predicted the time series of counts from this model refitted to the full time series (i.e. without Dec-Apr excluded). Excess mortality was the sum of observed minus predicted deaths in weeks when laboratory data breached their epidemic threshold, by influenza year. Baseline trend in mortality incidence was approximated by fitting the negative binomial model above to the death counts not labelled as excess. This model fit was then deconstructed and just the spline (i.e. trend) component was plotted in order to graphically assess its shape. Estimates of excess mortality and plots of baseline trends were determined separately for the age groups 65-74, 75+ and 45-64 (the latter age group being "unexposed" to a change in vaccine policy or coverage over the period). Any estimates of negative excess mortality were recoded to 0. No model was stratified by sex because an initial exploration of the data suggested similar trends by sex in the study period. A sensitivity analysis was carried out defining epidemic periods based on counts of combined laboratory-confirmed influenza A and influenza B virus infections (as opposed to the main analysis where this was done using counts of influenza A infections only).

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The impact of targeting all elderly persons in England & Wales for yearly influenza vaccination: excess mortality due to pneumonia or influenza and time trend study

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Original Research

The impact of targeting all elderly persons in England & Wales for yearly influenza vaccination: excess mortality due to pneumonia or influenza and time trend study

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Abstract

Objective

To investigate the impact on mortality due to pneumonia or influenza of the change from risk-based to age group-based targeting of the elderly for yearly influenza vaccination in England & Wales.

Design

Excess mortality estimated using time series of deaths registered to pneumonia or influenza, accounting for seasonality, trend and artefacts. Non-excess mortality plotted as proxy for long-term trend in mortality.

Setting

England & Wales

Participants

Persons aged 65-74 and 75+ whose deaths were registered to underlying pneumonia or influenza between 1975/76 and 2004/05

Outcome measures

Multiplicative effect on average excess pneumonia and influenza deaths each winter in the 4-6 winters since age group-based targeting of vaccination was introduced (in persons aged 75+ from 1998/99; in persons aged 65+ from 2000/01) estimated using multivariable regression adjusted for temperature, antigenic drift, and vaccine mismatch, and stratified by dominant circulating influenza subtype. Trend in baseline weekly pneumonia and influenza death rates.

Results

There is a suggestion of lower average excess mortality in the 6 winters after age group-based targeting began compared to before but the confidence interval for the 65-74 age group includes no

difference. Trend in baseline pneumonia and influenza mortality shows an apparent downwards turning point around 2000 for the 65-74 age group and from the mid-1990s in the 75+ age group.

Conclusions

There is weakly supportive evidence that the marked increases in vaccine coverage accompanying the switch from risk-based to age group-based targeting of the elderly for yearly influenza vaccination in England & Wales was associated with lower levels of pneumonia and influenza mortality in older people in the first 6 years after age group-based targeting began. The possible impact of these policy changes is observed both as weak evidence for lower average excess mortality and as a turning point in baseline mortality coincident with the changes.

Introduction

There has been no assessment of the impact on mortality of the switch from risk-based to age group-based targeting of yearly influenza vaccination of the elderly in England & Wales. The policy of targeting people for yearly influenza vaccination based on risk alone, in place until 1998/99, meant that only people with certain medical conditions (chronic heart, respiratory or renal disease, diabetes mellitus or immunosuppression) were offered free yearly influenza vaccination.(1) The age group-based targeting policies adopted in 1998-2000 meant that from then on, all those people aged 75 and over (from 1998) and aged 65 and over (from 2000) would be offered free yearly influenza vaccination. These policy changes were followed by a marked increase in vaccination coverage of those 65 years of age and over, from 46% in the winter of 1999/00 to 66% in 2000/01 (calculated based on reported coverage in high risk and low risk people 65+ in (2)). Vaccine coverage has continued to rise or stay above this level ever since.(2-4) Evidence for lower excess mortality due to pneumonia or influenza in the elderly in the years shortly following the move to age group-based targeting, or for a fall in baseline respiratory mortality in the elderly coincident with these policy changes, would be evidence that these changes have prevented more elderly deaths than the former risk-based approach to vaccine targeting.

Debate surrounds the question of the efficacy and effectiveness of influenza vaccine in the elderly.(5-8) Two systematic reviews concluded that there is insufficient good quality evidence,(9, 10) though one of these reviews did include a randomised controlled trial showing efficacy against influenza disease of 58% (95% CI 26 to 77%) in adults aged 60 and over.(11) Observational studies controlling for positive confounding by healthier people seeking vaccination have also demonstrated effectiveness against mortality.(12, 13) There has been much interest in measuring the mortality impact of influenza vaccination of the elderly in other settings and results have been mixed. In

Holland, all-cause excess mortality during influenza epidemics declined after the introduction of universal yearly vaccination of those aged 65 and over.(14) In contrast, three other studies, in the US, Italy and in Catalonia, did not detect an impact of rising vaccine coverage of the elderly on all-cause excess mortality.(15-17) Previous studies of influenza attributable or excess mortality in the UK have not related this to vaccination.(18-20)

While the level of mortality observed when influenza is circulating in the community (often quantified using excess mortality) varies from winter to winter, baseline respiratory mortality (i.e. excluding excess) has a seasonal pattern which is more or less constant from winter to winter, though it may change over the long-term.(21) Previous studies of the long-term trends in influenza-related mortality in England & Wales have covered earlier, and usually shorter, time periods. One study examined trends in pneumonia or influenza (P&I) mortality in England & Wales from 1994/95 to 2000/01 and showed a plot of rates of P&I mortality in the 65-74 age group in this period which appears to have little secular trend.(18) The shape of the trend in baseline respiratory mortality in England & Wales since 2000/01 is unclear.

This work evaluates a public health initiative, to specifically target all people 65 years of age and older for yearly influenza vaccination regardless of risk group, which has been in place since 2000. Studying patterns in excess mortality and trends in baseline mortality in the years shortly following the introduction of this initiative allows us to provide evidence for the impact of this policy.

Methods

Daily counts of deaths registered to underlying pneumonia or influenza (P&I) in England & Wales between 1975 and 2005, by date of death, sex and age group, were provided by the Office for National Statistics (ONS). Deaths registered to underlying P&I, not just confirmed influenza deaths, were analysed because deaths from influenza are rarely laboratory confirmed and because deaths in

the elderly which occur secondary to influenza often result from pneumonia.(22, 23) P&I mortality rates are a more specific measure of influenza activity than rates of all-cause mortality.(24)

The mortality data were adjusted by multiplying them by conversion factors estimated in a separate analysis to account for the following historical modifications to how the data are coded so that our assessment of trends would not be influenced by these artefactual step changes. The ICD changed from version 8 to 9 in 1979, leading to a small decline in deaths coded to underlying P&I.(25) In 1984, ONS introduced a broader interpretation of rule 3 for coding underlying cause of death, which led to an abrupt fall in deaths registered to underlying pneumonia, and to a rise in deaths registered to underlying cancer and ischemic heart disease.(26) In 1993, ONS adopted an automated system for coding underlying cause of death which narrowed the interpretation of rule 3 and approximately reversed the change adopted in 1984 (i.e. rates of deaths being registered to underlying pneumonia rose back to a level approximately equal to that pre-1984).(27) With the change from ICD 9 to 10 in 2000, deaths coded to underlying respiratory disease fell by approximately 22%, and deaths coded specifically to underlying pneumonia fell by 38%.(28)

The Health Protection Agency Centre for Infections (HPA CfI) provided an extract of all individual reports of laboratory-confirmed influenza A infections between 1975 to 2005 from their LabBase2 database. These reports, based on virus isolation and PCR, were reported voluntarily by National Health Service (NHS) and HPA laboratories in England & Wales. Records included individuals' age, sex and the earliest specimen date.

The statistical methods used are summarized below, with full details provided in the supplementary material. Vaccine coverage estimates for 1989/90 to 2004/05 were adapted from published sources. Published estimates of vaccine coverage were available by age group and separately for persons considered at high or low risk of influenza complications.(2, 3) Separate

estimates by risk group were combined proportionately according to the number of each group vaccinated to give coverage for that age group regardless of risk group.

There are numerous approaches in the literature to quantifying excess mortality as a measure of influenza severity and no gold standard approach. We elected to modify the method of Simonsen and colleagues,(15) used in their paper analysing influenza vaccine impact in the US, to examine both excess mortality and the long-term trend in non-excess mortality in relation to changes in vaccine policy and coverage. The Simonsen method is a modification of Serfling's cyclical regression approach,(21) where non-epidemic data are modeled to estimate expected mortality and mortality greater than expected is labelled as excess, but improves on the specificity of Serfling's model in that epidemic periods in the data are informed by a specific measure of influenza.

An influenza year was defined as week 26 of one year to week 25 of the next because the timing of influenza circulation during a given winter usually spans two calendar years (i.e. extends from October of one year to March of the next year). Mortality and laboratory data were collapsed into weekly counts for analysis. In order to differentiate excess from baseline mortality we used laboratory data to estimate which were the epidemic weeks in the time series. We then fitted models to the mortality time series to determine both excess and baseline mortality with reference to these epidemic weeks. Excess mortality was the sum of observed minus predicted deaths in weeks when laboratory data breached their epidemic threshold, by influenza year. Baseline trend in mortality incidence was approximated by fitting the mortality model to the death counts not labelled as excess. This model fit was then deconstructed and just the spline (i.e. trend) component was plotted in order to graphically assess its shape for changes, or turning points, in the direction of the trend coincident with policy changes. In the same way, estimates of excess mortality were plotted over time to look for evidence of turning points in the trend. Estimates of excess mortality and plots of baseline trends

were determined separately for the age groups 65-74, 75+ and 45-64 (the latter age group being "unexposed" to a change in vaccine policy or coverage over the period). Any estimates of negative excess mortality were recoded to 0. No model was stratified by sex because an initial exploration of the data suggested similar trends by sex in the study period. A sensitivity analysis was carried out defining epidemic periods based on counts of combined laboratory-confirmed influenza A and influenza B virus infections (as opposed to the main analysis where this was done using counts of influenza A infections only).

To quantify vaccine impact on excess mortality, we fitted age group-specific regression models of excess mortality for each influenza year against a) a dummy variable having a value of 0 for 1989/90 to 1999/00 and 1 for 2000/01 to 2004/05 to capture the start of the policy targeting all those 65+ for yearly influenza vaccination (exposure of interest), b) the minimum monthly temperature observed in each influenza year,(29) c) whether the influenza season experienced a large antigenic drift event or not,(30) and d) whether the influenza season was characterised by a mismatch between vaccine and circulating H3N2 viruses or not (references in Table). Excess deaths are right skewed so were transformed using log(excess + 1) to obtain a good approximation to normality. Models were fitted separately for influenza A/H3N2 virus-dominated influenza seasons and for influenza seasons dominated by other influenza virus subtypes. This was done to allow for greater mortality, and thus potentially greater vaccine impact, in influenza seasons dominated by influenza A/H3N2 viruses than those dominated by influenza A/H1N1 or B viruses.(31) Vaccine mismatch was not included in models where the outcome was excess mortality in non-influenza A/H3N2 virus-dominated seasons because both mismatch seasons were seasons when influenza A/H3N2 viruses dominated. Separate sensitivity analyses were carried out a) defining the vaccine coverage dummy variable with reference to 1998/99 rather than 2000/01 (because 1998/99 was the first influenza year of age group-based targeting of

vaccination (to those 75+)) and b) modelling vaccination as a linear term, using derived estimates of coverage by age group in each influenza year, rather than as a dummy variable.

To establish the extent of circulation of influenza in the community over the influenza years studied, weekly rates of consultation for influenza-like illness (ILI), and for infectious and parasitic diseases (which excludes ILI), with sentinel general practices in England & Wales for 0-4 and 5-14 years olds were plotted over time (data provided by the Royal College of General Practitioners weekly returns service). We also plotted weekly, all-age rates of laboratory-reported influenza A and B infections over time.

Models were fitted in R (R version 2.12.1 (2010-12-16), Copyright 2010 The R Foundation for Statistical Computing).

Results

Weekly deaths registered to underlying P&I in those 65 years of age and older in England & Wales in the period from 1975/76 to 2004/05 ranged from 34 deaths per 1,000,000 person weeks (in week 36 of 1984) to 481 deaths per 1,000,000 person weeks (in week 7 of 1976).

Excess mortality

Excess mortality for the 65-74 age group ranged from 0 to just over 2000 deaths per influenza year in the study period (Table). For the 75+ age group, the range was from 0 to over 14,000 deaths per influenza year. Mortality attributable to epidemic influenza was highly variable year to year. For neither age group does there appear to have been a turning point in the trend in excess mortality coinciding with the 2000/01 season, when the policy of targeting all persons aged 65 and over for yearly influenza vaccination was enacted (Figure 1). Similarily, there was no turning point in the trend in excess mortality in the 75+ age group around 1998/99 when this age group became fully targeted for yearly influenza vaccination. The direction of the trend in excess mortality over the whole time

period appears to be downwards or flat. Trend in excess mortality in the 45-64 age group is approximately flat in the same period (Supplementary Figure 1). Mean excess mortality was lower after the policy change for both the 65-74 and 75+ age groups but was also lower after 2000/01 than before among 45-64 year olds (Supplementary table 2).

Vaccine impact from multivariable regression

Point estimates for the multiplicative effect that the policy change had on excess mortality after 2000 compared to before, adjusting for cold weather and antigenic drift in influenza A/H3N2 viruses and stratified by dominant circulating virus subtype, are in the direction of lower excess mortality after 2000 than before for both the 65-74 and 75+ age groups, except for mortality in seasons dominated by influenza A/H1N1 or B viruses for the 75+ age group for which the coefficient suggested higher mortality after the policy change but with a very wide confidence interval (Figure 2). Point estimates indicate a modest impact in influenza A/H3N2 virus-dominated seasons, which is unlikely to be due to chance for the 75+ age group, while in seasons dominated by influenza A/H1N1 or B viruses confidence intervals are wide and include no effect. These findings are robust to modelling the vaccine policy change as occuring in 1998/99 instead of 2000/01 (data not shown). For the 45-64 age group, point estimates suggest lower excess mortality after 2000 than before for seasons dominated by influenza A/H3N2 viruses (Figure 2). For each of the three age groups, modelling the effect of change in vaccine coverage as a linear instead of binary (dummy) variable results in point estimates suggesting lower excess mortality per unit increase in vaccine coverage but with wide confidence intervals including the null (data not shown).

Trends in baseline mortality

Long-term trends in mortality not labelled as excess, analysed as a proxy for baseline P&I mortality, are complex, with three to four periods during which different trends were observed. For

the 65-74 age group, rates in the study period were highest until the late 1970s, declined to approximately 1990, plateaud to 2000 and fell after 2000 (Figure 3). For the 75+ age group, rates increased to the late 1970s, declined to the mid-1980s, plateaud to the mid-1990s and then fell. The 45-64 age group showed a broadly similar baseline trend to that of the 65-74 age group, though the trend was more tortuous due to smaller numbers (Supplementary figure 2). Residuals from fitted models were normally distributed with mean approximately 0 and standard deviation approximately 1 with some residual autocorrelation (data not shown). Findings are robust to defining epidemic periods using laboratory reports of influenza A infections alone or to using both influenza A and B infections for this purpose.

Secular trends in circulation of influenza in the community during the study period

During the period 2000-2005, ILI consultations for 0-4 and 5-14 year olds were lower than historically (supplementary fig 3). However, over the same time period consultations for infectious and parasitic diseases (which excludes ILI) also appeared to decline, especially in the 5-14 year age group (supplementary fig 4). Rates of laboratory reported influenza infections were lower in 2000-2005 than in the decade prior. (supplementary fig 5). Rates in 2000-2005 were similar to those observed around 1980 (figure 3).

Discussion

Statement of principal findings

There is weakly supportive evidence that the switch from risk-based to age group-based targeting of influenza vaccination for older people was associated with lower influenza-related mortality in the 4-6 years following this policy change. Results from our multivariable regression suggest that this policy change had a weak, positive impact on excess mortality in both the 65-74 and 75+ age groups. There is no indication of a downwards turning point in the trend in excess mortality

around 2000/01 (when all those 65+ began to be targeted for vaccination) or 1998/99 (when those 75+ began to be targeted). There were fewer excess deaths, on average, in seasons after the policy change than before (including in the 45-64 age group) which argues against a strong, specific impact of the policy change on excess mortality. Trends in baseline, as opposed to excess, mortality do show a suggestion of a downwards turning point in the mid-1990s for the 75+ age group and around 2000 for the 65-74 age group, coinciding approximately with the timing of the changes to specifically target these age groups for vaccination. Results obtained by fitting the various models to data for the 45-64 age group, in whom vaccine coverage was largely static over the study period, are in a similar direction but are of a smaller magnitude than the apparent impact in the 65-74 and 75+ age groups, suggesting there may have been other factors acting to bring down P&I mortality at the time of the policy changes. Thus our analysis is consistent with a small mortality impact in the 65-74 and 75+ age groups during the six years after policies to wholly target these age groups for yearly influenza vaccination were enacted.

Strengths and weaknesses of the study

There are a number of strengths to the work undertaken, as well as several limitations. The key strengths are that we estimated excess mortality and long-term trend in mortality over a long period (30 years). We carefully controlled for changes to death coding and laboratory practices which occurred over this time period. The analytical approach we used, which is similar to one used by many others,(15, 16) of modelling seasonality and trend using splines in addition to sinuisoidal terms (full details provided in the supplementary material), is a highly flexible method of fitting complex patterns and trends that is especially helpful when modelling a long time series. The outcome we chose to model (deaths from underlying P&I) is the most specific option available which allows sufficient numbers of deaths for analysis. This choice maximised our ability to discern high mortality impact

influenza years from those less so, and thus to detect vaccine impact. Analysing underlying P&I of course means our estimates of excess mortality underestimate the burden of mortality due to all respiratory disease (which includes bronchitis), cardiovascular disease and other causes of death which may be linked to influenza. (19, 20) However, it was not the aim of this work to estimate the total mortality burden due to influenza. Further adding to the specificity of our outcome was our designation of epidemic periods in the mortality data with reference to the time series of laboratory-confirmed influenza A infections. Better still might have been to use influenza A/H3N2 infections, the subtype most often associated with influenza years when there is substantial mortality,(53) but the laboratory data available for this analysis were not broken down by subtype. The limitations of our work include that our estimate of the extent of variability in excess mortality across influenza years is likely to be an underestimate because our model failed to explain all variability in the mortality data (as evidenced by a small amount of autocorrelation in residuals, data not shown). This may be because we did not include temperature or other climatic variables in the models estimating excess mortality. We did adjust for temperature in multivariable regression models of vaccine impact on excess mortality and as such our analysis of vaccine impact should not be confounded by temperature. However, our results regarding long-term trends in non-excess mortality may be confounded by temperature as there is evidence that minimum winter temperatures have increased since the early 1960s.(54) In using laboratory data to inform epidemic periods in the mortality data, we made no allowance for a lag between the increase, or peak, in incidence of laboratory-reported infections and the timing of excess deaths associated with these infections. This is likely to have led us to underestimate excess mortality, assuming the peak in deaths rarely precedes and generally coincides or follows the peak in laboratory reports. However, the rise in influenza activity in the community in terms of GP consultations generally coincides with the rise in numbers of laboratory

reports of influenza infections,(36) and, during influenza years dominated by circulation of influenza A viruses, peak weekly GP consultation rates for influenza-like illness in the 45–64, 65–74 and >=75 years age groups tend to coincide with same-age peaks in respiratory deaths, plus or minus 1 week (e.g. 1995/1996, 1996/1997, 1998/1999 and 1999/2000).(18) Hence the potential bias in our estimates of excess mortality is likely to be minimal because the weeks we might have missed by not allowing for a lag will be close to the start or end of the period of influenza circulation and thus will make up a small proportion of the total influenza attributable P&I deaths in a given winter. Our estimates of long-term trends may be confounded by the trends in co-morbidities linked to smoking or by long-term patterns in other co-morbidities associated with respiratory mortality, which we have not accounted for. While it would have been possible to test for a change in slope of the long-term trend with a piecewise linear approximation, we did not do this because issues of confounding by these types of time-varying covariates, which we are only able to speculate about, would limit the interpretability of any coefficient. Finally, the separate vaccine coverage estimates we present for the 65-74 and 75+ age groups from 2000/01 onwards are sensitive to our assumption of a constant ratio of vaccine coverage in the 65-74 to 75+ age groups from 2000/01 onwards (described in the supplementary file). The assumption of a constant ratio is unlikely to be true and as such we have probably underestimated coverage in the 65-74 age group and overestimated it in the 75+ age group; the increase in coverage in 2000/01 was probably disproportionately accounted for by an increase in coverage in the 65-74 age group, newly targeted as fully “at risk” from the 2000/01 influenza season. Our main findings are unaffected by this because we focus on results from regression models of the effect of change in vaccination policy as a binary variable.

Strengths and weaknesses in relation to other studies, discussing important differences in results

Using as a reference the previous estimates which exist of excess respiratory mortality in

England & Wales, our estimates appear to be a valid reflection of variability between years and between age groups in influenza-attributable mortality. Findings as to vaccine impact from other settings have been mixed, thus our observation of perhaps some limited impact is not inconsistent with reports from other settings which analysed the impact of similar levels of vaccine coverage to that achieved in the UK. Previous estimates of excess, all-age respiratory mortality for the influenza years 1975/76, 1976/77 and 1977/78 are higher than our excess P&I estimates for these years but the relative magnitude of the excess mortality between these years matches our estimates well. (supplementary table 1). The absolute value of the previous estimates is higher than ours because the authors included bronchitis deaths and analysed all-ages combined, not just the elderly. For the influenza years 1994/95 to 1999/2000, published estimates of average influenza-attributable respiratory mortality by age group (45-64, 65-74 and 75+) are higher than our averages for the same age groups over the same period but ratios between different age groups are similar to our estimates. Differences in the magnitude of estimates from the two methods will be because they include bronchitis deaths and but also because the rate difference-type method used by Fleming and colleagues tends to produce higher estimates of excess than the Serfling-type method we used, due to a lower reference mortality and the mortality rate in the "influenza-active periods" being entirely attributed to influenza.(55) There has been much interest in measuring the impact of influenza vaccination campaigns in other settings.(14, 15, 17, 56) Excess all-cause mortality declined in Dutch elderly after the introduction of universal yearly vaccination of those aged 65 and over which saw yearly coverage reach 80%.(14) Excess all-cause mortality and influenza-related hospitalisations and GP visits declined more in Ontario than in other Canadian provinces after the introduction of universal yearly vaccination for all Ontario residents.(56) Analyses of the impact of rising vaccine coverage of the elderly on excess all-cause mortality in the US, Italy and in Catalonia did not detect impact

perhaps because, in the case of the US and Italy, coverage did not reach high enough levels for long enough during the study period, or because, as in Catalonia, there were limited data available, prior to coverage exceeding 60%, to provide a baseline against which to estimate impact.(15-17) Because ratios of our estimates of excess P&I between adjacent seasons, and between age groups, are consistent with previous work using different models, we are confident that our impression of the relative magnitude of P&I mortality between age groups and from one influenza year to the next are a true reflection of patterns in influenza mortality during the study period. Our having observed some evidence for vaccine impact on excess mortality in the 6 years after implementation of age group-based influenza vaccination is consistent with findings from other temperate nothern hemisphere settings which have attained similar levels of vaccine coverage in the elderly, where some studies have demonstrated impact and others have not.

Meaning of the study: possible explanations and implications for clinicians and policymakers

Our analysis suggests high yearly vaccination coverage of the elderly had a small impact on P&I deaths in the 4-6 years following implementation of age group-based targeting of the elderly for influenza vaccination. Alternative explanations are that there was less influenza around during the time of high vaccine coverage, making it look like vaccination produced an impact on mortality when it did not. The fact that we observed smaller magnitude but same direction associations between the timing of policy changes in the elderly and mortality in the 45-64 age group, in whom vaccination policy and coverage were approximately constant over the study period, support this alternative explanation. However, our analysis of to what extent influenza circulated in the community in the study period does not provide clear answers: consultations among children for both ILI and infectious and parasitic diseases (which excludes respiratory disease) were lower in the 2000-2005 period than earlier in the study period. It is difficult to interpret lower ILI rates as strong evidence for less

influenza circulating in 2000-2005 than previously since the decline in rates of infectious and parasitic diseases rates then still needs explaining. It may in part be that there was progressively lower use of GP services in the 2000-2005 period. Rates of laboratory reported influenza infections for all-ages, reported to the HPA CfI, were certainly lower in 2000-2005 than in the decade prior, and were similar to rates observed around 1980 when excess mortality also appeared to be low for several consecutive years. It is difficult to interpret long-term trends in laboratory reports of influenza infections because of changing testing practices and changing volumes of test requisitions over the time period. For example, between 1975 and 1992, the number of laboratory reports of viral infections doubled (57); this is unlikely to reflect a doubling of viral infections over this period. If more tests were requisitioned in 2000-2005 than in the years around 1980 similar rates of positive reports in the two periods would suggest less viral activity in 2000-2005 than around 1980. However, it is hard to see how less influenza in circulation later than earlier in the study period could explain a turning point in baseline mortality in the 65-74 and 75+ age groups approximately coincident with policy changes to specifically target these age groups for vaccination. We think the observation of a turning point in baseline mortality reflects partly a non-specific impact of influenza vaccination on respiratory mortality in the elderly that is not directly attributable to influenza as well as partly a specific impact of influenza vaccination given that analysing excess mortality necessarily means some truly influenza-attributable mortality (i.e. that which does not breach the epidemic threshold) contributes to baseline. A further possible alternative explanation for the apparent, small influenza vaccine impact we have observed is that this is really an impact of pneumococcal vaccination. This is unlikely to be true; to the end of the 2004/05 influenza year, less than 30% of people 65 years of age and over had received the recommended 23-valent pneumococcal polysaccharide vaccine.(58) Pneumococcal conjugate vaccination of infants and children, which might be expected to provide indirect protection to the elderly, has only been

routinely recommended since 2006. It is possible that there is some other factor which also changed over the time period and which explains part of the mortality impact we observed (e.g. trends in co-morbidities linked to smoking).

Unanswered questions and future research

Influenza vaccine impact can be difficult to measure due to its reliance on surveillance data which are generally not collected in a consistent way over time, and because of the variable nature of influenza activity over time. One way of adding to the evidence base is to look at vaccine effectiveness. In order to strenghthen the evidence base for influenza vaccine effectiveness in the elderly, further good quality cohort and case-control studies across multiple influenza seasons with varying degrees of match between vaccine and circulating variants, and adequate control for negative confounding by indication (sicker elderly being preferentially offered vaccination) and positive confounding by healthier older people putting themselves forward for vaccination, are required. It remains unclear to what extent our findings are due to there being less influenza around 2000-2005 than before this time or to confounding by factors such as trends in co-morbidities linked to smoking. Analyses including more recent influenza seasons, which experienced a pandemic (2009/10) and a severe influenza season dominated by H1N1pdm09 virus (2010/11) and which saw vaccine uptake of the elderly further increase, will help to answer these questions and to monitor whether the modest mortality impact we observed in the 6 years after age group-based targeting of vaccination began has been sustained. This analysis will be complicated by the presence of pneumococcal vaccination of infants and the elderly, making teasing apart the effects of how much influenza circulated during the time period, the impact of influenza vaccination and the impact of pneumococcal vaccination a challenge. A way of addressing this would be to calculate attack rates based on serological data now being collected by the HPA CfI.

Article Summary

1) Article focus:

> There has been no assessment of the impact on mortality of the switch from risk-based to age group-based targeting of yearly influenza vaccination of the elderly in England & Wales which was phased in from 1998/99 and which resulted in a marked increase in yearly vaccine coverage.

> Our aim was to investigate the impact on mortality due to pneumonia or influenza of the change from risk-based to age group-based targeting of the elderly for yearly influenza vaccination in England & Wales.

2) Key messages:

> Our study provides weak evidence for lower influenza-related mortality under age group-based targeting compared with risk based targeting of yearly influenza vaccination of the elderly.

3) Strengths and limitations:

> Strengths are that we analysed a long-time series of data, carefully controlling for changes to coding and laboratory practices and using the most specific mortality outcome available

> Limitations include potential underestimation of mortality and residual confounding

Competing interest

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: that funding for the submitted work was provided by the National Institute of Health Research in the UK (fellowship to AGM) and that none was garnered from elsewhere; that JCW is currently employed by, and holds stock options with, GlaxoSmithKline but that the relationship of JCW to GSK had no influence on the work or on the decision to publish it; that there are no other

relationships or activities that could appear to have influenced the submitted work.

Contributors

AGM, PM and JCW conceived of the study, AGM conducted the analysis, led on the interpretation and wrote the paper; JCW, PM and CAR contributed to interpretation and to subsequent drafts of the paper. All authors approved the final version to be published. AGM is the guarantor for the study. P&I data were provided by Cleo Rooney and Emma Gordon from the Office for National Statistics. Laboratory data were provided by Carol Joseph and Joy Field of the Health Protection Agency Centre for Infections. GP consultation data were provided by Douglas Fleming and Alex Elliot of the Royal College of General Practitioners.

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Access

AGM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing

There are no additional data available.

Ethics

This study was approved by the ethics committee of the London School of Hygiene & Tropical Medicine (approval number 5109).

Licence

Table title

Tab: Influenza seasons in England & Wales, 1974/75-2004/05: dominant variant, antigenic drift events in evoluation of influenza A/H3N2 viruses,vaccine mismatch, vaccine coverage and numbers of excess P&I deaths by age group. Bolding means H3N2 dominant and vaccine variants are from different antigenic clusters.

Figure legends

Fig 1: Excess mortality in the a) 65-74 and b) 75+ age groups in each influenza season in England & Wales, stratified by the dominant influenza virus in circulation (black 'x' = A/H3N2 viruses were dominant or co-dominant; grey '+' = A/H1N1 or B viruses were dominant). Vaccine coverage in the respective age group from published data is also shown (dots and asterisks, right axis). Asterisks indicate that vaccine coverage in these years was inferred from observed vaccine coverage in the 65+ age group and the average ratio of coverage in the 65+ to 65-74 (or 75+) age group.

Fig 2: Summary of estimated vaccine impact from log(excess + 1) regression models of the binary effect of the switch to age group-based targeting of yearly influenza vaccination to all those 65 years of age and older (from 2000/01 onwards) compared to before 2000/01. Coefficients are shown on the original scale and are therefore multiplicative. Squares are the 65-74 age group, circles the 75+ age group and triangles the 45-64 age group. Filled symbols represent seasons dominated by influenza A/H3N2 viruses, open symbols seasons dominated by influenza A/H1N1 or B viruses**.**

Fig 3: Model fit: The observed time series of weekly P&I deaths in the a) 65-74 sand b) 75+ age group in England & Wales between 1975 and 2005 (light dotted line on each plot). The fitted curve from the log-linear Simonsen-like model fitted excluding December to April and accounting for seasonality, long-term trend and artefacts is overlayed (dark line). Vaccine coverage (in the 65-74 and 75+ age groups) adapted from published data is shown on the right axis of each plot (dots and asterisks). Asterisks indicate that vaccine coverage in these years was inferred from observed vaccine coverage in the 65+ age group and the average ratio of coverage in the 65-74 (or 75+) to 65+ age group. The fitted curve can be deconstructed into its constituent parts. Thus c) and d) show just the long-term trend (i.e. cubic spline) component of the fitted curve (dark lines), with its 95% confidence interval (light lines), for the 65-74 and 75+ age groups, respectively. Doing this allows a better visualisation of the shape of the long-term trend.

Table

Influenza season	Dominant influenza variant(s)	Antigenic drift events(30)	Vaccine cluster*	Minimum monthly temperature (°C)	Vaccine coverage, 65-74 yrs	Excess deaths (n), 65-74 yrs	Vaccine coverage, 75+ yrs	Excess deaths (n), 75+ yrs	Vaccine coverage, 45-64 yrs	Excess 45-64
1975/76	H3N2/B(32)	EN72-VI75		4.5	0%	1910	0%	9389	0%	863
1976/77	H3N2(33)			2	0%	456	0%	2986	0%	203
1977/78	H3N2/H1N1(32)	VI75-TX77		2.8	0%	419	0%	2563	0%	158
1978/79	B(32)			-0.4	0%	14	0%	25	0%	0
1979/80	H3N2(32)	TX77-BA79		2.3	0%	0	0%	95	0%	0
1980/81	H1N1/H3N2(32)			3	0%	89	0%	605	0%	73
1981/82	B/H3N2(34)			0.3	0%	174	0%	501	0%	4
1982/83	H3N2(34)			1.7	0%	264	0%	1947	0%	48
1983/84	H1N1/B(34)			3.3	0%	88	0%	742	0%	38
1984/85	H3N2/B(34)			0.8	0%	74	0%	395	0%	5
1985/86	B(35)			-1.1	0%	0	0%	0	0%	14
1986/87	H1N1(35)			0.8	0%	0	0%	0	0%	0
1987/88	H3N2/H1N1(36)	BA79-SI87		4.9	0%	0	0%	5	0%	4
1988/89	H1N1/H3N2(36)			5.2	0%	374	0%	2023	0%	119
1989/90	H3N2(36)	SI87-BE89	SI87(37)	4.9	22%	2007	27%	14115	9%	638
1990/91	B(36)		BE89(38)	1.5	24%	0	31%	178	9%	0
1991/92	H3N2(36)		BE89(39)	3.7	27%	413	33%	3302	10%	111
1992/93	B/H1N1(36)	BE89-BE92	BE89(40)	3.6	26%	0	33%	0	10%	0
1993/94	H3N2(36)		BE92(41)	3.2	32%	557	39%	4238	12%	137
1994/95	B(36)		BE92(42)	4.8	33%	0	40%	0	12%	0
1995/96	H3N2(36)	BE92-WU95	BE92(43)	2.3	33%	651	42%	5365	12%	226
1996/97	H3N2(36)		WU95(44)	2.5	33%	0	41%	15	12%	9
1997/98	H3N2/H1N1(45)	WU95-SY97	**WU95(45)**	5.2	38%	0	46%	9	14%	10
1998/99	H3N2/B(46)		SY97(46)	5.3	37%	628	49%	6802	13%	233
1999/00	H3N2(47)		SY97(47)	4.9	40%	1083	53%	10554	14%	560
2000/01	B/H1N1(48)		SY97(48)	3.2	59%**	0	74%**	109	16%	0
2001/02	H3N2/H1N2(49)		SY97(49)	3.6	61%**	21	76%**	0	17%	0
2002/03	B/H3N2(50)	SY97-FU02	SY97(50)	3.9	63%**	0	78%**	0	17%	10
2003/04	H3N2(51)		**SY97(51)**	4.8	65%**	338	82%**	2704	18%	152
2004/05	H3N2(52)		FU02(52)	4.3	64%**	1	81%**	27	NA	9

* Bolding indicates a mismatch between vaccine and dominant circulating A/H3N2-virus cluster

** Estimated from coverage 65+ and mean ratio of coverage in the 65-74 to 65+ age group and 75+ to 65+ age group for 1989/90-1999/00

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Original Research

The impact of targeting all elderly persons in England & Wales for yearly influenza vaccination: excess mortality due to pneumonia or influenza and time trend study

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Running title (40 ch): England & Wales elderly flu vaccine impact
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Abstract

Objective

To investigate the impact on mortality due to pneumonia or influenza of the change from risk-based to age group-based targeting of the elderly for yearly influenza vaccination in England & Wales.

Design

Excess mortality estimated using time series of deaths registered to pneumonia or influenza, accounting for seasonality, trend and artefacts. Non-excess mortality plotted as proxy for long-term trend in mortality.

Setting

England & Wales

Participants

Persons aged 65-74 and 75+ whose deaths were registered to underlying pneumonia or influenza between 1975/76 and 2004/05

Outcome measures

Multiplicative effect on a~~A~~verage ~~difference in~~ excess pneumonia and influenza deaths each winter in the 4-6 winters since age group-based targeting of vaccination was introduced (in persons aged 75+ from 1998/99; in persons aged 65+ from 2000/01)~~, compared to before,~~ estimated using ~~linear~~ multivariable regression adjusted for temperature, antigenic drift, and vaccine mismatch, and stratified by dominant circulating influenza subtype. Trend in baseline weekly pneumonia and influenza death rates.

Results

There is a suggestion of lower average excess mortality in the 6 winters after age group-based

targeting began compared to before but the confidence interval for the 65-74 age groups includes no difference. Trend in baseline pneumonia and influenza mortality shows an apparent downwards turning point around 2000 for the 65-74 age group and from the mid-1990s in the 75+ age group.

Conclusions

There is weakly supportive evidence that the marked increases in vaccine coverage accompanying the switch from risk-based to age group-based targeting of the elderly for yearly influenza vaccination in England & Wales was associated with lower levels of pneumonia and influenza mortality in older people in the first 6 years after age group-based targeting began. The possible impact of these policy changes is observed both as weak evidence for lower average excess mortality and as a turning point in baseline mortality coincident with the changes. Further work is required to exclude residual confounding.

Introduction

There has been no assessment of the impact on mortality of the switch from risk-based to age group-based targeting of yearly influenza vaccination of the elderly in England & Wales. The policy of targeting people for yearly influenza vaccination based on risk alone, in place until 1998/99, meant that only people with certain medical conditions (chronic heart, respiratory or renal disease, diabetes mellitus or immunosuppression) were offered free yearly influenza vaccination.(1) The age group-based targeting policies adopted in 1998-2000 meant that from then on, all those people aged 75 and over (from 1998) and aged 65 and over (from 2000) would be offered free yearly influenza vaccination. These policy changes were followed by a marked increase in vaccination coverage of those 65 years of age and over, from 46% in the winter of 1999/00 to 66% in 2000/01 (calculated based on reported coverage in high risk and low risk people 65+ in (2)). Vaccine coverage has continued to rise or stay above this level ever since.(2-4) Evidence for lower excess mortality due to pneumonia or influenza in the elderly in the years shortly following the move to age group-based targeting, or for a fall in baseline respiratory mortality in the elderly coincident with these policy changes, would be evidence that these changes have prevented more elderly deaths than the former risk-based approach to vaccine targeting.

Debate surrounds the question of the efficacy and effectiveness of influenza vaccine in the elderly.(5-8) Two systematic reviews concluded that there is insufficient good quality evidence,(9, 10) though one of these reviews did include a randomised controlled trial showing efficacy against influenza disease of 58% (95% CI 26 to 77%) in adults aged 60 and over.(11) Observational studies controlling for positive confounding by healthier people seeking vaccination have also demonstrated effectiveness against mortality.(12, 13) There has been much interest in measuring the mortality impact of influenza vaccination of the elderly in other settings and results have been mixed. In

Holland, all-cause excess mortality during influenza epidemics declined after the introduction of universal yearly vaccination of those aged 65 and over.(14) In contrast, three other studies, in the US, Italy and in Catalonia, did not detect an impact of rising vaccine coverage of the elderly on all-cause excess mortality.(15-17) Previous studies of influenza attributable or excess mortality in the UK have not related this to vaccination.(18-20)

While the level of mortality observed when influenza is circulating in the community (often quantified using excess mortality) varies from winter to winter, baseline respiratory mortality (i.e. excluding excess) has a seasonal pattern which is more or less constant from winter to winter, though it may change over the long-term.(21) Previous studies of the long-term trends in influenza-related mortality in England & Wales have covered earlier, and usually shorter, time periods. One study examined trends in pneumonia or influenza (P&I) mortality in England & Wales from 1994/95 to 2000/01 and showed a plot of rates of P&I mortality in the 65-74 age group in this period which appears to have little secular trend.(18) The shape of the trend in baseline respiratory mortality in England & Wales since 2000/01 is unclear.

This work evaluates a public health initiative, to specifically target all people 65 years of age and older for yearly influenza vaccination regardless of risk group, which has been in place since 2000. Studying patterns in excess mortality and trends in baseline mortality in the years shortly following the introduction of this initiative allows us to provide evidence for the impact of this policy.

Methods

Daily counts of deaths registered to underlying pneumonia or influenza (P&I) in England & Wales between 1975 and 2005, by date of death, sex and age group, were provided by the Office for National Statistics (ONS). Deaths registered to underlying P&I, not just confirmed influenza deaths, were analysed because deaths from influenza are rarely laboratory confirmed and because deaths in

the elderly which occur secondary to influenza often result from pneumonia.(22, 23) P&I mortality rates are a more specific measure of influenza activity than rates of all-cause mortality.(24)

The mortality data were adjusted by multiplying them by conversion factors estimated in a separate analysis to account for the following historical modifications to how the data are coded so that our assessment of trends would not be influenced by these artefactual step changes. The ICD changed from version 8 to 9 in 1979, leading to a small decline in deaths coded to underlying P&I.(25) In 1984, ONS introduced a broader interpretation of rule 3 for coding underlying cause of death, which led to an abrupt fall in deaths registered to underlying pneumonia, and to a rise in deaths registered to underlying cancer and ischemic heart disease.(26) In 1993, ONS adopted an automated system for coding underlying cause of death which narrowed the interpretation of rule 3 and approximately reversed the change adopted in 1984 (i.e. rates of deaths being registered to underlying pneumonia rose back to a level approximately equal to that pre-1984).(27) With the change from ICD 9 to 10 in 2000, deaths coded to underlying respiratory disease fell by approximately 22%, and deaths coded specifically to underlying pneumonia fell by 38%.(28)

The Health Protection Agency Centre for Infections (HPA CfI) provided an extract of all individual reports of laboratory-confirmed influenza A infections between 1975 to 2005 from their LabBase2 database. These reports, based on virus isolation and PCR, were reported voluntarily by National Health Service (NHS) and HPA laboratories in England & Wales. Records included individuals' age, sex and the earliest specimen date.

The statistical methods used are summarized below, with full details provided in the supplementary material. Vaccine coverage estimates for 1989/90 to 2004/05 were adapted from published sources. Published estimates of vaccine coverage were available by age group and separately for persons considered at high or low risk of influenza complications.(2, 3) Separate

estimates by risk group were combined proportionately according to the number of each group vaccinated to give coverage for that age group regardless of risk group.

There are numerous approaches in the literature to quantifying excess mortality as a measure of influenza severity and no gold standard approach. We elected to modify the method of Simonsen and colleagues,(15) used in their paper analysing influenza vaccine impact in the US, to examine both excess mortality and the long-term trend in non-excess mortality in relation to changes in vaccine policy and coverage. The Simonsen method is a modification of Serfling's cyclical regression approach,(21) where non-epidemic data are modeled to estimate expected mortality and mortality greater than expected is labelled as excess, but improves on the specificity of Serfling's model in that epidemic periods in the data are informed by a specific measure of influenza.

An influenza year was defined as week 26 of one year to week 25 of the next because the timing of influenza circulation during a given winter usually spans two calendar years (i.e. extends from October of one year to March of the next year). Mortality and laboratory data were collapsed into weekly counts for analysis. In order to differentiate excess from baseline mortality we used laboratory data to estimate which were the epidemic weeks in the time series. We then fitted models to the mortality time series to determine both excess and baseline mortality with reference to these epidemic weeks. Excess mortality was the sum of observed minus predicted deaths in weeks when laboratory data breached their epidemic threshold, by influenza year. Baseline trend in mortality incidence was approximated by fitting the mortality model to the death counts not labelled as excess. This model fit was then deconstructed and just the spline (i.e. trend) component was plotted in order to graphically assess its shape for changes, or turning points, in the direction of the trend coincident with policy changes. In the same way, estimates of excess mortality were plotted over time to look for evidence of turning points in the trend. Estimates of excess mortality and plots of baseline trends

were determined separately for the age groups 65-74, 75+ and 45-64 (the latter age group being "unexposed" to a change in vaccine policy or coverage over the period). Any estimates of negative excess mortality were recoded to 0. No model was stratified by sex because an initial exploration of the data suggested similar trends by sex in the study period. A sensitivity analysis was carried out defining epidemic periods based on counts of combined laboratory-confirmed influenza A and influenza B virus infections (as opposed to the main analysis where this was done using counts of influenza A infections only).

To quantify vaccine impact on excess mortality, we fitted age group-specific ~~linear~~ regression models of excess mortality for each influenza year against a) a dummy variable having a value of 0 for 1989/90 to 1999/00 and 1 for 2000/01 to 2004/05 to capture the start of the policy targeting all those 65+ for yearly influenza vaccination (exposure of interest), b) the minimum monthly temperature observed in each influenza year,(29) c) whether the influenza season experienced a large antigenic drift event or not,(30) and d) whether the influenza season was characterised by a mismatch between vaccine and circulating H3N2 viruses or not (references in Table). Excess deaths are right skewed so were transformed using log(excess + 1) to obtain a good approximation to normality. Models were fitted separately for influenza A/H3N2 virus-dominated influenza seasons and for influenza seasons dominated by other influenza virus subtypes. This was done to allow for greater mortality, and thus potentially greater vaccine impact, in influenza seasons dominated by influenza A/H3N2 viruses than those dominated by influenza A/H1N1 or B viruses.(31) Vaccine mismatch was not included in models where the outcome was excess mortality in non-influenza A/H3N2 virus-dominated seasons because both mismatch seasons were seasons when influenza A/H3N2 viruses dominated. Separate sensitivity analyses were carried out a) defining the vaccine coverage dummy variable with reference to 1998/99 rather than 2000/01 (because 1998/99 was the first influenza year of age group-based targeting of

vaccination (to those 75+)) and b) modelling vaccination as a linear term, using derived estimates of coverage by age group in each influenza year, rather than as a dummy variable.

To establish the extent of circulation of influenza in the community over the influenza years studied, weekly rates of consultation for influenza-like illness (ILI), and for infectious and parasitic diseases (which excludes ILI), with sentinel general practices in England & Wales for 0-4 and 5-14 years olds were plotted over time (data provided by the Royal College of General Practitioners weekly returns service). We also plotted weekly, all-age rates of laboratory-reported influenza A and B infections over time.

Models were fitted in R (R version 2.12.1 (2010-12-16), Copyright 2010 The R Foundation for Statistical Computing).

Results

Weekly deaths registered to underlying P&I in those 65 years of age and older in England & Wales in the period from 1975/76 to 2004/05 ranged from 34 deaths per 1,000,000 person weeks (in week 36 of 1984) to 481 deaths per 1,000,000 person weeks (in week 7 of 1976).

Excess mortality

Excess mortality for the 65-74 age group ranged from 0 to just over 2000 deaths per influenza year in the study period (Table). For the 75+ age group, the range was from 0 to over 14,000 deaths per influenza year. Mortality attributable to epidemic influenza was highly variable year to year. For neither age group does there appear to have been a turning point in the trend in excess mortality coinciding with the 2000/01 season, when the policy of targeting all persons aged 65 and over for yearly influenza vaccination was enacted (Figure 1). Similarly, there was no turning point in the trend in excess mortality in the 75+ age group around 1998/99 when this age group became fully targeted for yearly influenza vaccination. The direction of the trend in excess mortality over the whole time

period appears to be downwards or flat. Trend in excess mortality in the 45-64 age group is approximately flat in the same period (Supplementary Figure 1). Mean excess mortality was lower after the policy change for both the 65-74 and 75+ age groups but was also lower after 2000/01 than before among 45-64 year olds (Supplementary table 2).

Vaccine impact from ~~linear~~ multivariable regression

Point estimates for the ~~average~~ multiplicative effect that the policy change had on~~difference between~~ excess mortality after 2000 compared to before, adjusting for cold weather and antigenic drift in influenza A/H3N2 viruses and stratified by dominant circulating virus subtype, are in the direction of lower excess mortality after 2000 than before for both the 65-74 and 75+ age groups, except for mortality in seasons dominated by influenza A/H1N1 or B viruses for the ~~65-74~~75+ age group for which the coefficient suggested higher mortality after the policy change but with a very wide confidence interval~~which was similar after 2000 to before~~ (Figure 2). ~~However, confidence intervals include no difference.~~ Point estimates indicate a modest~~greater~~ impact in influenza A/H3N2 virus-dominated seasons, which is unlikely to be due to chance for the 75+ age group, while in seasons dominated by~~than in~~ influenza A/H1N1 or B viruses confidence intervals are wide and include no effect~~rus-dominated seasons~~. These findings are robust to modelling the vaccine policy change as occuring in 1998/99 instead of 2000/01 (data not shown). For the 45-64 age group, point estimates suggest lower excess mortality after 2000 than before for seasons dominated by influenza A/H3N2 viruses~~, but the confidence interval again includes the null~~ (Figure 2). For each of the three age groups, modelling the effect of change in vaccine coverage as a linear instead of binary (dummy) variable results in point estimates suggesting lower excess mortality per unit increase in vaccine coverage but with wide confidence intervals including the null (data not shown).

Trends in baseline mortality

Long-term trends in mortality not labelled as excess, analysed as a proxy for baseline P&I mortality, are complex, with three to four periods during which different trends were observed. For the 65-74 age group, rates in the study period were highest until the late 1970s, declined to approximately 1990, plateaud to 2000 and fell after 2000 (Figure 3). For the 75+ age group, rates increased to the late 1970s, declined to the mid-1980s, plateaud to the mid-1990s and then fell. The 45-64 age group showed a broadly similar baseline trend to that of the 65-74 age group, though the trend was more tortuous due to smaller numbers (Supplementary figure 2). Residuals from fitted models were normally distributed with mean approximately 0 and standard deviation approximately 1 with some residual autocorrelation (data not shown). Findings are robust to defining epidemic periods using laboratory reports of influenza A infections alone or to using both influenza A and B infections for this purpose.

Secular trends in circulation of influenza in the community during the study period

During the period 2000-2005, ILI consultations for 0-4 and 5-14 year olds were lower than historically (supplementary fig 3). However, over the same time period consultations for infectious and parasitic diseases (which excludes ILI) also appeared to decline, especially in the 5-14 year age group (supplementary fig 4). Rates of laboratory reported influenza infections were lower in 2000-2005 than in the decade prior. (supplementary fig 5). Rates in 2000-2005 were similar to those observed around 1980 (figure 3).

Discussion

Statement of principal findings

There is weakly supportive evidence that the switch from risk-based to age group-based targeting of influenza vaccination for older people was associated with lower influenza-related mortality in the 4-6 years following this policy change. Results from our multivariable ~~linear~~ regression

suggest that this policy change had a weak, positive impact on excess mortality in both the 65-74 and 75+ age groups. There is no indication of a downwards turning point in the trend in excess mortality around 2000/01 (when all those 65+ began to be targeted for vaccination) or 1998/99 (when those 75+ began to be targeted). There were fewer excess deaths, on average, in seasons after the policy change than before (including in the 45-64 age group) which argues against a strong, specific impact of ~~this~~ the policy change on excess mortality ~~in either age group~~. Trends in baseline, as opposed to excess, mortality do show a suggestion of a downwards turning point in the mid-1990s for the 75+ age group and around 2000 for the 65-74 age group, coinciding approximately with the timing of the changes to specifically target these age groups for vaccination. Results obtained by fitting the various models to data for the 45-64 age group, in whom vaccine coverage was largely static over the study period, are in a similar direction but are of a smaller magnitude than the apparent impact in the 65-74 and 75+ age groups, suggesting there may have been other factors acting to bring down P&I mortality at the time of the policy changes. Thus our analysis is consistent with a small mortality impact in the 65-74 and 75+ age groups during the six years after policies to wholly target these age groups for yearly influenza vaccination were enacted.

Strengths and weaknesses of the study

There are a number of strengths to the work undertaken, as well as several limitations. The key strengths are that we estimated excess mortality and long-term trend in mortality over a long period (30 years). We carefully controlled for changes to death coding and laboratory practices which occurred over this time period. The analytical approach we used, which is similar to one used by many others,(15, 16) of modelling seasonality and trend using splines in addition to sinuisoidal terms (full details provided in the supplementary material), is a highly flexible method of fitting complex patterns and trends that is especially helpful when modelling a long time series. The outcome we chose to

model (deaths from underlying P&I) is the most specific option available which allows sufficient numbers of deaths for analysis. This choice maximised our ability to discern high mortality impact influenza years from those less so, and thus to detect vaccine impact. Analysing underlying P&I of course means our estimates of excess mortality underestimate the burden of mortality due to all respiratory disease (which includes bronchitis), cardiovascular disease and other causes of death which may be linked to influenza. (19, 20) However, it was not the aim of this work to estimate the total mortality burden due to influenza. Further adding to the specificity of our outcome was our designation of epidemic periods in the mortality data with reference to the time series of laboratory-confirmed influenza A infections. Better still might have been to use influenza A/H3N2 infections, the subtype most often associated with influenza years when there is substantial mortality,(53) but the laboratory data available for this analysis were not broken down by subtype. The limitations of our work include that our estimate of the extent of variability in excess mortality across influenza years is likely to be an underestimate because our model failed to explain all variability in the mortality data (as evidenced by a small amount of autocorrelation in residuals, data not shown). This may be because we did not include temperature or other climatic variables in the models estimating excess mortality. We did adjust for temperature in ~~linear~~ multivariable regression models of vaccine impact on excess mortality and as such our analysis of vaccine impact should not be confounded by temperature. However, our results regarding long-term trends in non-excess mortality may be confounded by temperature as there is evidence that minimum winter temperatures have increased since the early 1960s.(54) In using laboratory data to inform epidemic periods in the mortality data, we made no allowance for a lag between the increase, or peak, in incidence of laboratory-reported infections and the timing of excess deaths associated with these infections. This is likely to have led us to underestimate excess mortality, assuming the peak in deaths rarely precedes and generally

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coincides or follows the peak in laboratory reports. However, the rise in influenza activity in the community in terms of GP consultations generally coincides with the rise in numbers of laboratory reports of influenza infections,(36) and, during influenza years dominated by circulation of influenza A viruses, peak weekly GP consultation rates for influenza-like illness in the 45–64, 65–74 and >=75 years age groups tend to coincide with same-age peaks in respiratory deaths, plus or minus 1 week (e.g. 1995/1996, 1996/1997, 1998/1999 and 1999/2000).(18) Hence the potential bias in our estimates of excess mortality is likely to be minimal because the weeks we might have missed by not allowing for a lag will be close to the start or end of the period of influenza circulation and thus will make up a small proportion of the total influenza attributable P&I deaths in a given winter. Our estimates of long-term trends may be confounded by the trends in co-morbidities linked to smoking or by long-term patterns in other co-morbidities associated with respiratory mortality, which we have not accounted for. While it would have been possible to test for a change in slope of the long-term trend with a piecewise linear approximation, we did not do this because issues of confounding by these types of time-varying covariates, which we are only able to speculate about, would limit the interpretability of any coefficient. Finally, the separate vaccine coverage estimates we present for the 65-74 and 75+ age groups from 2000/01 onwards are sensitive to our assumption of a constant ratio of vaccine coverage in the 65-74 to 75+ age groups from 2000/01 onwards (described in the supplementary file). The assumption of a constant ratio is unlikely to be true and as such we have probably underestimated coverage in the 65-74 age group and overestimated it in the 75+ age group; the increase in coverage in 2000/01 was probably disproportionately accounted for by an increase in coverage in the 65-74 age group, newly targeted as fully “at risk” from the 2000/01 influenza season. Our main findings are unaffected by this because we focus on results from ~~linear~~ regression models of the effect of change in vaccination policy as a binary variable.

Strengths and weaknesses in relation to other studies, discussing important differences in results

Using as a reference the previous estimates which exist of excess respiratory mortality in England & Wales, our estimates appear to be a valid reflection of variability between years and between age groups in influenza-attributable mortality. Findings as to vaccine impact from other settings have been mixed, thus our observation of perhaps some limited impact is not inconsistent with reports from other settings which analysed the impact of similar levels of vaccine coverage to that achieved in the UK. Previous estimates of excess, all-age respiratory mortality for the influenza years 1975/76, 1976/77 and 1977/78 are higher than our excess P&I estimates for these years but the relative magnitude of the excess mortality between these years matches our estimates well. (supplementary table 1). The absolute value of the previous estimates is higher than ours because the authors included bronchitis deaths and analysed all-ages combined, not just the elderly. For the influenza years 1994/95 to 1999/2000, published estimates of average influenza-attributable respiratory mortality by age group (45-64, 65-74 and 75+) are higher than our averages for the same age groups over the same period but ratios between different age groups are similar to our estimates. Differences in the magnitude of estimates from the two methods will be because they include bronchitis deaths and but also because the rate difference-type method used by Fleming and colleagues tends to produce higher estimates of excess than the Serfling-type method we used, due to a lower reference mortality and the mortality rate in the "influenza-active periods" being entirely attributed to influenza.(55) There has been much interest in measuring the impact of influenza vaccination campaigns in other settings.(14, 15, 17, 56) Excess all-cause mortality declined in Dutch elderly after the introduction of universal yearly vaccination of those aged 65 and over which saw yearly coverage reach 80%.(14) Excess all-cause mortality and influenza-related hospitalisations and GP visits declined more in Ontario than in other Canadian provinces after the introduction of universal

yearly vaccination for all Ontario residents.(56) Analyses of the impact of rising vaccine coverage of the elderly on excess all-cause mortality in the US, Italy and in Catalonia did not detect impact perhaps because, in the case of the US and Italy, coverage did not reach high enough levels for long enough during the study period, or because, as in Catalonia, there were limited data available, prior to coverage exceeding 60%, to provide a baseline against which to estimate impact.(15-17) Because ratios of our estimates of excess P&I between adjacent seasons, and between age groups, are consistent with previous work using different models, we are confident that our impression of the relative magnitude of P&I mortality between age groups and from one influenza year to the next are a true reflection of patterns in influenza mortality during the study period. Our having observed some evidence for vaccine impact on excess mortality in the 6 years after implementation of age group-based influenza vaccination is consistent with findings from other temperate nothern hemisphere settings which have attained similar levels of vaccine coverage in the elderly, where some studies have demonstrated impact and others have not.

Meaning of the study: possible explanations and implications for clinicians and policymakers

Our analysis suggests high yearly vaccination coverage of the elderly had a small impact on P&I deaths in the 4-6 years following implementation of age group-based targeting of the elderly for influenza vaccination. Alternative explanations are that there was less influenza around during the time of high vaccine coverage, making it look like vaccination produced an impact on mortality when it did not. The fact that we observed smaller magnitude but same direction associations between the timing of policy changes in the elderly and mortality in the 45-64 age group, in whom vaccination policy and coverage were approximately constant over the study period, support this alternative explanation. However, our analysis of to what extent influenza circulated in the community in the study period does not provide clear answers: consultations among children for both ILI and infectious

and parasitic diseases (which excludes respiratory disease) were lower in the 2000-2005 period than earlier in the study period. It is difficult to interpret lower ILI rates as strong evidence for less influenza circulating in 2000-2005 than previously since the decline in rates of infectious and parasitic diseases rates then still needs explaining. It may in part be that there was progressively lower use of GP services in the 2000-2005 period. Rates of laboratory reported influenza infections for all-ages, reported to the HPA CfI, were certainly lower in 2000-2005 than in the decade prior, and were similar to rates observed around 1980 when excess mortality also appeared to be low for several consecutive years. It is difficult to interpret long-term trends in laboratory reports of influenza infections because of changing testing practices and changing volumes of test requisitions over the time period. For example, between 1975 and 1992, the number of laboratory reports of viral infections doubled (57); this is unlikely to reflect a doubling of viral infections over this period. If more tests were requisitioned in 2000-2005 than in the years around 1980 similar rates of positive reports in the two periods would suggest less viral activity in 2000-2005 than around 1980. However, it is hard to see how less influenza in circulation later than earlier in the study period could explain a turning point in baseline mortality in the 65-74 and 75+ age groups approximately coincident with policy changes to specifically target these age groups for vaccination. We think the observation of a turning point in baseline mortality reflects partly a non-specific impact of influenza vaccination on respiratory mortality in the elderly that is not directly attributable to influenza as well as partly a specific impact of influenza vaccination given that analysing excess mortality necessarily means some truly influenza-attributable mortality (i.e. that which does not breach the epidemic threshold) contributes to baseline. A further possible alternative explanation for the apparent, small influenza vaccine impact we have observed is that this is really an impact of pneumococcal vaccination. This is unlikely to be true; to the end of the 2004/05 influenza year, less than 30% of people 65 years of age and over had received the recommended 23-

valent pneumococcal polysaccharide vaccine.(58) Pneumococcal conjugate vaccination of infants and children, which might be expected to provide indirect protection to the elderly, has only been routinely recommended since 2006. It is possible that there is some other factor which also changed over the time period and which explains part of the mortality impact we observed (e.g. trends in co-morbidities linked to smoking).

Unanswered questions and future research

Influenza vaccine impact can be difficult to measure due to its reliance on surveillance data which are generally not collected in a consistent way over time, and because of the variable nature of influenza activity over time. One way of adding to the evidence base is to look at vaccine effectiveness. In order to strenghthen the evidence base for influenza vaccine effectiveness in the elderly, further good quality cohort and case-control studies across multiple influenza seasons with varying degrees of match between vaccine and circulating variants, and adequate control for negative confounding by indication (sicker elderly being preferentially offered vaccination) and positive confounding by healthier older people putting themselves forward for vaccination, are required. It remains unclear to what extent our findings are due to there being less influenza around 2000-2005 than before this time or to confounding by factors such as trends in co-morbidities linked to smoking. Analyses including more recent influenza seasons, which experienced a pandemic (2009/10) and a severe influenza season dominated by H1N1pdm09 virus (2010/11) and which saw vaccine uptake of the elderly further increase, will help to answer these questions and to monitor whether the modest mortality impact we observed in the 6 years after age group-based targeting of vaccination began has been sustained. This analysis will be complicated by the presence of pneumococcal vaccination of infants and the elderly, making teasing apart the effects of how much influenza circulated during the time period, the impact of influenza vaccination and the impact of pneumococcal vaccination a

challenge. A way of addressing this would be to calculate attack rates based on serological data now being collected by the HPA CfI.

Article Summary

1) Article focus:

> There has been no assessment of the impact on mortality of the switch from risk-based to age group-based targeting of yearly influenza vaccination of the elderly in England & Wales which was phased in from 1998/99 and which resulted in a marked increase in yearly vaccine coverage.

> Our aim was to investigate the impact on mortality due to pneumonia or influenza of the change from risk-based to age group-based targeting of the elderly for yearly influenza vaccination in England & Wales.

2) Key messages:

> Our study provides weak evidence for lower influenza-related mortality under age group-based targeting compared with risk based targeting of yearly influenza vaccination of the elderly.

3) Strengths and limitations:

> Strengths are that we analysed a long-time series of data, carefully controlling for changes to coding and laboratory practices and using the most specific mortality outcome available

> Limitations include potential underestimation of mortality and residual confounding

Competing interest

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: that funding for the submitted work was provided by the National Institute of Health Research in the UK (fellowship to AGM) and that none was garnered from elsewhere; that JCW is

currently employed by, and holds stock options with, GlaxoSmithKline but that the relationship of JCW to GSK had no influence on the work or on the decision to publish it; that there are no other relationships or activities that could appear to have influenced the submitted work.

Contributors

AGM, PM and JCW conceived of the study, AGM conducted the analysis, led on the interpretation and wrote the paper; JCW, PM and CAR contributed to interpretation and to subsequent drafts of the paper. All authors approved the final version to be published. AGM is the guarantor for the study. P&I data were provided by Cleo Rooney and Emma Gordon from the Office for National Statistics. Laboratory data were provided by Carol Joseph and Joy Field of the Health Protection Agency Centre for Infections. GP consultation data were provided by Douglas Fleming and Alex Elliot of the Royal College of General Practitioners.

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Access

AGM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing

There are no additional data available.

Ethics

This study was approved by the ethics committee of the London School of Hygiene & Tropical Medicine (approval number 5109).

Licence

Table title

Tab: Influenza seasons in England & Wales, 1974/75-2004/05: dominant variant, antigenic drift events in evoluation of influenza A/H3N2 viruses,vaccine mismatch, vaccine coverage and numbers of excess P&I deaths by age group. Bolding means H3N2 dominant and vaccine variants are from different antigenic clusters.

Figure legends

Fig 1: Excess mortality in the a) 65-74 and b) 75+ age groups in each influenza season in England & Wales, stratified by the dominant influenza virus in circulation (black 'x' = A/H3N2 viruses were dominant or co-dominant; grey '+' = A/H1N1 or B viruses were dominant). ~~Best-fitting trend lines in excess mortality, with 95% CIs, are overlayed.~~ Vaccine coverage in the respective age group from published data is also shown (dots and asterisks, right axis). Asterisks indicate that vaccine coverage in these years was inferred from observed vaccine coverage in the 65+ age group and the average ratio of coverage in the 65+ to 65-74 (or 75+) age group.

Fig 2: Summary of estimated vaccine impact from ~~linear~~ log(excess + 1) regression models of the binary effect of the switch to age group-based targeting of yearly influenza vaccination to all those 65 years of age and older (from 2000/01 onwards) compared to before 2000/01. Coefficients are shown on the original scale and are therefore multiplicative. Squares are the 65-74 age group, circles the 75+ age group and triangles the 45-64 age group. Filled symbols represent seasons dominated by influenza A/H3N2 viruses, open symbols seasons dominated by influenza A/H1N1 or B viruses.

Fig 3: Model fit: The observed time series of weekly P&I deaths in the a) 65-74 sand b) 75+ age group in England & Wales between 1975 and 2005 (light dotted line on each plot). The fitted curve from the log-linear Simonsen-like model fitted excluding December to April and accounting for seasonality, long-term trend and artefacts is overlayed (dark line). Vaccine coverage (in the 65-74 and 75+ age groups) adapted from published data is shown on the right axis of each plot (dots and asterisks). Asterisks indicate that vaccine coverage in these years was inferred from observed vaccine coverage in the 65+ age group and the average ratio of coverage in the 65-74 (or 75+) to 65+ age group. The fitted curve can be deconstructed into its constituent parts. Thus c) and d) show just the long-term trend (i.e. cubic spline) component of the fitted curve (dark lines), with its 95% confidence interval (light lines), for the 65-74 and 75+ age groups, respectively. Doing this allows a better visualisation of the shape of the long-term trend.

Table

Influenza season	Dominant influenza variant(s)	Antigenic drift events(30)	Vaccine cluster*	Minimum monthly temperature (°C)	Vaccine coverage, 65-74 yrs	Excess deaths (n), 65-74 yrs	Vaccine coverage, 75+ yrs	Excess deaths (n), 75+ yrs	Vaccine coverage, 45-64 yrs	Excess deaths (n), 45-64 yrs
1975/76	H3N2/B(32)	EN72-VI75		4.5	0%	1910	0%	9389	0%	863
1976/77	H3N2(33)			2	0%	456	0%	2986	0%	203
1977/78	H3N2/H1N1(32)	VI75-TX77		2.8	0%	419	0%	2563	0%	158
1978/79	B(32)			-0.4	0%	14	0%	25	0%	0
1979/80	H3N2(32)	TX77-BA79		2.3	0%	0	0%	95	0%	0
1980/81	H1N1/H3N2(32)			3	0%	89	0%	605	0%	73
1981/82	B/H3N2(34)			0.3	0%	174	0%	501	0%	4
1982/83	H3N2(34)			1.7	0%	264	0%	1947	0%	48
1983/84	H1N1/B(34)			3.3	0%	88	0%	742	0%	38
1984/85	H3N2/B(34)			0.8	0%	74	0%	395	0%	5
1985/86	B(35)			-1.1	0%	0	0%	0	0%	14
1986/87	H1N1(35)			0.8	0%	0	0%	0	0%	0
1987/88	H3N2/H1N1(36)	BA79-SI87		4.9	0%	0	0%	5	0%	4
1988/89	H1N1/H3N2(36)			5.2	0%	374	0%	2023	0%	119
1989/90	H3N2(36)	SI87-BE89	SI87(37)	4.9	22%	2007	27%	14115	9%	638
1990/91	B(36)		BE89(38)	1.5	24%	0	31%	178	9%	0
1991/92	H3N2(36)		BE89(39)	3.7	27%	413	33%	3302	10%	111
1992/93	B/H1N1(36)	BE89-BE92	BE89(40)	3.6	26%	0	33%	0	10%	0
1993/94	H3N2(36)		BE92(41)	3.2	32%	557	39%	4238	12%	137
1994/95	B(36)		BE92(42)	4.8	33%	0	40%	0	12%	0
1995/96	H3N2(36)	BE92-WU95	BE92(43)	2.3	33%	651	42%	5365	12%	226
1996/97	H3N2(36)		WU95(44)	2.5	33%	0	41%	15	12%	9
1997/98	H3N2/H1N1(45)	WU95-SY97	**WU95(45)**	5.2	38%	0	46%	9	14%	10
1998/99	H3N2/B(46)		SY97(46)	5.3	37%	628	49%	6802	13%	233
1999/00	H3N2(47)		SY97(47)	4.9	40%	1083	53%	10554	14%	560
2000/01	B/H1N1(48)		SY97(48)	3.2	59%**	0	74%**	109	16%	0
2001/02	H3N2/H1N2(49)		SY97(49)	3.6	61%**	21	76%**	0	17%	0
2002/03	B/H3N2(50)	SY97-FU02	SY97(50)	3.9	63%**	0	78%**	0	17%	10
2003/04	H3N2(51)		**SY97(51)**	4.8	65%**	338	82%**	2704	18%	152
2004/05	H3N2(52)		FU02(52)	4.3	64%**	1	81%**	27	NA	9

* Bolding indicates a mismatch between vaccine and dominant circulating A/H3N2-virus cluster

** Estimated from coverage 65+ and mean ratio of coverage in the 65-74 to 65+ age group and 75+ to 65+ age group for 1989/90-1999/00

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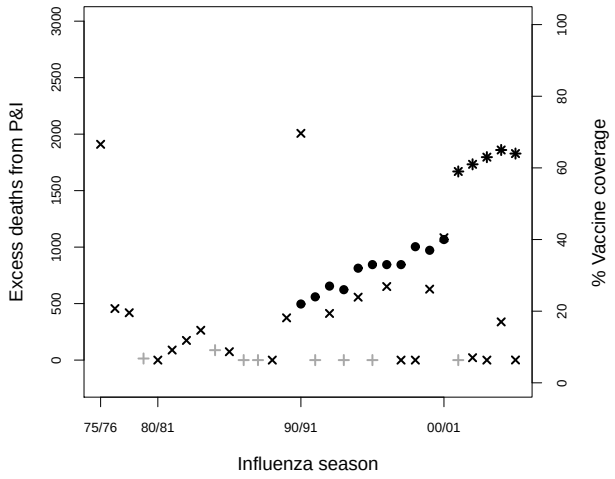
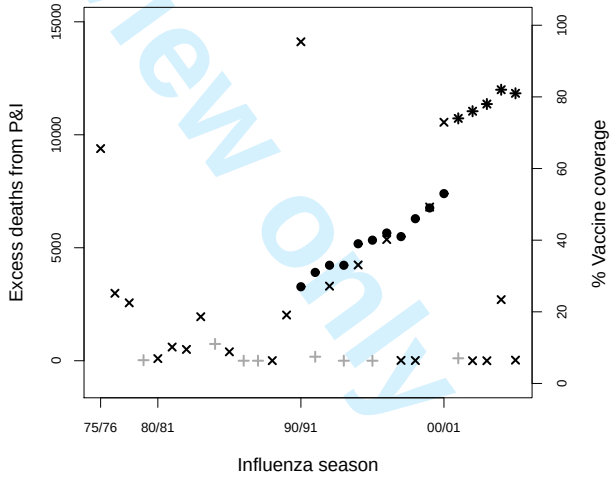


(a) 65-74 yrs



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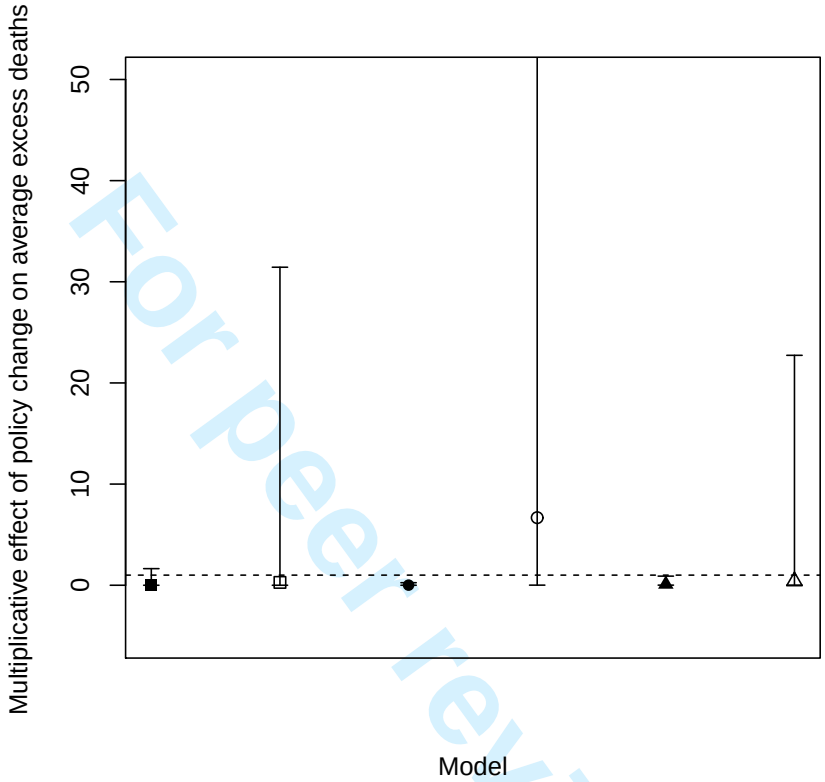

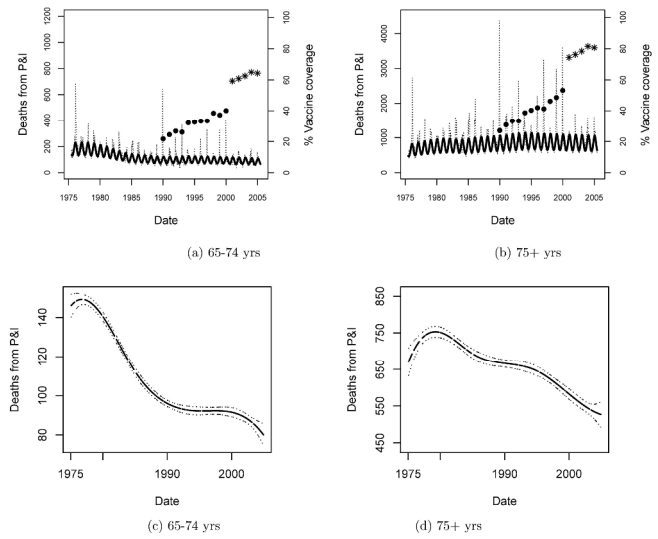

Fig 3: Model fit: The observed time series of weekly P&I deaths in the a) 65-74 sand b) 75+ age group in England & Wales between 1975 and 2005 (light dotted line on each plot). The fitted curve from the log-linear Simonsen-like model fitted excluding December to April and accounting for seasonality, long-term trend and artefacts is overlayed (dark line). Vaccine coverage (in the 65-74 and 75+ age groups) adapted from published data is shown on the right axis of each plot (dots and asterisks). Asterisks indicate that vaccine coverage in these years was inferred from observed vaccine coverage in the 65+ age group and the average ratio of coverage in the 65-74 (or 75+) to 65+ age group. The fitted curve can be deconstructed into its constituent parts. Thus c) and d) show just the long-term trend (i.e. cubic spline) component of the fitted curve (dark lines), with its 95% confidence interval (light lines), for the 65-74 and 75+ age groups, respectively. Doing this allows a better visualisation of the shape of the long-term trend.
297x420mm (300 x 300 DPI)

STATISTICAL METHODS: FURTHER DETAIL

Article title: The impact of targeting all elderly persons in England & Wales for yearly influenza vaccination: excess mortality due to pneumonia or influenza and time trend study

Journal: BMJ Open

Authors: Andrea G. Mann, Punam Mangtani, Colin A. Russell, John C. Whittaker

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Calculating vaccine coverage

Vaccine coverage estimates for 1989/90 to 2004/05 were adapted from published sources as follows. Published estimates of vaccine coverage were available by age group and separately for persons considered at high or low risk of influenza complications.(1, 2) Vaccine coverage for the 45-64 age group overall (i.e. regardless of risk group) was derived from the published estimates of coverage in those 45-64 at high risk and coverage in those 45-64 at low risk and the number of vaccinees in the two risk categories. The denominator (number of persons 45-64 eligible for vaccination) was calculated as the sum across risk groups of the number vaccinated divided by the percentage vaccinated. The sum of the number of vaccinees in the two risk categories was then divided by the total number eligible for vaccination, giving coverage in the 45-64 age group regardless of risk group. The same procedure was undertaken to derive coverage for the 65-74 and 75+ age groups regardless of risk group, with a necessary modification. In the published estimates from 2000/01 onwards, coverage was not broken down into 65-74 and 75+ years. Coverage for the 75+

age group from 2000/01-2004/05 was therefore derived by calculating the coverage for those 65+ (regardless of risk group), using the method described above for the 45-64 age group, for all years and determining the average ratio of coverage in the 75+ age group to 65+ age group for years when coverage in those 75+ was reported (1989/90-1999/00). Multiplying coverage in the 65+ age group for 2000/01 by this average ratio gave estimated coverage in the 75+ age group for 2000/01 (and so on for 2001/02-2004/05). The same procedure was followed to estimate coverage for the 65-74 age group.

Estimating excess and baseline mortality

There are numerous approaches in the literature to quantifying excess mortality as a measure of influenza severity and no gold standard approach. The different methods produce different estimates of excess mortality when fitted to the same data.(3) We elected to modify the method of Simonsen and colleagues,(4) used in their paper analysing influenza vaccine impact in the US, to examine both excess mortality and the long-term trend in non-excess mortality in relation to changes in vaccine policy and coverage. The Simonsen method is a modification of Serfling's cyclical regression approach,(5) where non-epidemic data are modeled to estimate expected mortality and mortality greater than expected is labelled as excess, but improves on the specificity of Serfling's model in that epidemic periods in the data are informed by a specific measure of influenza. We adapted Simonsen's approach to the specifics of our data in two ways. We fitted log-linear negative binomial, instead of Poisson, models to allow for overdispersion apparent in the P&I data from England & Wales. Also, we used all-age laboratory reports for influenza A to inform epidemic periods in the data instead of laboratory-confirmed influenza deaths because there are too few laboratory-confirmed influenza deaths in England & Wales to allow them to be modelled (a given year may have only 25 laboratory-confirmed influenza deaths

(Emma Gordon, personal communication)). Our modelling approach differed from Simonsen's in two additional ways. Firstly, we controlled for the changing size of the population at risk via the offset term rather than fitting models in fine age bands and calculating age-standardized sums of excess deaths. Second, we directly modelled long-term trend using cubic splines (with default knot points) rather than first removing trend from the data with a smoothing spline. This was done so that we could pull out the long-term trend component of the fitted model to plot and visualise in its own right. Our approach to analysis is decribed in full below.

An influenza year was defined as week 26 of one year to week 25 of the next because the timing of influenza circulation during a given winter usually spans two calendar years (i.e. extends from October of one year to March of the next year). Mortality and laboratory data were collapsed into weekly counts for analysis. In order to differentiate excess from baseline mortality we used laboratory data to estimate which were the epidemic weeks in the time series. We then fitted models to the mortality time series to determine both excess and baseline mortality with reference to these epidemic weeks. Specifically, in the first instance we fitted a negative binomial model to all-age weekly counts of laboratory-confirmed influenza A infections excluding counts from the period when influenza is most likely to be circulating in the community (December to April, week numbers 48 of one calendar year to 18 of the next (4)). This negative binomial model included the following terms: as an offset the decennial census population of England & Wales from census years and an inter-census estimate from years between censuses,(6) cubic splines with 6 degrees of freedom to model trend, 1 Fourier term (ie. 1 sine and 1 cosine term) with period 52.2 weeks to model seasonality, and dummy variables to account for minor artefacts. (An initial exploration of options to model trend as linear, quadratic or

with a cubic spline with up to 20 degrees of freedom (df) was undertaken to determine how to fit trend (data not shown)). A time series of counts was predicted from this model when refitted to the full time series of influenza A counts (i.e. not excluding Dec – Apr). The epidemic threshold for each week was defined as the upper 95% confidence bound on the predicted laboratory count for that week. We then fitted the same negative binomial model (except with trend modeled using a cubic spline with 5 df, informed based on our earlier model selection exercise) to the time series of death counts with December to April deleted. We again predicted the time series of counts from this model refitted to the full time series (i.e. without Dec-Apr excluded). Excess mortality was the sum of observed minus predicted deaths in weeks when laboratory data breached their epidemic threshold, by influenza year. Baseline trend in mortality incidence was approximated by fitting the negative binomial model above to the death counts not labelled as excess. This model fit was then deconstructed and just the spline (i.e. trend) component was plotted in order to graphically assess its shape. Estimates of excess mortality and plots of baseline trends were determined separately for the age groups 65-74, 75+ and 45-64 (the latter age group being "unexposed" to a change in vaccine policy or coverage over the period). Any estimates of negative excess mortality were recoded to 0. No model was stratified by sex because an initial exploration of the data suggested similar trends by sex in the study period. A sensitivity analysis was carried out defining epidemic periods based on counts of combined laboratory-confirmed influenza A and influenza B virus infections (as opposed to the main analysis where this was done using counts of influenza A infections only).

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SUPPLEMENTARY FIGURES

Article title: "The impact of targeting all elderly persons in England & Wales for yearly influenza vaccination: excess mortality due to pneumonia or influenza and time trend study"

Journal: BMJ Open

Authors: Andrea G. Mann, Punam Mangtani, Colin A. Russell, John C. Whittaker

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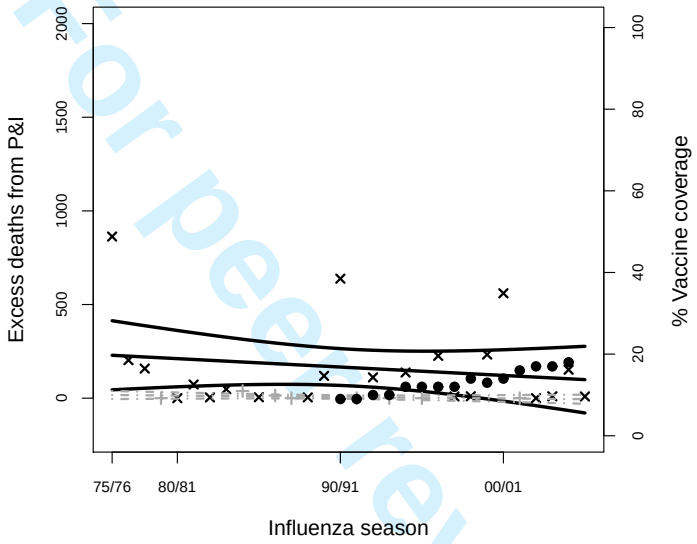
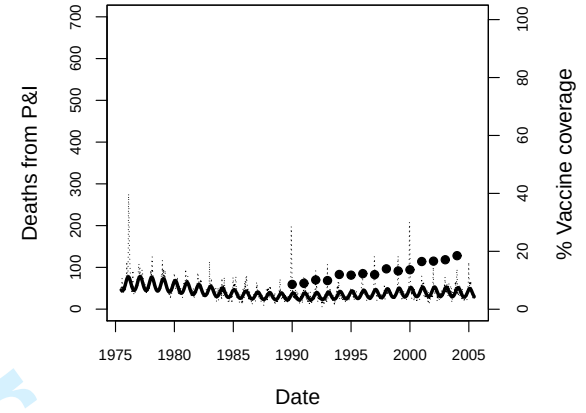


(a)

Figure 1: **Excess mortality in the 45-64 age group in each influenza season from 1975/76 to 2004/05, stratified by the dominant influenza virus in circulation (black 'x' = A/H3N2 viruses were dominant or co-dominant; grey '+' = A/H1N1 or B viruses were dominant). Best-fitting trend lines in excess mortality, with 95% confidence intervals, are overlayed. Vaccine coverage in the 45-64 age group from published data is also shown (dots, right axis).**



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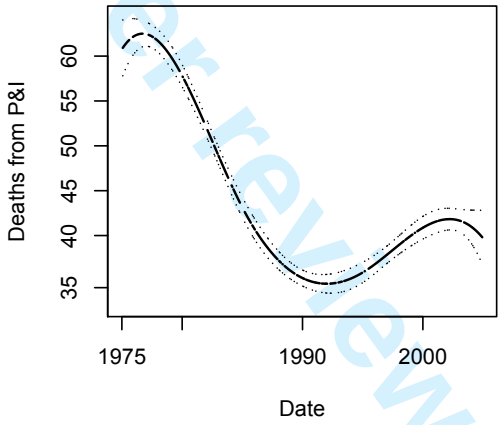
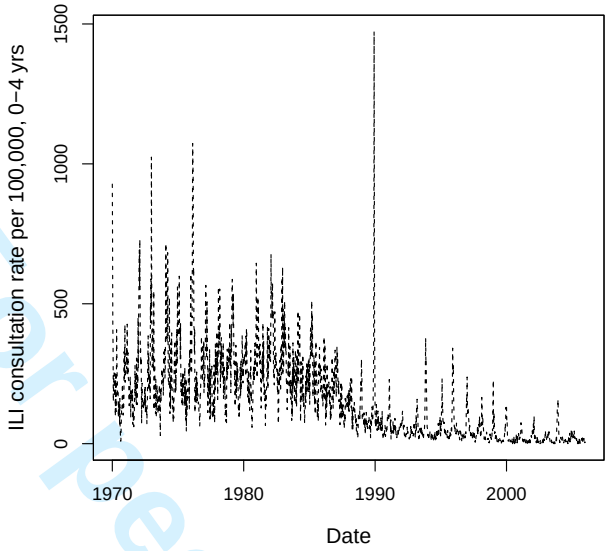


(b)

Figure 2: **Model fit: (a) The observed time series of weekly P&I deaths in the 45-64 age group in England & Wales between 1975 and 2005 (light dotted line). The fitted curve from the log-linear Simonsen-like model fitted excluding incidence from December to April and accounting for seasonality, long-term trend and artefacts is overlayed (dark line). Vaccine coverage in the 45-64 age group from published sources is also shown (dots, right axis). The fitted curve can be deconstructed into its constituent parts. Thus (b) shows just the long-term trend (i.e. cubic spline) component of the fitted curve (dark line), with its 95% confidence interval (light lines). Doing this allows a better visualisation of the shape of the long-term trend.**



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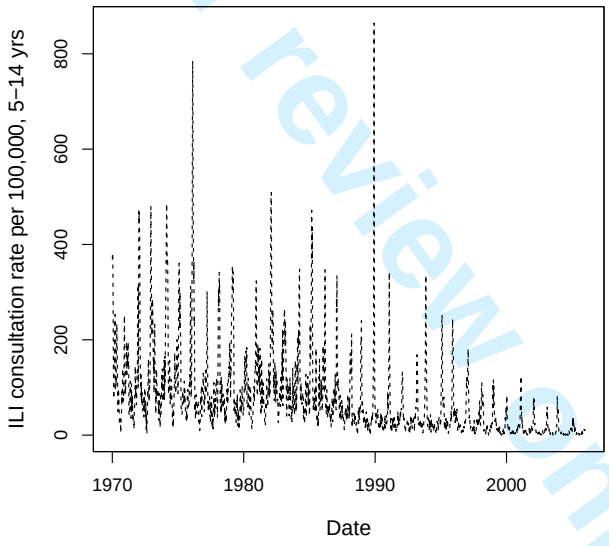
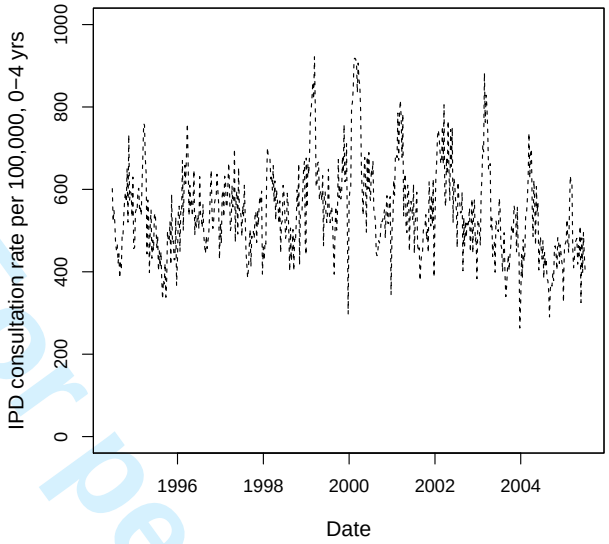
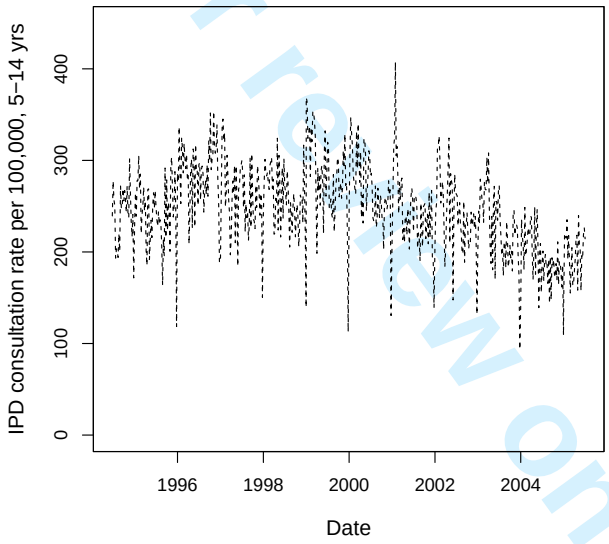


(b)

Figure 3: **The weekly rate of GP consultations for influenza-like illness in the (a) 0-4 and (b) 5-14 age groups, per 100,000 population, in sentinel general practices in England & Wales.**



(a)



(b)

Figure 4: **The weekly rate of GP consultations for infectious and parasitic diseases (which excludes respiratory diseases) in the (a) 0-4 and (b) 5-14 age groups, per 100,000 population, in sentinel general practices in England & Wales.**

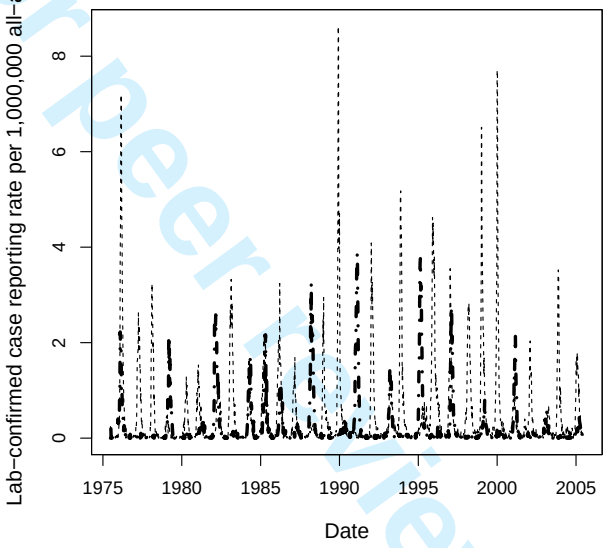


Figure 5: **The weekly rate of laboratory reports for influenza A (light dotted line) and influenza B (dark dotted line) per 1,000,000 population, voluntarily reported to the Health Protection Agency Centre for Infections, England & Wales.**

SUPPLEMENTARY TABLES

Article title: The impact of targeting all elderly persons in England & Wales for yearly influenza vaccination: excess mortality due to pneumonia or influenza and time trend study

Journal: BMJ Open

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Supplementary table 1. Comparison of estimates of excess mortality in previous work to our estimates.

Study	Estimates	Comparison with our estimates
Tillett, 1980 (1)	Number of all-age excess respiratory deaths for 1975/76 3.4 times that for 1976/77 and 3.8 times that for 1977/78	Summing our excess P&I estimates for the 65-74 and 75+ age groups gives combined 65+ excess P&I estimate for 1975/76 of 3.3 times 1976/77 and 3.8 times 1977/78
Fleming, 2005 (2)	For the influenza years 1994/95 to 1999/2000, average mortality in 65-74 age group 2.6 times that in 45-64 age group and 0.2 times that in 75+ age group	Equivalent ratios calculated from our estimates: 2.3 and 0.1.

Supplementary table 2. Mean (range) excess deaths per influenza season before and after vaccination policy changes.

Age group	Mean number of excess deaths per influenza season before policy change*	Range of number of excess deaths per influenza season before policy change*	Mean number of excess deaths per influenza season after policy change**	Range of number of excess deaths per influenza season after policy change**
65-74	485	0 to 2007	72	0 to 338
75+	3025	0 to 14,115	2885	0 to 10,554
45-64, 1998/99 as season of policy change	126	0 to 638	138	0 to 560
45-64, 2000/01 as season of policy change	175	0 to 638	34	0 to 152

* Before policy change defined as 1989/90 to 1999/00 for 65-74 and 1989/90 to 1997/98 for 75+. For the 45-64 age group, mean (range) deaths using both definitions are shown.
** After policy change defined as 2000/01 to 2004/05 for 65-74 and 1998/99 to 2004/05 for 75+. For the 45-64 age group, mean (range) deaths using both definitions are shown.

References

1. Tillett HE, Smith JW, Clifford RE. Excess morbidity and mortality associated with influenza in England and Wales. Lancet. 1980 Apr 12;315(8172):793-5.
2. Fleming DM, Cross KW, Pannell RS. Influenza and its relationship to circulatory disorders. Epidemiol Infect. 2005 Apr;133(2):255-62.