



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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-002743
Article Type:	Research
Date Submitted by the Author:	17-Feb-2013
Complete List of Authors:	Mann, Andrea; London School of Hygiene & Tropical Medicine, Infectious Disease Epidemiology mangtani, punam; London School of Hygiene & Tropical Medicine, Infectious Disease Epidemiology Russell, Colin; University of Cambridge, Zoology Whittaker, John; London School of Hygiene & Tropical Medicine, Non-communicable Disease Epidemiology
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases
Keywords:	Influenza, Mortality, Mass Vaccination, Aged, Trends

SCHOLARONE™
Manuscripts

Original Research

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

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

Department of Infectious Disease Epidemiology, Faculty of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK Andrea G Mann
Lecturer

Department of Infectious Disease Epidemiology, Faculty of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK Punam Mangtani
Clinical Senior Lecturer

Department of Zoology, University of Cambridge, Downing Street, Cambridge, UK, CB2 3EJ and Fogarty International Center, National Institutes of Health, Bethesda, 20892-2220, USA Colin A Russell
Research Fellow

Department of Non-Communicable Disease Epidemiology, Faculty of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK and Statistical Platforms and Technologies, GlaxoSmithKline, Medicines Research Centre, Mailstop 1S101, Gunnels Wood Road, Stevenage, SG1 2NY, UK John C Whittaker
Professor

Correspondence to: A G Mann andrea.mann@lshtm.ac.uk

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

Key words: influenza; mortality; aged; mass vaccination; trends

Word count: 4816

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

1
2 England & Wales was associated with lower levels of pneumonia and influenza mortality in older
3
4 people in the first 6 years after age group-based targeting began. The possible impact of these policy
5
6 changes is observed both as weak evidence for lower average excess mortality and as a turning point
7
8 in baseline mortality coincident with the changes. Further work is required to exclude residual
9
10
11
12 confounding.
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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

1
2 Holland, all-cause excess mortality during influenza epidemics declined after the introduction of
3
4 universal yearly vaccination of those aged 65 and over.(14) In contrast, three other studies, in the US,
5
6 Italy and in Catalonia, did not detect an impact of rising vaccine coverage of the elderly on all-cause
7
8 excess mortality.(15-17) Previous studies of influenza attributable or excess mortality in the UK have
9
10 not related this to vaccination.(18-20)
11
12

13
14 While the level of mortality observed when influenza is circulating in the community (often
15
16 quantified using excess mortality) varies from winter to winter, baseline respiratory mortality (i.e.
17
18 excluding excess) has a seasonal pattern which is more or less constant from winter to winter, though
19
20 it may change over the long-term.(21) Previous studies of the long-term trends in influenza-related
21
22 mortality in England & Wales have covered earlier, and usually shorter, time periods. One study
23
24 examined trends in pneumonia or influenza (P&I) mortality in England & Wales from 1994/95 to
25
26 2000/01 and showed a plot of rates of P&I mortality in the 65-74 age group in this period which
27
28 appears to have little secular trend.(18) The shape of the trend in baseline respiratory mortality in
29
30 England & Wales since 2000/01 is unclear.
31
32
33
34
35
36

37 This work evaluates a public health initiative, to specifically target all people 65 years of age
38
39 and older for yearly influenza vaccination regardless of risk group, which has been in place since 2000.
40
41 Studying patterns in excess mortality and trends in baseline mortality in the years shortly following
42
43 the introduction of this initiative allows us to provide evidence for the impact of this policy.
44
45
46

47 **Methods**

48
49 Daily counts of deaths registered to underlying pneumonia or influenza (P&I) in England &
50
51 Wales between 1975 and 2005, by date of death, sex and age group, were provided by the Office for
52
53 National Statistics (ONS). Deaths registered to underlying P&I, not just confirmed influenza deaths,
54
55 were analysed because deaths from influenza are rarely laboratory confirmed and because deaths in
56
57
58
59
60

1
2 the elderly which occur secondary to influenza often result from pneumonia.(22, 23) P&I mortality
3
4 rates are a more specific measure of influenza activity than rates of all-cause mortality.(24)
5
6

7 The mortality data were adjusted to account for the following historical modifications to how
8
9 the data are coded so that our assessment of trends would not be influenced by these artefactual
10
11 step changes. The ICD changed from version 8 to 9 in 1979, leading to a small decline in deaths coded
12
13 to underlying P&I.(25) In 1984, ONS introduced a broader interpretation of rule 3 for coding
14
15 underlying cause of death, which led to an abrupt fall in deaths registered to underlying pneumonia,
16
17 and to a rise in deaths registered to underlying cancer and ischemic heart disease.(26) In 1993, ONS
18
19 adopted an automated system for coding underlying cause of death which narrowed the
20
21 interpretation of rule 3 and approximately reversed the change adopted in 1984 (i.e. rates of deaths
22
23 being registered to underlying pneumonia rose back to a level approximately equal to that pre-
24
25 1984).(27) With the change from ICD 9 to 10 in 2000, deaths coded to underlying respiratory disease
26
27 fell by approximately 22%, and deaths coded specifically to underlying pneumonia fell by 38%.(28)
28
29
30
31
32
33
34

35 The Health Protection Agency Centre for Infections (HPA CfI) provided an extract of all
36
37 individual reports of laboratory-confirmed influenza A infections between 1975 to 2005 from their
38
39 LabBase2 database. These reports, based on virus isolation and PCR, were reported voluntarily by
40
41 National Health Service (NHS) and HPA laboratories in England & Wales. Records included individuals'
42
43 age, sex and the earliest specimen date.
44
45
46

47 The statistical methods used are summarized below, with full details provided in the
48
49 supplementary material. Vaccine coverage estimates for 1989/90 to 2004/05 were adapted from
50
51 published sources. Published estimates of vaccine coverage were available by age group and
52
53 separately for persons considered at high or low risk of influenza complications.(2, 3) Separate
54
55 estimates by risk group were combined proportionately according to the number of each group
56
57
58
59
60

1
2 vaccinated to give coverage for that age group regardless of risk group.
3
4

5 There are numerous approaches in the literature to quantifying excess mortality as a measure
6
7 of influenza severity and no gold standard approach. We elected to modify the method of Simonsen
8
9 and colleagues,(15) used in their paper analysing influenza vaccine impact in the US, to examine both
10
11 excess mortality and the long-term trend in non-excess mortality in relation to changes in vaccine
12
13 policy and coverage. The Simonsen method is a modification of Serfling's cyclical regression
14
15 approach,(21) where non-epidemic data are modeled to estimate expected mortality and mortality
16
17 greater than expected is labelled as excess, but improves on the specificity of Serfling's model in that
18
19 epidemic periods in the data are informed by a specific measure of influenza.
20
21
22
23

24 An influenza year was defined as week 26 of one year to week 25 of the next because the
25
26 timing of influenza circulation during a given winter usually spans two calendar years (i.e. extends
27
28 from October of one year to March of the next year). Mortality and laboratory data were collapsed
29
30 into weekly counts for analysis. In order to differentiate excess from baseline mortality we used
31
32 laboratory data to estimate which were the epidemic weeks in the time series. We then fitted models
33
34 to the mortality time series to determine both excess and baseline mortality with reference to these
35
36 epidemic weeks. Excess mortality was the sum of observed minus predicted deaths in weeks when
37
38 laboratory data breached their epidemic threshold, by influenza year. Baseline trend in mortality
39
40 incidence was approximated by fitting the mortality model to the death counts not labelled as excess.
41
42 This model fit was then deconstructed and just the spline (i.e. trend) component was plotted in order
43
44 to graphically assess its shape for changes, or turning points, in the direction of the trend coincident
45
46 with policy changes. In the same way, estimates of excess mortality were plotted over time to look for
47
48 evidence of turning points in the trend. Estimates of excess mortality and plots of baseline trends
49
50 were determined separately for the age groups 65-74, 75+ and 45-64 (the latter age group being
51
52
53
54
55
56
57
58
59
60

1
2 “unexposed” to a change in vaccine policy or coverage over the period). Any estimates of negative
3
4 excess mortality were recoded to 0. No model was stratified by sex because an initial exploration of
5
6 the data suggested similar trends by sex in the study period. A sensitivity analysis was carried out
7
8 defining epidemic periods based on counts of combined laboratory-confirmed influenza A and
9
10 influenza B virus infections (as opposed to the main analysis where this was done using counts of
11
12 influenza A infections only).
13
14
15

16
17 To quantify vaccine impact on excess mortality, we fitted age group-specific linear regression
18
19 models of excess mortality for each influenza year against a) a dummy variable having a value of 0 for
20
21 1989/90 to 1999/00 and 1 for 2000/01 to 2004/05 to capture the start of the policy targeting all those
22
23 65+ for yearly influenza vaccination (exposure of interest), b) the minimum monthly temperature
24
25 observed in each influenza year,(29) c) whether the influenza season experienced a large antigenic
26
27 drift event or not,(30) and d) whether the influenza season was characterised by a mismatch between
28
29 vaccine and circulating H3N2 viruses or not (references in Table). Models were fitted separately for
30
31 influenza A/H3N2 virus-dominated influenza seasons and for influenza seasons dominated by other
32
33 influenza virus subtypes. This was done to allow for greater mortality, and thus potentially greater
34
35 vaccine impact, in influenza seasons dominated by influenza A/H3N2 viruses than those dominated by
36
37 influenza A/H1N1 or B viruses.(31) Vaccine mismatch was not included in models where the outcome
38
39 was excess mortality in non-influenza A/H3N2 virus-dominated seasons because both mismatch
40
41 seasons were seasons when influenza A/H3N2 viruses dominated. Separate sensitivity analyses were
42
43 carried out a) defining the vaccine coverage dummy variable with reference to 1998/99 rather than
44
45 2000/01 (because 1998/99 was the first influenza year of age group-based targeting of vaccination (to
46
47 those 75+)) and b) modelling vaccination as a linear term, using derived estimates of coverage by age
48
49 group in each influenza year, rather than as a dummy variable.
50
51
52
53
54
55
56
57
58
59
60

1
2 To establish the extent of circulation of influenza in the community over the influenza years
3
4 studied, weekly rates of consultation for influenza-like illness (ILI), and for infectious and parasitic
5
6 diseases (which excludes ILI), with sentinel general practices in England & Wales for 0-4 and 5-14
7
8 years olds were plotted over time (data provided by the Royal College of General Practitioners weekly
9
10 returns service). We also plotted weekly, all-age rates of laboratory-reported influenza A and B
11
12 infections over time.
13
14

15
16
17 Models were fitted in R (R version 2.12.1 (2010-12-16), Copyright 2010 The R Foundation for
18
19 Statistical Computing).
20
21

22 Results

23
24
25 Weekly deaths registered to underlying P&I in those 65 years of age and older in England &
26
27 Wales in the period from 1975/76 to 2004/05 ranged from 34 deaths per 1,000,000 person weeks (in
28
29 week 36 of 1984) to 481 deaths per 1,000,000 person weeks (in week 7 of 1976).
30
31
32

33 Excess mortality

34
35 Excess mortality for the 65-74 age group ranged from 0 to just over 2000 deaths per influenza
36
37 year in the study period (Table). For the 75+ age group, the range was from 0 to over 14,000 deaths
38
39 per influenza year. Mortality attributable to epidemic influenza was highly variable year to year. For
40
41 neither age group does there appear to have been a turning point in the trend in excess mortality
42
43 coinciding with the 2000/01 season, when the policy of targeting all persons aged 65 and over for
44
45 yearly influenza vaccination was enacted (Figure 1). Similarly, there was no turning point in the trend
46
47 in excess mortality in the 75+ age group around 1998/99 when this age group became fully targeted
48
49 for yearly influenza vaccination. The direction of the trend in excess mortality over the whole time
50
51 period appears to be downwards or flat. Trend in excess mortality in the 45-64 age group is
52
53 approximately flat in the same period (Supplementary Figure 1).
54
55
56
57
58
59
60

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 occurring 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, plateaued to 2000 and fell after 2000 (Figure 3). For the 75+ age group, rates increased to the late 1970s, declined to the mid-1980s, plateaued 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

1
2 models were normally distributed with mean approximately 0 and standard deviation approximately
3
4 1 with some residual autocorrelation (data not shown). Findings are robust to defining epidemic
5
6 periods using laboratory reports of influenza A infections alone or to using both influenza A and B
7
8 infections for this purpose.
9
10

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

12
13
14 During the period 2000-2005, ILI consultations for 0-4 and 5-14 year olds were lower than
15
16 historically (supplementary fig 3). However, over the same time period consultations for infectious
17
18 and parasitic diseases (which excludes ILI) also appeared to decline, especially in the 5-14 year age
19
20 group (supplementary fig 4). Rates of laboratory reported influenza infections were lower in 2000-
21
22 2005 than in the decade prior. (supplementary fig 5). Rates in 2000-2005 were similar to those
23
24 observed around 1980 (figure 3).
25
26
27
28
29

30 **Discussion**

31 **Statement of principal findings**

32
33
34
35 There is weakly supportive evidence that the switch from risk-based to age group-based
36
37 targeting of influenza vaccination for older people was associated with lower influenza-related
38
39 mortality in the 4-6 years following this policy change. Results from our multivariable linear regression
40
41 suggest that this policy change had a weak, positive impact on excess mortality in both the 65-74 and
42
43 75+ age groups. There is no indication of a downwards turning point in the trend in excess mortality
44
45 around 2000/01 (when all those 65+ began to be targeted for vaccination) or 1998/99 (when those
46
47 75+ began to be targeted) which argues against a strong, specific impact of this policy change on
48
49 excess mortality in either age group. Trends in baseline, as opposed to excess, mortality do show a
50
51 suggestion of a downwards turning point in the mid-1990s for the 75+ age group and around 2000 for
52
53 the 65-74 age group, coinciding approximately with the timing of the changes to specifically target
54
55
56
57
58
59
60

1
2 these age groups for vaccination. Results obtained by fitting the various models to data for the 45-64
3
4 age group, in whom vaccine coverage was largely static over the study period, are in a similar
5
6 direction but are of a smaller magnitude than the apparent impact in the 65-74 and 75+ age groups,
7
8 suggesting there may have been other factors acting to bring down P&I mortality at the time of the
9
10 policy changes. Thus our analysis is consistent with a small mortality impact in the 65-74 and 75+ age
11
12 groups during the six years after policies to wholly target these age groups for yearly influenza
13
14 vaccination were enacted.
15
16
17
18

19 **Strengths and weaknesses of the study**

20
21
22 There are a number of strengths to the work undertaken, as well as several limitations. The
23
24 key strengths are that we estimated excess mortality and long-term trend in mortality over a long
25
26 period (30 years). We carefully controlled for changes to death coding and laboratory practices which
27
28 occurred over this time period. The analytical approach we used, which is similar to one used by many
29
30 others,(15, 16) of modelling seasonality and trend using splines in addition to sinusoidal terms (full
31
32 details provided in the supplementary material), is a highly flexible method of fitting complex patterns
33
34 and trends that is especially helpful when modelling a long time series. The outcome we chose to
35
36 model (deaths from underlying P&I) is the most specific option available which allows sufficient
37
38 numbers of deaths for analysis. This choice maximised our ability to discern high mortality impact
39
40 influenza years from those less so, and thus to detect vaccine impact. Analysing underlying P&I of
41
42 course means our estimates of excess mortality underestimate the burden of mortality due to all
43
44 respiratory disease (which includes bronchitis), cardiovascular disease and other causes of death
45
46 which may be linked to influenza. (19, 20) However, it was not the aim of this work to estimate the
47
48 total mortality burden due to influenza. Further adding to the specificity of our outcome was our
49
50 designation of epidemic periods in the mortality data with reference to the time series of laboratory-
51
52
53
54
55
56
57
58
59
60

1 confirmed influenza A infections. Better still might have been to use influenza A/H3N2 infections, the
2
3 subtype most often associated with influenza years when there is substantial mortality,(53) but the
4
5 laboratory data available for this analysis were not broken down by subtype. The limitations of our
6
7 work include that our estimate of the extent of variability in excess mortality across influenza years is
8
9 likely to be an underestimate because our model failed to explain all variability in the mortality data
10
11 (as evidenced by a small amount of autocorrelation in residuals, data not shown). This may be
12
13 because we did not include temperature or other climatic variables in the models estimating excess
14
15 mortality. We did adjust for temperature in linear regression models of vaccine impact on excess
16
17 mortality and as such our analysis of vaccine impact should not be confounded by temperature.
18
19 However, our results regarding long-term trends in non-excess mortality may be confounded by
20
21 temperature as there is evidence that minimum winter temperatures have increased since the early
22
23 1960s.(54) In using laboratory data to inform epidemic periods in the mortality data, we made no
24
25 allowance for a lag between the increase, or peak, in incidence of laboratory-reported infections and
26
27 the timing of excess deaths associated with these infections. This is likely to have led us to
28
29 underestimate excess mortality, assuming the peak in deaths rarely precedes and generally coincides
30
31 or follows the peak in laboratory reports. However, the rise in influenza activity in the community in
32
33 terms of GP consultations generally coincides with the rise in numbers of laboratory reports of
34
35 influenza infections,(36) and, during influenza years dominated by circulation of influenza A viruses,
36
37 peak weekly GP consultation rates for influenza-like illness in the 45–64, 65–74 and ≥ 75 years age
38
39 groups tend to coincide with same-age peaks in respiratory deaths, plus or minus 1 week (e.g.
40
41 1995/1996, 1996/1997, 1998/1999 and 1999/2000).(18) Hence the potential bias in our estimates of
42
43 excess mortality is likely to be minimal because the weeks we might have missed by not allowing for a
44
45 lag will be close to the start or end of the period of influenza circulation and thus will make up a small
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2 proportion of the total influenza attributable P&I deaths in a given winter. Our estimates of long-term
3
4 trends may be confounded by the trends in co-morbidities linked to smoking or by long-term patterns
5
6 in other co-morbidities associated with respiratory mortality, which we have not accounted for.
7
8

9
10 Finally, the separate vaccine coverage estimates we present for the 65-74 and 75+ age groups from
11
12 2000/01 onwards are sensitive to our assumption of a constant ratio of vaccine coverage in the 65-74
13
14 to 75+ age groups from 2000/01 onwards (described in the supplementary file). The assumption of a
15
16 constant ratio is unlikely to be true and as such we have probably underestimated coverage in the 65-
17
18 74 age group and overestimated it in the 75+ age group; the increase in coverage in 2000/01 was
19
20 probably disproportionately accounted for by an increase in coverage in the 65-74 age group, newly
21
22 targeted as fully “at risk” from the 2000/01 influenza season. Our main findings are unaffected by this
23
24 because we focus on results from linear models of the effect of change in vaccination policy as a
25
26 binary variable.
27
28
29
30
31

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

33

34
35 Using as a reference the previous estimates which exist of excess respiratory mortality in
36
37 England & Wales, our estimates appear to be a valid reflection of variability between years and
38
39 between age groups in influenza-attributable mortality. Findings as to vaccine impact from other
40
41 settings have been mixed, thus our observation of perhaps some limited impact is not inconsistent
42
43 with reports from other settings which analysed the impact of similar levels of vaccine coverage to
44
45 that achieved in the UK. Previous estimates of excess, all-age respiratory mortality for the influenza
46
47 years 1975/76, 1976/77 and 1977/78 are higher than our excess P&I estimates for these years but the
48
49 relative magnitude of the excess mortality between these years matches our estimates well.
50
51 (supplementary table). The absolute value of the previous estimates is higher than ours because the
52
53 authors included bronchitis deaths and analysed all-ages combined, not just the elderly. For the
54
55
56
57
58
59
60

1
2 influenza years 1994/95 to 1999/2000, published estimates of average influenza-attributable
3
4 respiratory mortality by age group (45-64, 65-74 and 75+) are higher than our averages for the same
5
6 age groups over the same period but ratios between different age groups are similar to our estimates.
7
8 Differences in the magnitude of estimates from the two methods will be because they include
9
10 bronchitis deaths and but also because the rate difference-type method used by Fleming and
11
12 colleagues tends to produce higher estimates of excess than the Serfling-type method we used, due
13
14 to a lower reference mortality and the mortality rate in the “influenza-active periods” being entirely
15
16 attributed to influenza.(55) There has been much interest in measuring the impact of influenza
17
18 vaccination campaigns in other settings.(14, 15, 17, 56) Excess all-cause mortality declined in Dutch
19
20 elderly after the introduction of universal yearly vaccination of those aged 65 and over which saw
21
22 yearly coverage reach 80%.(14) Excess all-cause mortality and influenza-related hospitalisations and
23
24 GP visits declined more in Ontario than in other Canadian provinces after the introduction of universal
25
26 yearly vaccination for all Ontario residents.(56) Analyses of the impact of rising vaccine coverage of
27
28 the elderly on excess all-cause mortality in the US, Italy and in Catalonia did not detect impact
29
30 perhaps because, in the case of the US and Italy, coverage did not reach high enough levels for long
31
32 enough during the study period, or because, as in Catalonia, there were limited data available, prior
33
34 to coverage exceeding 60%, to provide a baseline against which to estimate impact.(15-17) Because
35
36 ratios of our estimates of excess P&I between adjacent seasons, and between age groups, are
37
38 consistent with previous work using different models, we are confident that our impression of the
39
40 relative magnitude of P&I mortality between age groups and from one influenza year to the next are a
41
42 true reflection of patterns in influenza mortality during the study period. Our having observed some
43
44 evidence for vaccine impact on excess mortality in the 6 years after implementation of age group-
45
46 based influenza vaccination is consistent with findings from other temperate northern hemisphere
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2 settings which have attained similar levels of vaccine coverage in the elderly, where some studies
3
4 have demonstrated impact and others have not.
5
6

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

8

9
10 Our analysis suggests high yearly vaccination coverage of the elderly had a small impact on P&I
11
12 deaths in the 4-6 years following implementation of age group-based targeting of the elderly for
13
14 influenza vaccination. Alternative explanations are that there was less influenza around during the
15
16 time of high vaccine coverage, making it look like vaccination produced an impact on mortality when
17
18 it did not. The fact that we observed smaller magnitude but same direction associations between the
19
20 timing of policy changes in the elderly and mortality in the 45-64 age group, in whom vaccination
21
22 policy and coverage were approximately constant over the study period, support this alternative
23
24 explanation. However, our analysis of to what extent influenza circulated in the community in the
25
26 study period does not provide clear answers: consultations among children for both ILI and infectious
27
28 and parasitic diseases (which excludes respiratory disease) were lower in the 2000-2005 period than
29
30 earlier in the study period. It is difficult to interpret lower ILI rates as strong evidence for less
31
32 influenza circulating in 2000-2005 than previously since the decline in rates of infectious and parasitic
33
34 diseases rates then still needs explaining. It may in part be that there was progressively lower use of
35
36 GP services in the 2000-2005 period. Rates of laboratory reported influenza infections for all-ages,
37
38 reported to the HPA CfI, were certainly lower in 2000-2005 than in the decade prior, and were similar
39
40 to rates observed around 1980 when excess mortality also appeared to be low for several consecutive
41
42 years. It is difficult to interpret long-term trends in laboratory reports of influenza infections because
43
44 of changing testing practices and changing volumes of test requisitions over the time period. For
45
46 example, between 1975 and 1992, the number of laboratory reports of viral infections doubled (57);
47
48 this is unlikely to reflect a doubling of viral infections over this period. If more tests were requisitioned
49
50
51
52
53
54
55
56
57
58
59
60

1
2 in 2000-2005 than in the years around 1980 similar rates of positive reports in the two periods would
3
4 suggest less viral activity in 2000-2005 than around 1980. However, it is hard to see how less influenza
5
6 in circulation later than earlier in the study period could explain a turning point in baseline mortality
7
8 in the 65-74 and 75+ age groups approximately coincident with policy changes to specifically target
9
10 these age groups for vaccination. We think the observation of a turning point in baseline mortality
11
12 reflects partly a non-specific impact of influenza vaccination on respiratory mortality in the elderly
13
14 that is not directly attributable to influenza as well as partly a specific impact of influenza vaccination
15
16 given that analysing excess mortality necessarily means some truly influenza-attributable mortality
17
18 (i.e. that which does not breach the epidemic threshold) contributes to baseline. A further possible
19
20 alternative explanation for the apparent, small influenza vaccine impact we have observed is that this
21
22 is really an impact of pneumococcal vaccination. This is unlikely to be true; to the end of the 2004/05
23
24 influenza year, less than 30% of people 65 years of age and over had received the recommended 23-
25
26 valent pneumococcal polysaccharide vaccine.(58) Pneumococcal conjugate vaccination of infants and
27
28 children, which might be expected to provide indirect protection to the elderly, has only been
29
30 routinely recommended since 2006. It is possible that there is some other factor which also changed
31
32 over the time period and which explains part of the mortality impact we observed (e.g. trends in co-
33
34 morbidities linked to smoking).

45 **Unanswered questions and future research**

46
47 Influenza vaccine impact can be difficult to measure due to its reliance on surveillance data
48
49 which are generally not collected in a consistent way over time, and because of the variable nature of
50
51 influenza activity over time. One way of adding to the evidence base is to look at vaccine
52
53 effectiveness. In order to strengthen the evidence base for influenza vaccine effectiveness in the
54
55 elderly, further good quality cohort and case-control studies across multiple influenza seasons with
56
57
58
59
60

1
2 varying degrees of match between vaccine and circulating variants, and adequate control for negative
3
4 confounding by indication (sicker elderly being preferentially offered vaccination) and positive
5
6 confounding by healthier older people putting themselves forward for vaccination, are required. It
7
8 remains unclear to what extent our findings are due to there being less influenza around 2000-2005
9
10 than before this time or to confounding by factors such as trends in co-morbidities linked to smoking.
11
12 Analyses including more recent influenza seasons will help to answer these questions and to monitor
13
14 whether the modest mortality impact we observed in the 6 years after age group-based targeting of
15
16 vaccination began has been sustained. This analysis will be complicated by the presence of
17
18 pneumococcal vaccination of infants and the elderly, making teasing apart the effects of how much
19
20 influenza circulated during the time period, the impact of influenza vaccination and the impact of
21
22 pneumococcal vaccination a challenge.
23
24
25
26
27
28
29

30 **Competing interest**

31
32 All authors have completed the Unified Competing Interest form at
33
34 http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and
35
36 declare: that funding for the submitted work was provided by the National Institute of Health
37
38 Research in the UK (fellowship to AGM) and that none was garnered from elsewhere; that JCW is
39
40 currently employed by, and holds stock options with, GlaxoSmithKline but that the relationship of
41
42 JCW to GSK had no influence on the work or on the decision to publish it; that there are no other
43
44 relationships or activities that could appear to have influenced the submitted work.
45
46
47
48
49

50 **Contributors**

51
52
53
54 AGM, PM and JCW conceived of the study, AGM conducted the analysis, led on the
55
56 interpretation and wrote the paper; JCW, PM and CAR contributed to interpretation and to
57
58
59
60

1
2 subsequent drafts of the paper. All authors approved the final version to be published. AGM is the
3
4 guarantor for the study. P&I data were provided by Cleo Rooney and Emma Gordon from the Office
5
6 for National Statistics. Laboratory data were provided by Carol Joseph and Joy Field of the Health
7
8 Protection Agency Centre for Infections. GP consultation data were provided by Douglas Fleming and
9
10 Alex Elliot of the Royal College of General Practitioners.
11
12

13 14 **Funding**

15
16
17
18 This work was supported by a Researcher Development Award to AGM from the National
19
20 Institute of Health Research, UK [fellowship grant number RDA06/068]. The funder had no role in the
21
22 study design, in the collection, analysis, or interpretation of data, in the writing of the report or in the
23
24 decision to submit the article for publication. We the authors are independent from the funders.
25
26
27

28 29 **Access**

30
31 AGM had full access to all of the data in the study and takes responsibility for the integrity of
32
33 the data and the accuracy of the data analysis.
34
35

36 37 **Data sharing**

38
39 There are no additional data available.
40
41

42 43 **Ethics**

44
45 This study was approved by the ethics committee of the London School of Hygiene & Tropical
46
47 Medicine (approval number 5109).
48
49

50 51 **Licence**

52
53
54 The Corresponding Author has the right to grant on behalf of all authors and does grant on
55
56 behalf of all authors, an exclusive licence on a worldwide basis to the BMJ Publishing Group Ltd and
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

its Licensees to permit this article (if accepted) to be published in BMJ editions and any other BMJPG
products and sublicences to exploit all subsidiary rights, as set out in our licence (
<http://resources.bmj.com/bmj/authors/checklists-forms/licence-for-publication>).

For peer review only

1
2 **Table title**
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Tab: Influenza seasons in England & Wales, 1974/75-2004/05: dominant variant, antigenic drift events in evolution 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.

For peer review only

1
2 **Figure legends**
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2 **Fig 1:** Excess mortality in the a) 65-74 and b) 75+ age groups in each influenza season in England &
3 Wales, stratified by the dominant influenza virus in circulation (black 'x' = A/H3N2 viruses were
4 dominant or co-dominant; grey '+' = A/H1N1 or B viruses were dominant). Best-fitting trend lines in
5 excess mortality, with 95% CIs, are overlayed. Vaccine coverage in the respective age group from
6 published data is also shown (dots and asterisks, right axis). Asterisks indicate that vaccine coverage in
7 these years was inferred from observed vaccine coverage in the 65+ age group and the average ratio
8 of coverage in the 65+ to 65-74 (or 75+) age group.
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2 **Fig 2:** Summary of estimated vaccine impact from linear regression models of the binary effect of the
3 switch to age group-based targeting of yearly influenza vaccination to all those 65 years of age and
4 older (from 2000/01 onwards) compared to before 2000/01. Squares are the 65-74 age group, circles
5 the 75+ age group and triangles the 45-64 age group. Filled symbols represent seasons dominated by
6 influenza A/H3N2 viruses, open symbols seasons dominated by influenza A/H1N1 or B viruses.
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2 **Fig 3:** Model fit: The observed time series of weekly P&I deaths in the a) 65-74 and b) 75+ age group
3 in England & Wales between 1975 and 2005 (light dotted line on each plot). The fitted curve from the
4 log-linear Simonsen-like model fitted excluding December to April and accounting for seasonality,
5 long-term trend and artefacts is overlaid (dark line). Vaccine coverage (in the 65-74 and 75+ age
6 groups) adapted from published data is shown on the right axis of each plot (dots and asterisks).
7 Asterisks indicate that vaccine coverage in these years was inferred from observed vaccine coverage
8 in the 65+ age group and the average ratio of coverage in the 65-74 (or 75+) to 65+ age group. The
9 fitted curve can be deconstructed into its constituent parts. Thus c) and d) show just the long-term
10 trend (i.e. cubic spline) component of the fitted curve (dark lines), with its 95% confidence interval
11 (light lines), for the 65-74 and 75+ age groups, respectively. Doing this allows a better visualisation of
12 the shape of the long-term trend.
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

References

1. Department of Health: From the Chief Medical Officer, the Chief Nursing Officer and the Chief Pharmaceutical Officer. Influenza immunisation. PL/CMO/2000/3. London: Department of Health, 2000.
2. Joseph C, Goddard N, Gelb D. Influenza vaccine uptake and distribution in England and Wales using data from the General Practice Research Database, 1989/90-2003/04. *J Public Health (Oxf)* 2005;**27**:371-7.
3. Butt S, Zhang N, Joseph CA. Vaccination uptake among the 65 years and over and under 65 years at risk in England 2006-07. London: Health Protection Agency Centre for Infections, 2007.
4. Begum F, Pebody R. Seasonal influenza vaccine uptake amongst GP patient groups in England. London: Department of Health, 2012.
5. Fedson DS, Nichol KL. Influenza vaccination: policy versus evidence: no gap between policy and evidence. *BMJ* 2006;**333**:1020.
6. Jefferson T. Influenza vaccination: policy versus evidence. *BMJ* 2006;**333**:912-5.
7. Mangtani P, Hall AJ, Armstrong BG. Influenza vaccination: the case for a gap in the evidence is flawed. *BMJ* 2006;**333**.
8. Simonsen L, Viboud C, Taylor R. Influenza vaccination in elderly people. *Lancet* 2005;**366**:2086.
9. Jefferson T, Di Pietrantonj C, Al-Ansary LA, et al. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev* 2010:CD004876.
10. Osterholm MT, Kelley NS, Sommer A, et al. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;**12**:36-44.
11. Govaert TM, Thijs CT, Masurel N, et al. The efficacy of influenza vaccination in elderly

- 1
2 individuals. A randomized double-blind placebo-controlled trial. *JAMA* 1994;**272**:1661-5.
3
4
5 12. Mangtani P, Cumberland P, Hodgson CR, et al. A cohort study of the effectiveness of influenza
6
7 vaccine in older people, performed using the United Kingdom general practice research database. *J*
8
9 *Infect Dis* 2004;**190**:1-10.
10
11
12 13. Ortqvist A, Granath F, Askling J, et al. Influenza vaccination and mortality: prospective cohort
13
14 study of the elderly in a large geographical area. *Eur Respir J* 2007;**30**:414-22.
15
16
17 14. Jansen AGSC, Sanders EAM, Nichol KL, et al. Decline in influenza-associated mortality among
18
19 Dutch elderly following the introduction of a nationwide vaccination program. *Vaccine* 2008;**26**:5567-
20
21 74.
22
23
24 15. Simonsen L, Reichert TA, Viboud C, et al. Impact of influenza vaccination on seasonal mortality
25
26 in the US elderly population. *Arch Intern Med* 2005;**165**:265-72.
27
28
29 16. Rizzo C, Viboud C, Montomoli E, et al. Influenza-related mortality in the Italian elderly: no
30
31 decline associated with increasing vaccination coverage. *Vaccine* 2006;**24**:6468-75.
32
33
34 17. Muñoz MP, Soldevila N, Martínez A, et al. Influenza vaccine coverage, influenza-associated
35
36 morbidity and all-cause mortality in Catalonia (Spain). *Vaccine* 2011;**29**:5047-52.
37
38
39 18. Fleming DM, Cross KW, Pannell RS. Influenza and its relationship to circulatory disorders.
40
41 *Epidemiol Infect* 2005;**133**:255-62.
42
43
44 19. Hardelid P, Pebody R, Andrews N. Mortality caused by influenza and respiratory syncytial virus
45
46 by age group in England and Wales 1999–2010. *Influenza Other Respi Viruses* 2013;**7**:35-45.
47
48
49 20. Pitman RJ, Melegaro A, Gelb D, et al. Assessing the burden of influenza and other respiratory
50
51 infections in England and Wales. *J Infect* 2007;**54**:530-8.
52
53
54 21. Serfling RE. Methods of current statistical analysis of excess pneumonitis-influenza death. *Public*
55
56 *Health Rep* 1963;**78**:494-506.
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
22. Fleming D, Wood M. The clinical diagnosis of influenza. *Curr Med Res Opin* 2002;**18**:338-41.
 23. Barker WH, Mullooly JP. Underestimation of the role of pneumonia and influenza in causing excess mortality. *Am J Public Health* 1981;**71**:643-5.
 24. Housworth J, Langmuir AD. Excess mortality from epidemic influenza, 1957-1966. *Am J Epidemiol* 1974;**100**:40-8.
 25. Janssen F, Kunst AE. ICD coding changes and discontinuities in trends in cause-specific mortality in six European countries, 1950-99. *Bull World Health Organ* 2004;**82**:904-13.
 26. Devis T, Rooney C. Death certification and the epidemiologist. *Health Stat Quarterly* 1999;**01**:21-33.
 27. Rooney C, Griffiths C, Cook L. The implementation of ICD-10 for cause of death coding - some preliminary results from the bridge coding study. *Health Stat Quarterly* 2002;**13**:31-41.
 28. Brock A, Griffiths C, Rooney C. The impact of introducing ICD-10 on analysis of respiratory mortality trends in England and Wales. *Health Stat Quarterly* 2006;**29**:9-17.
 29. Met Office Hadley Centre Central England Temperature Data: Monthly HadCET mean [database on the Internet]. [Accessed 18 June 2008]. Available from: www.metoffice.gov.uk/research/hadleycentre/CR_data/Daily/HadCET_act.txt.
 30. Smith DJ, Lapedes AS, de Jong JC, et al. Mapping the Antigenic and Genetic Evolution of Influenza Virus. *Science* 2004;**305**:371-6.
 31. Fleming DM. The contribution of influenza to combined acute respiratory infections, hospital admissions, and deaths in winter. *Commun Dis Public Health* 2000;**3**:32-8.
 32. Pereira MS, Chakraverty P. Influenza in the United Kingdom 1977-1981. *J Hyg (Lond)* 1982;**88**:501-12.
 33. Pereira M, Assaad FA, Delon PJ. Influenza surveillance. *Bull World Health Organ* 1978;**56**:192-

- 1
2 203.
3
4
5 34. Chakraverty P, Cunningham P, Shen GZ, et al. Influenza in the United Kingdom 1982-85. *J Hyg*
6
7 (*Lond*) 1986;**97**:347-58.
8
9
10 35. Smith DJ, Forrest S, Ackley DH, et al. Variable efficacy of repeated annual influenza
11
12 vaccination. *Proc Natl Acad Sci U S A* 1999;**96**:14001-6.
13
14 36. Fleming DM, Zambon M, Bartelds AI, et al. The duration and magnitude of influenza
15
16 epidemics: a study of surveillance data from sentinel general practices in England, Wales and the
17
18 Netherlands. *Eur J Epidemiol* 1999;**15**:467-73.
19
20
21
22 37. Recommended composition of influenza virus vaccines for use in the 1989-1990 season. *Wkly*
23
24 *Epidemiol Rec* 1989;**64**:53-60.
25
26
27 38. Recommended composition of influenza virus vaccines for use in the 1990-1991 season. *Wkly*
28
29 *Epidemiol Rec* 1990;**65**:53-6.
30
31
32 39. Joseph CA, Dedman D, Fern K, et al. Influenza surveillance in England and Wales: November
33
34 1991-June 1992. *Commun Dis Rep CDR Rev* 1992;**2**:R149-52.
35
36
37 40. Dedman D, Joseph CA, Chakraverty P, et al. Influenza surveillance, England and Wales: October
38
39 1992-June 1993. *Commun Dis Rep CDR Rev* 1993;**3**:R184-6.
40
41
42 41. Dedman DJ, Joseph CA, Chakraverty P, et al. Influenza surveillance, England and Wales:
43
44 October 1993 to June 1994. *Commun Dis Rep CDR Rev* 1994;**4**:R164-8.
45
46
47 42. Hutchinson EJ, Joseph CA, Chakraverty P, et al. Influenza surveillance in England and Wales:
48
49 October 1994 to June 1995. *Commun Dis Rep CDR Rev* 1995;**5**:R200-4.
50
51
52 43. Hutchinson EJ, Joseph CA, Zambon M, et al. Influenza surveillance in England and Wales:
53
54 October 1995 to June 1996. *Commun Dis Rep CDR Rev* 1996;**6**:R163-9.
55
56
57 44. Dedman DJ, Joseph CA, Zambon M, et al. Influenza surveillance in England and Wales: October
58
59
60

1
2 1996 to June 1997. *Commun Dis Rep CDR Rev* 1997;**7**:R212-9.

3
4 45. Dedman DJ, Zambon M, Buynder PV, et al. Influenza surveillance in England and Wales:
5
6 October 1997 to June 1998. *Commun Dis Public Health* 1998;**1**:244-51.

7
8 46. Whiting P, Joseph CA, Zambon M, et al. Influenza activity in England and Wales: October 1998
9
10 to June 1999. *Commun Dis Public Health* 1999;**2**:273-9.

11
12 47. Goddard NL, Joseph CA, Zambon M, et al. Influenza surveillance in England and Wales:
13
14 October 1999 to May 2000. *Commun Dis Public Health* 2000;**3**:261-6.

15
16 48. Goddard NL, Joseph CA, Zambon M, et al. Influenza surveillance in the United Kingdom:
17
18 October 2000 to May 2001. *Commun Dis Rep CDR Suppl* 2001:1-7.

19
20 49. Crofts JP, Goddard NL, Joseph CA, et al. Influenza surveillance in the United Kingdom: October
21
22 2001 to May 2002. *Commun Dis Rep CDR Suppl* 2002:1-7.

23
24 50. Crofts JP, Joseph CA, Zambon M, et al. Influenza surveillance in the United Kingdom: October
25
26 2002 to May 2003. *Commun Dis Rep CDR Suppl* 2004;**14**:1-9.

27
28 51. Cooke MK, Crofts JP, Joseph CA, et al. Influenza and other respiratory viruses surveillance in
29
30 the United Kingdom: October 2003 to May 2004. *Commun Dis Rep CDR Suppl* 2005;**15**:1-8.

31
32 52. Zhao H, Cooke MK, Joseph CA, et al. Surveillance of influenza and other respiratory viruses in
33
34 the United Kingdom: October 2004 to May 2005. *Commun Dis Rep CDR Suppl* 2006;**16**:1-8.

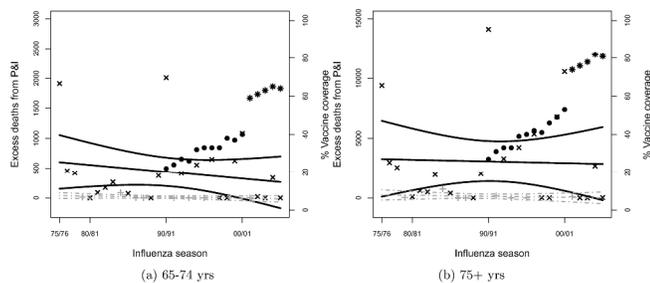
35
36 53. Thompson WW, Shay DK, Weintraub E, et al. Mortality Associated With Influenza and
37
38 Respiratory Syncytial Virus in the United States. *JAMA* 2003;**289**:179-86.

39
40 54. Perry M. Climate memorandum no 21: A spatial analysis of trends in the UK climate since 1914
41
42 using gridded datasets. London: Met Office, 2006.

43
44 55. Thompson WW, Weintraub E, Dhankhar P, et al. Estimates of US influenza-associated deaths
45
46 made using four different methods. *Influenza Other Respi Viruses* 2009;**3**:37-49.

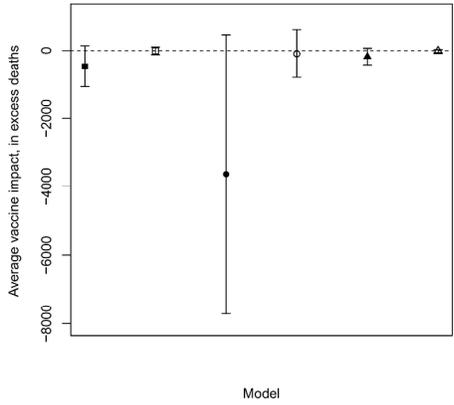
- 1
2 56. Kwong JC, Stukel TA, Lim J, et al. The Effect of Universal Influenza Immunization on Mortality
3
4 and Health Care Use. *PLoS Med* 2008;**5**:e211.
5
6
7 57. Grant AD, Eke B. Application of information technology to the laboratory reporting of
8
9 communicable disease in England and Wales. *Commun Dis Rep CDR Rev* 1993;**3**:R75-8.
10
11 58. Health Protection Agency Centre for Infections. Pneumococcal Vaccination Uptake Monitoring
12
13 on behalf of the Department of Health. [Accessed 18 Sept 2012]; Available from:
14
15 <http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/Pneumococcal/PPVUptake/>.
16
17
18
19 59. Baguelin M, Jit M, Miller E, et al. Health and economic impact of the seasonal influenza
20
21 vaccination programme in England. *Vaccine* 2012;**30**:3459-62.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



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 overlaid. 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.
297x420mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

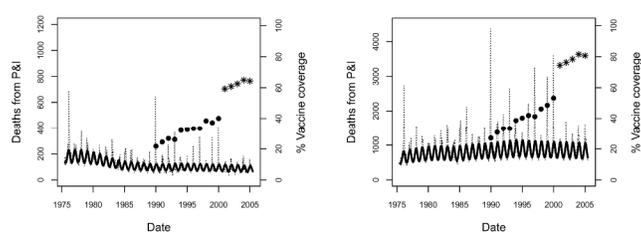


Summary of estimated vaccine impact from linear regression models of the binary effect of the switch to age group-based targeting of yearly influenza vaccination to all those 65 years of age and older (from 2000/01 onwards) compared to before 2000/01. Squares are the 65-74 age group, circles the 75+ 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.

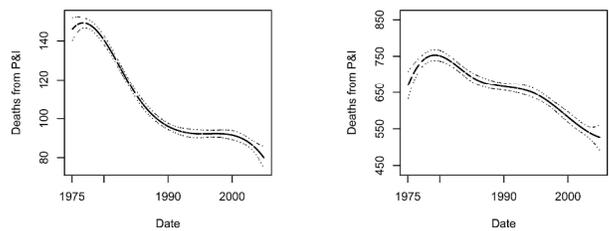
297x420mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

.....
.....
.....



(a) 65-74 yrs (b) 75+ yrs



(c) 65-74 yrs (d) 75+ yrs

.....
.....

Model fit: The observed time series of weekly P&I deaths in the a) 65-74 and 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 overlaid (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)

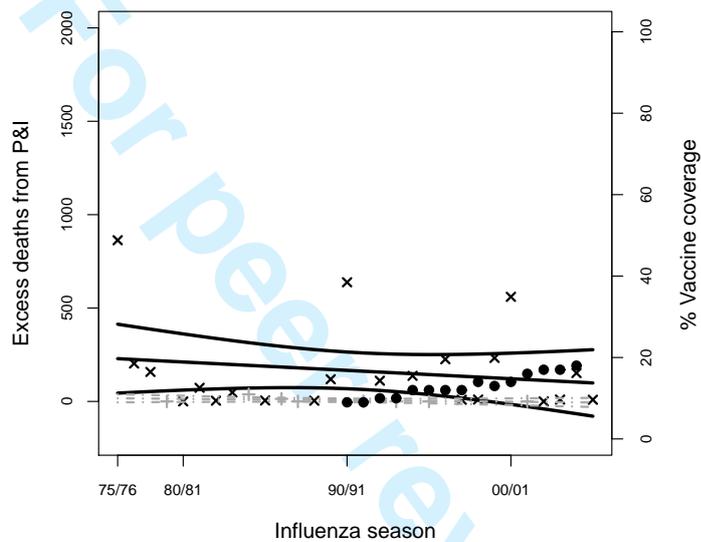
SUPPLEMENTARY FIGURES

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

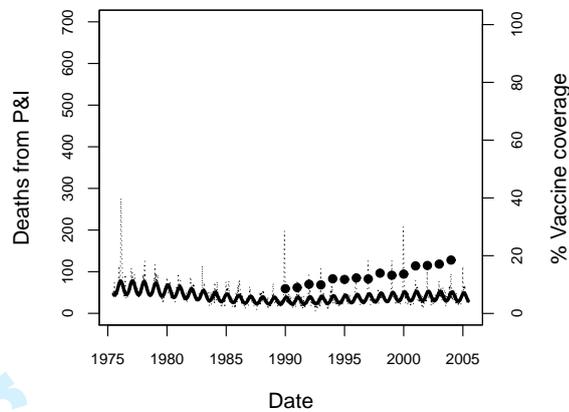
Authors: Andrea G. Mann, Punam Mangtani, Colin A. Russell, John C. Whittaker

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

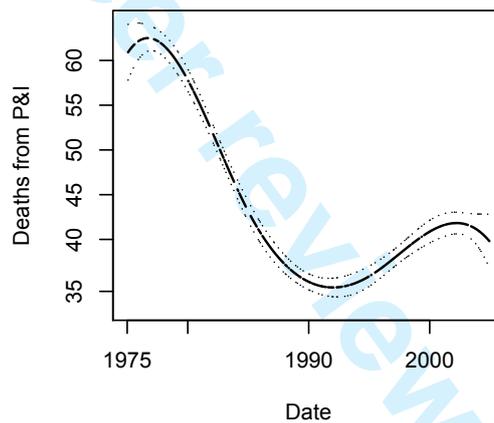


(a)

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 overlaid. Vaccine coverage in the 45-64 age group from published data is also shown (dots, right axis).



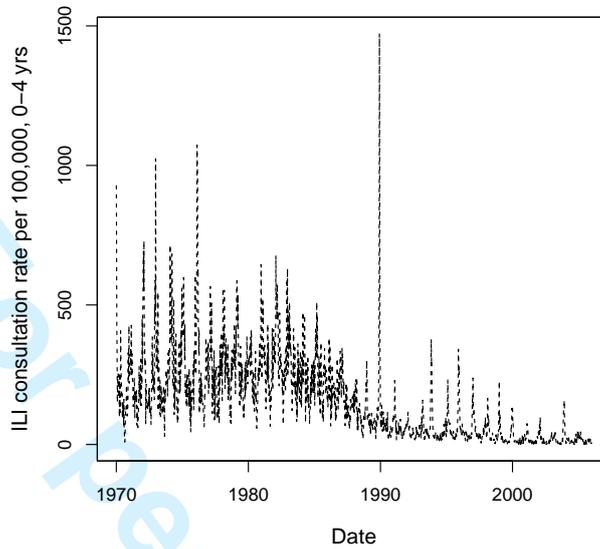
(a)



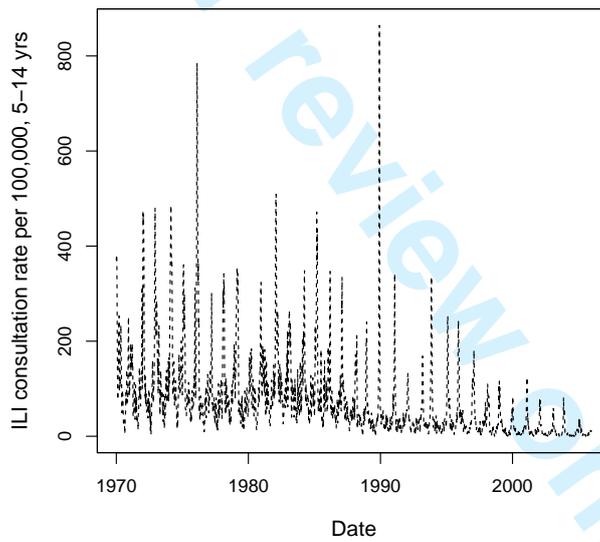
(b)

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 overlaid (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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

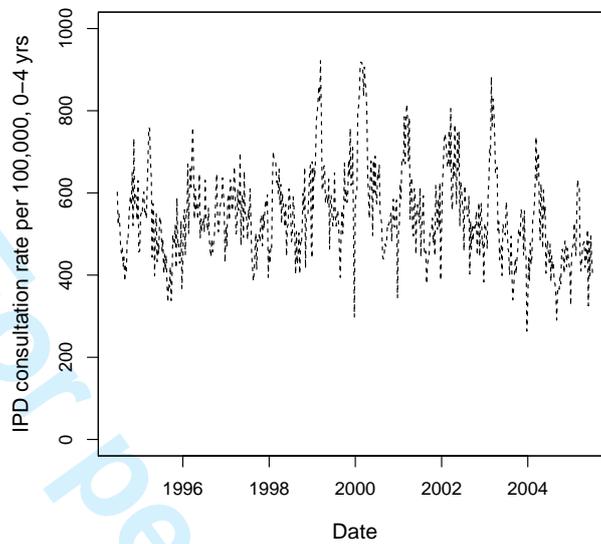


(a)

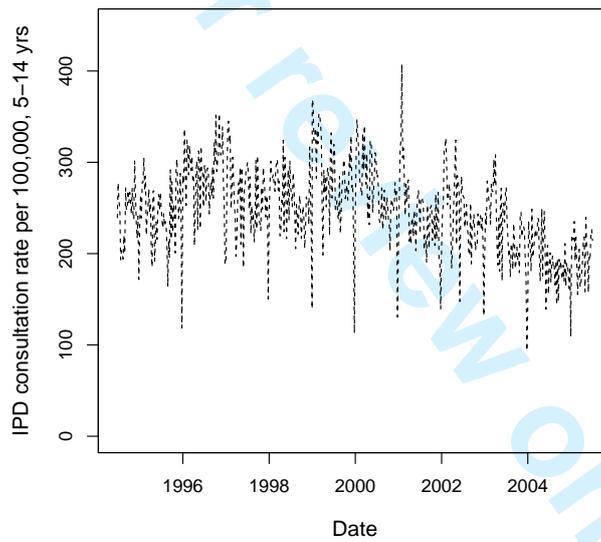


(b)

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.

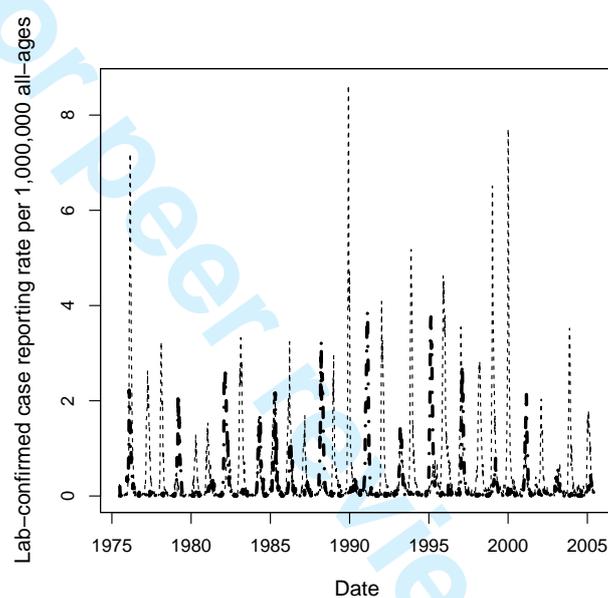


Figure 5: The weekly rate of laboratory reports for influenza A (light dotted line) and influenza B (dark dotted line) per 1,000,000 population, voluntarily reported to the Health Protection Agency Centre for Infections, England & Wales.

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.

References

1. Tillett HE, Smith JW, Clifford RE. Excess morbidity and mortality associated with influenza in England and Wales. *Lancet*. 1980;315(8172):793-5.
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

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

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+

1
2
3 age group from 2000/01-2004/05 was therefore derived by calculating the coverage for
4
5 those 65+ (regardless of risk group), using the method described above for the 45-64 age
6
7 group, for all years and determining the average ratio of coverage in the 75+ age group to
8
9 65+ age group for years when coverage in those 75+ was reported (1989/90-1999/00).
10
11 Multiplying coverage in the 65+ age group for 2000/01 by this average ratio gave estimated
12
13 coverage in the 75+ age group for 2000/01 (and so on for 2001/02-2004/05). The same
14
15 procedure was followed to estimate coverage for the 65-74 age group.
16
17
18

19 **Estimating excess and baseline mortality**

20
21 There are numerous approaches in the literature to quantifying excess mortality as a
22
23 measure of influenza severity and no gold standard approach. The different methods
24
25 produce different estimates of excess mortality when fitted to the same data.(3) We elected
26
27 to modify the method of Simonsen and colleagues,(4) used in their paper analysing
28
29 influenza vaccine impact in the US, to examine both excess mortality and the long-term
30
31 trend in non-excess mortality in relation to changes in vaccine policy and coverage. The
32
33 Simonsen method is a modification of Serfling's cyclical regression approach,(5) where non-
34
35 epidemic data are modeled to estimate expected mortality and mortality greater than
36
37 expected is labelled as excess, but improves on the specificity of Serfling's model in that
38
39 epidemic periods in the data are informed by a specific measure of influenza. We adapted
40
41 Simonsen's approach to the specifics of our data in two ways. We fitted log-linear negative
42
43 binomial, instead of Poisson, models to allow for overdispersion apparent in the P&I data
44
45 from England & Wales. Also, we used all-age laboratory reports for influenza A to inform
46
47 epidemic periods in the data instead of laboratory-confirmed influenza deaths because
48
49 there are too few laboratory-confirmed influenza deaths in England & Wales to allow them
50
51 to be modelled (a given year may have only 25 laboratory-confirmed influenza deaths
52
53
54
55
56
57
58
59
60

1
2
3 (Emma Gordon, personal communication)). Our modelling approach differed from
4
5 Simonsen's in two additional ways. Firstly, we controlled for the changing size of the
6
7 population at risk via the offset term rather than fitting models in fine age bands and
8
9 calculating age-standardized sums of excess deaths. Second, we directly modelled long-term
10
11 trend using cubic splines rather than first removing trend from the data with a smoothing
12
13 spline. This was done so that we could pull out the long-term trend component of the fitted
14
15 model to plot and visualise in its own right. Our approach to analysis is described in full
16
17 below.
18
19
20

21
22 An influenza year was defined as week 26 of one year to week 25 of the next
23
24 because the timing of influenza circulation during a given winter usually spans two calendar
25
26 years (i.e. extends from October of one year to March of the next year). Mortality and
27
28 laboratory data were collapsed into weekly counts for analysis. In order to differentiate
29
30 excess from baseline mortality we used laboratory data to estimate which were the
31
32 epidemic weeks in the time series. We then fitted models to the mortality time series to
33
34 determine both excess and baseline mortality with reference to these epidemic weeks.
35
36 Specifically, in the first instance we fitted a negative binomial model to all-age weekly
37
38 counts of laboratory-confirmed influenza A infections excluding counts from the period
39
40 when influenza is most likely to be circulating in the community (December to April, week
41
42 numbers 48 of one calendar year to 18 of the next (4)). This negative binomial model
43
44 included the following terms: as an offset the decennial census population of England &
45
46 Wales from census years and an inter-census estimate from years between censuses,(6)
47
48 cubic splines with 6 degrees of freedom to model trend, 1 Fourier term (ie. 1 sine and 1
49
50 cosine term) with period 52.2 weeks to model seasonality, and dummy variables to account
51
52 for minor artefacts. (An initial exploration of options to model trend as linear, quadratic or
53
54
55
56
57
58
59
60

1
2
3 with a cubic spline with up to 20 degrees of freedom (df) was undertaken to determine how
4
5 to fit trend (data not shown)). A time series of counts was predicted from this model when
6
7 refitted to the full time series of influenza A counts (i.e. not excluding Dec – Apr). The
8
9 epidemic threshold for each week was defined as the upper 95% confidence bound on the
10
11 predicted laboratory count for that week. We then fitted the same negative binomial model
12
13 (except with trend modeled using a cubic spline with 5 df, informed based on our earlier
14
15 model selection exercise) to the time series of death counts with December to April deleted.
16
17 We again predicted the time series of counts from this model refitted to the full time series
18
19 (i.e. without Dec-Apr excluded). Excess mortality was the sum of observed minus predicted
20
21 deaths in weeks when laboratory data breached their epidemic threshold, by influenza year.
22
23
24 Baseline trend in mortality incidence was approximated by fitting the negative binomial
25
26 model above to the death counts not labelled as excess. This model fit was then
27
28 deconstructed and just the spline (i.e. trend) component was plotted in order to graphically
29
30 assess its shape. Estimates of excess mortality and plots of baseline trends were determined
31
32 separately for the age groups 65-74, 75+ and 45-64 (the latter age group being “unexposed”
33
34 to a change in vaccine policy or coverage over the period). Any estimates of negative excess
35
36 mortality were recoded to 0. No model was stratified by sex because an initial exploration of
37
38 the data suggested similar trends by sex in the study period. A sensitivity analysis was
39
40 carried out defining epidemic periods based on counts of combined laboratory-confirmed
41
42 influenza A and influenza B virus infections (as opposed to the main analysis where this was
43
44 done using counts of influenza A infections only).
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

1. Butt S, Zhang N, Joseph CA. Vaccination uptake among the 65 years and over and under 65 years at risk in England 2006-07. London: Health Protection Agency Centre for Infections, 2007.
2. Joseph C, Goddard N, Gelb D. Influenza vaccine uptake and distribution in England and Wales using data from the General Practice Research Database, 1989/90-2003/04. *J Public Health (Oxf)*. 2005;27(4):371-7.
3. Thompson WW, Weintraub E, Dhankhar P, Cheng PY, Brammer L, Meltzer MI, et al. Estimates of US influenza-associated deaths made using four different methods. *Influenza Other Respi Viruses*. 2009;3(1):37-49.
4. Simonsen L, Reichert TA, Viboud C, Blackwelder WC, Taylor RJ, Miller MA. Impact of influenza vaccination on seasonal mortality in the US elderly population. *Arch Intern Med*. 2005;165(3):265-72.
5. Serfling RE. Methods of current statistical analysis of excess pneumonitis-influenza death. *Public Health Rep*. 1963;78(6):494-506.
6. Mid-year population estimates [database on the Internet]. [cited November 21st 2007]. Available from: <http://www.statistics.gov.uk/statbase/explorer.asp?CTG=3&SL=4819,4824,3880&D=4426&DCT=0&DT=32#4426>.
7. Met Office Hadley Centre Central England Temperature Data: Monthly HadCET mean [database on the Internet]. [cited 18 June 2008]. Available from: www.metoffice.gov.uk/research/hadleycentre/CR_data/Daily/HadCET_act.txt.
8. Smith DJ, Lapedes AS, de Jong JC, Bestebroer TM, Rimmelzwaan GF, Osterhaus ADME, et al. Mapping the Antigenic and Genetic Evolution of Influenza Virus. *Science*. 2004;305(5682):371-6.
9. Fleming DM. The contribution of influenza to combined acute respiratory infections, hospital admissions, and deaths in winter. *Commun Dis Public Health*. 2000;3(1):32-8.



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:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-002743.R1
Article Type:	Research
Date Submitted by the Author:	01-May-2013
Complete List of Authors:	Mann, Andrea; London School of Hygiene & Tropical Medicine, Infectious Disease Epidemiology mangtani, punam; London School of Hygiene & Tropical Medicine, Infectious Disease Epidemiology Russell, Colin; University of Cambridge, Zoology Whittaker, John; London School of Hygiene & Tropical Medicine, Non-communicable Disease Epidemiology
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases
Keywords:	Influenza, Mortality, Mass Vaccination, Aged, Trends

SCHOLARONE™
Manuscripts

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

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

Department of Infectious Disease Epidemiology, Faculty of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK Andrea G Mann Lecturer

Department of Infectious Disease Epidemiology, Faculty of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK Punam Mangtani Clinical Senior Lecturer

Department of Zoology, University of Cambridge, Downing Street, Cambridge, UK, CB2 3EJ and Fogarty International Center, National Institutes of Health, Bethesda, 20892-2220, USA Colin A Russell Research Fellow

Department of Non-Communicable Disease Epidemiology, Faculty of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK and Statistical Platforms and Technologies, GlaxoSmithKline, Medicines Research Centre, Mailstop 1S101, Gunnels Wood Road, Stevenage, SG1 2NY, UK John C Whittaker Professor

Correspondence to: A G Mann andrea.mann@lshtm.ac.uk

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

Key words: influenza; mortality; aged; mass vaccination; trends

Word count: 5026

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

1
2 difference. Trend in baseline pneumonia and influenza mortality shows an apparent downwards
3
4 turning point around 2000 for the 65-74 age group and from the mid-1990s in the 75+ age group.
5
6

7 Conclusions

8
9 There is weakly supportive evidence that the marked increases in vaccine coverage accompanying the
10
11 switch from risk-based to age group-based targeting of the elderly for yearly influenza vaccination in
12
13 England & Wales was associated with lower levels of pneumonia and influenza mortality in older
14
15 people in the first 6 years after age group-based targeting began. The possible impact of these policy
16
17 changes is observed both as weak evidence for lower average excess mortality and as a turning point
18
19 in baseline mortality coincident with the changes.
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2 Holland, all-cause excess mortality during influenza epidemics declined after the introduction of
3
4 universal yearly vaccination of those aged 65 and over.(14) In contrast, three other studies, in the US,
5
6 Italy and in Catalonia, did not detect an impact of rising vaccine coverage of the elderly on all-cause
7
8 excess mortality.(15-17) Previous studies of influenza attributable or excess mortality in the UK have
9
10 not related this to vaccination.(18-20)
11
12

13
14 While the level of mortality observed when influenza is circulating in the community (often
15
16 quantified using excess mortality) varies from winter to winter, baseline respiratory mortality (i.e.
17
18 excluding excess) has a seasonal pattern which is more or less constant from winter to winter, though
19
20 it may change over the long-term.(21) Previous studies of the long-term trends in influenza-related
21
22 mortality in England & Wales have covered earlier, and usually shorter, time periods. One study
23
24 examined trends in pneumonia or influenza (P&I) mortality in England & Wales from 1994/95 to
25
26 2000/01 and showed a plot of rates of P&I mortality in the 65-74 age group in this period which
27
28 appears to have little secular trend.(18) The shape of the trend in baseline respiratory mortality in
29
30 England & Wales since 2000/01 is unclear.
31
32
33
34
35
36

37 This work evaluates a public health initiative, to specifically target all people 65 years of age
38
39 and older for yearly influenza vaccination regardless of risk group, which has been in place since 2000.
40
41 Studying patterns in excess mortality and trends in baseline mortality in the years shortly following
42
43 the introduction of this initiative allows us to provide evidence for the impact of this policy.
44
45
46

47 **Methods**

48
49 Daily counts of deaths registered to underlying pneumonia or influenza (P&I) in England &
50
51 Wales between 1975 and 2005, by date of death, sex and age group, were provided by the Office for
52
53 National Statistics (ONS). Deaths registered to underlying P&I, not just confirmed influenza deaths,
54
55 were analysed because deaths from influenza are rarely laboratory confirmed and because deaths in
56
57
58
59
60

1
2 the elderly which occur secondary to influenza often result from pneumonia.(22, 23) P&I mortality
3
4 rates are a more specific measure of influenza activity than rates of all-cause mortality.(24)
5
6

7 The mortality data were adjusted by multiplying them by conversion factors estimated in a
8
9 separate analysis to account for the following historical modifications to how the data are coded so
10
11 that our assessment of trends would not be influenced by these artefactual step changes. The ICD
12
13 changed from version 8 to 9 in 1979, leading to a small decline in deaths coded to underlying P&I.(25)
14
15 In 1984, ONS introduced a broader interpretation of rule 3 for coding underlying cause of death,
16
17 which led to an abrupt fall in deaths registered to underlying pneumonia, and to a rise in deaths
18
19 registered to underlying cancer and ischemic heart disease.(26) In 1993, ONS adopted an automated
20
21 system for coding underlying cause of death which narrowed the interpretation of rule 3 and
22
23 approximately reversed the change adopted in 1984 (i.e. rates of deaths being registered to
24
25 underlying pneumonia rose back to a level approximately equal to that pre-1984).(27) With the
26
27 change from ICD 9 to 10 in 2000, deaths coded to underlying respiratory disease fell by approximately
28
29 22%, and deaths coded specifically to underlying pneumonia fell by 38%.(28)
30
31
32
33
34
35
36

37 The Health Protection Agency Centre for Infections (HPA CfI) provided an extract of all
38
39 individual reports of laboratory-confirmed influenza A infections between 1975 to 2005 from their
40
41 LabBase2 database. These reports, based on virus isolation and PCR, were reported voluntarily by
42
43 National Health Service (NHS) and HPA laboratories in England & Wales. Records included individuals'
44
45 age, sex and the earliest specimen date.
46
47
48

49 The statistical methods used are summarized below, with full details provided in the
50
51 supplementary material. Vaccine coverage estimates for 1989/90 to 2004/05 were adapted from
52
53 published sources. Published estimates of vaccine coverage were available by age group and
54
55 separately for persons considered at high or low risk of influenza complications.(2, 3) Separate
56
57
58
59
60

1
2 estimates by risk group were combined proportionately according to the number of each group
3
4 vaccinated to give coverage for that age group regardless of risk group.
5
6

7 There are numerous approaches in the literature to quantifying excess mortality as a measure
8
9 of influenza severity and no gold standard approach. We elected to modify the method of Simonsen
10 and colleagues,(15) used in their paper analysing influenza vaccine impact in the US, to examine both
11
12 excess mortality and the long-term trend in non-excess mortality in relation to changes in vaccine
13
14 policy and coverage. The Simonsen method is a modification of Serfling's cyclical regression
15
16 approach,(21) where non-epidemic data are modeled to estimate expected mortality and mortality
17
18 greater than expected is labelled as excess, but improves on the specificity of Serfling's model in that
19
20 epidemic periods in the data are informed by a specific measure of influenza.
21
22
23
24
25
26

27 An influenza year was defined as week 26 of one year to week 25 of the next because the
28
29 timing of influenza circulation during a given winter usually spans two calendar years (i.e. extends
30
31 from October of one year to March of the next year). Mortality and laboratory data were collapsed
32
33 into weekly counts for analysis. In order to differentiate excess from baseline mortality we used
34
35 laboratory data to estimate which were the epidemic weeks in the time series. We then fitted models
36
37 to the mortality time series to determine both excess and baseline mortality with reference to these
38
39 epidemic weeks. Excess mortality was the sum of observed minus predicted deaths in weeks when
40
41 laboratory data breached their epidemic threshold, by influenza year. Baseline trend in mortality
42
43 incidence was approximated by fitting the mortality model to the death counts not labelled as excess.
44
45 This model fit was then deconstructed and just the spline (i.e. trend) component was plotted in order
46
47 to graphically assess its shape for changes, or turning points, in the direction of the trend coincident
48
49 with policy changes. In the same way, estimates of excess mortality were plotted over time to look for
50
51 evidence of turning points in the trend. Estimates of excess mortality and plots of baseline trends
52
53
54
55
56
57
58
59
60

1
2 were determined separately for the age groups 65-74, 75+ and 45-64 (the latter age group being
3
4 “unexposed” to a change in vaccine policy or coverage over the period). Any estimates of negative
5
6 excess mortality were recoded to 0. No model was stratified by sex because an initial exploration of
7
8 the data suggested similar trends by sex in the study period. A sensitivity analysis was carried out
9
10 defining epidemic periods based on counts of combined laboratory-confirmed influenza A and
11
12 influenza B virus infections (as opposed to the main analysis where this was done using counts of
13
14 influenza A infections only).
15
16
17
18
19

20 To quantify vaccine impact on excess mortality, we fitted age group-specific regression models
21
22 of excess mortality for each influenza year against a) a dummy variable having a value of 0 for
23
24 1989/90 to 1999/00 and 1 for 2000/01 to 2004/05 to capture the start of the policy targeting all those
25
26 65+ for yearly influenza vaccination (exposure of interest), b) the minimum monthly temperature
27
28 observed in each influenza year,(29) c) whether the influenza season experienced a large antigenic
29
30 drift event or not,(30) and d) whether the influenza season was characterised by a mismatch between
31
32 vaccine and circulating H3N2 viruses or not (references in Table). Excess deaths are right skewed so
33
34 were transformed using $\log(\text{excess} + 1)$ to obtain a good approximation to normality. Models were
35
36 fitted separately for influenza A/H3N2 virus-dominated influenza seasons and for influenza seasons
37
38 dominated by other influenza virus subtypes. This was done to allow for greater mortality, and thus
39
40 potentially greater vaccine impact, in influenza seasons dominated by influenza A/H3N2 viruses than
41
42 those dominated by influenza A/H1N1 or B viruses.(31) Vaccine mismatch was not included in models
43
44 where the outcome was excess mortality in non-influenza A/H3N2 virus-dominated seasons because
45
46 both mismatch seasons were seasons when influenza A/H3N2 viruses dominated. Separate sensitivity
47
48 analyses were carried out a) defining the vaccine coverage dummy variable with reference to 1998/99
49
50 rather than 2000/01 (because 1998/99 was the first influenza year of age group-based targeting of
51
52
53
54
55
56
57
58
59
60

1
2 vaccination (to those 75+)) and b) modelling vaccination as a linear term, using derived estimates of
3
4 coverage by age group in each influenza year, rather than as a dummy variable.
5
6

7 To establish the extent of circulation of influenza in the community over the influenza years
8
9 studied, weekly rates of consultation for influenza-like illness (ILI), and for infectious and parasitic
10
11 diseases (which excludes ILI), with sentinel general practices in England & Wales for 0-4 and 5-14
12
13 years olds were plotted over time (data provided by the Royal College of General Practitioners weekly
14
15 returns service). We also plotted weekly, all-age rates of laboratory-reported influenza A and B
16
17 infections over time.
18
19
20

21
22 Models were fitted in R (R version 2.12.1 (2010-12-16), Copyright 2010 The R Foundation for
23
24 Statistical Computing).
25
26

27 Results

28
29
30 Weekly deaths registered to underlying P&I in those 65 years of age and older in England &
31
32 Wales in the period from 1975/76 to 2004/05 ranged from 34 deaths per 1,000,000 person weeks (in
33
34 week 36 of 1984) to 481 deaths per 1,000,000 person weeks (in week 7 of 1976).
35
36
37

38 Excess mortality

39
40 Excess mortality for the 65-74 age group ranged from 0 to just over 2000 deaths per influenza
41
42 year in the study period (Table). For the 75+ age group, the range was from 0 to over 14,000 deaths
43
44 per influenza year. Mortality attributable to epidemic influenza was highly variable year to year. For
45
46 neither age group does there appear to have been a turning point in the trend in excess mortality
47
48 coinciding with the 2000/01 season, when the policy of targeting all persons aged 65 and over for
49
50 yearly influenza vaccination was enacted (Figure 1). Similarly, there was no turning point in the trend
51
52 in excess mortality in the 75+ age group around 1998/99 when this age group became fully targeted
53
54 for yearly influenza vaccination. The direction of the trend in excess mortality over the whole time
55
56
57
58
59
60

1
2 period appears to be downwards or flat. Trend in excess mortality in the 45-64 age group is
3
4 approximately flat in the same period (Supplementary Figure 1). Mean excess mortality was lower
5
6 after the policy change for both the 65-74 and 75+ age groups but was also lower after 2000/01 than
7
8 before among 45-64 year olds (Supplementary table 2).
9
10

11 **Vaccine impact from multivariable regression**

12
13
14 Point estimates for the multiplicative effect that the policy change had on excess mortality
15
16 after 2000 compared to before, adjusting for cold weather and antigenic drift in influenza A/H3N2
17
18 viruses and stratified by dominant circulating virus subtype, are in the direction of lower excess
19
20 mortality after 2000 than before for both the 65-74 and 75+ age groups, except for mortality in
21
22 seasons dominated by influenza A/H1N1 or B viruses for the 75+ age group for which the coefficient
23
24 suggested higher mortality after the policy change but with a very wide confidence interval (Figure 2).
25
26 Point estimates indicate a modest impact in influenza A/H3N2 virus-dominated seasons, which is
27
28 unlikely to be due to chance for the 75+ age group, while in seasons dominated by influenza A/H1N1
29
30 or B viruses confidence intervals are wide and include no effect. These findings are robust to
31
32 modelling the vaccine policy change as occurring in 1998/99 instead of 2000/01 (data not shown). For
33
34 the 45-64 age group, point estimates suggest lower excess mortality after 2000 than before for
35
36 seasons dominated by influenza A/H3N2 viruses (Figure 2). For each of the three age groups,
37
38 modelling the effect of change in vaccine coverage as a linear instead of binary (dummy) variable
39
40 results in point estimates suggesting lower excess mortality per unit increase in vaccine coverage but
41
42 with wide confidence intervals including the null (data not shown).
43
44
45
46
47
48
49
50
51

52 **Trends in baseline mortality**

53
54 Long-term trends in mortality not labelled as excess, analysed as a proxy for baseline P&I
55
56 mortality, are complex, with three to four periods during which different trends were observed. For
57
58
59
60

1
2 the 65-74 age group, rates in the study period were highest until the late 1970s, declined to
3
4 approximately 1990, plateaued to 2000 and fell after 2000 (Figure 3). For the 75+ age group, rates
5
6 increased to the late 1970s, declined to the mid-1980s, plateaued to the mid-1990s and then fell. The
7
8 45-64 age group showed a broadly similar baseline trend to that of the 65-74 age group, though the
9
10 trend was more tortuous due to smaller numbers (Supplementary figure 2). Residuals from fitted
11
12 models were normally distributed with mean approximately 0 and standard deviation approximately
13
14 1 with some residual autocorrelation (data not shown). Findings are robust to defining epidemic
15
16 periods using laboratory reports of influenza A infections alone or to using both influenza A and B
17
18 infections for this purpose.
19
20
21
22
23

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

25
26
27 During the period 2000-2005, ILI consultations for 0-4 and 5-14 year olds were lower than
28
29 historically (supplementary fig 3). However, over the same time period consultations for infectious
30
31 and parasitic diseases (which excludes ILI) also appeared to decline, especially in the 5-14 year age
32
33 group (supplementary fig 4). Rates of laboratory reported influenza infections were lower in 2000-
34
35 2005 than in the decade prior. (supplementary fig 5). Rates in 2000-2005 were similar to those
36
37 observed around 1980 (figure 3).
38
39
40
41

42 **Discussion**

43 **Statement of principal findings**

44
45
46
47
48 There is weakly supportive evidence that the switch from risk-based to age group-based
49
50 targeting of influenza vaccination for older people was associated with lower influenza-related
51
52 mortality in the 4-6 years following this policy change. Results from our multivariable regression
53
54 suggest that this policy change had a weak, positive impact on excess mortality in both the 65-74 and
55
56 75+ age groups. There is no indication of a downwards turning point in the trend in excess mortality
57
58
59
60

1
2 around 2000/01 (when all those 65+ began to be targeted for vaccination) or 1998/99 (when those
3
4 75+ began to be targeted). There were fewer excess deaths, on average, in seasons after the policy
5
6 change than before (including in the 45-64 age group) which argues against a strong, specific impact
7
8 of the policy change on excess mortality. Trends in baseline, as opposed to excess, mortality do show
9
10 a suggestion of a downwards turning point in the mid-1990s for the 75+ age group and around 2000
11
12 for the 65-74 age group, coinciding approximately with the timing of the changes to specifically target
13
14 these age groups for vaccination. Results obtained by fitting the various models to data for the 45-64
15
16 age group, in whom vaccine coverage was largely static over the study period, are in a similar
17
18 direction but are of a smaller magnitude than the apparent impact in the 65-74 and 75+ age groups,
19
20 suggesting there may have been other factors acting to bring down P&I mortality at the time of the
21
22 policy changes. Thus our analysis is consistent with a small mortality impact in the 65-74 and 75+ age
23
24 groups during the six years after policies to wholly target these age groups for yearly influenza
25
26 vaccination were enacted.
27
28
29
30
31
32
33

34 **Strengths and weaknesses of the study**

35
36
37 There are a number of strengths to the work undertaken, as well as several limitations. The
38
39 key strengths are that we estimated excess mortality and long-term trend in mortality over a long
40
41 period (30 years). We carefully controlled for changes to death coding and laboratory practices which
42
43 occurred over this time period. The analytical approach we used, which is similar to one used by many
44
45 others,(15, 16) of modelling seasonality and trend using splines in addition to sinusoidal terms (full
46
47 details provided in the supplementary material), is a highly flexible method of fitting complex patterns
48
49 and trends that is especially helpful when modelling a long time series. The outcome we chose to
50
51 model (deaths from underlying P&I) is the most specific option available which allows sufficient
52
53 numbers of deaths for analysis. This choice maximised our ability to discern high mortality impact
54
55
56
57
58
59
60

1
2 influenza years from those less so, and thus to detect vaccine impact. Analysing underlying P&I of
3
4 course means our estimates of excess mortality underestimate the burden of mortality due to all
5
6 respiratory disease (which includes bronchitis), cardiovascular disease and other causes of death
7
8 which may be linked to influenza. (19, 20) However, it was not the aim of this work to estimate the
9
10 total mortality burden due to influenza. Further adding to the specificity of our outcome was our
11
12 designation of epidemic periods in the mortality data with reference to the time series of laboratory-
13
14 confirmed influenza A infections. Better still might have been to use influenza A/H3N2 infections, the
15
16 subtype most often associated with influenza years when there is substantial mortality,(53) but the
17
18 laboratory data available for this analysis were not broken down by subtype. The limitations of our
19
20 work include that our estimate of the extent of variability in excess mortality across influenza years is
21
22 likely to be an underestimate because our model failed to explain all variability in the mortality data
23
24 (as evidenced by a small amount of autocorrelation in residuals, data not shown). This may be
25
26 because we did not include temperature or other climatic variables in the models estimating excess
27
28 mortality. We did adjust for temperature in multivariable regression models of vaccine impact on
29
30 excess mortality and as such our analysis of vaccine impact should not be confounded by
31
32 temperature. However, our results regarding long-term trends in non-excess mortality may be
33
34 confounded by temperature as there is evidence that minimum winter temperatures have increased
35
36 since the early 1960s.(54) In using laboratory data to inform epidemic periods in the mortality data,
37
38 we made no allowance for a lag between the increase, or peak, in incidence of laboratory-reported
39
40 infections and the timing of excess deaths associated with these infections. This is likely to have led us
41
42 to underestimate excess mortality, assuming the peak in deaths rarely precedes and generally
43
44 coincides or follows the peak in laboratory reports. However, the rise in influenza activity in the
45
46 community in terms of GP consultations generally coincides with the rise in numbers of laboratory
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 reports of influenza infections,(36) and, during influenza years dominated by circulation of influenza A
2
3
4 viruses, peak weekly GP consultation rates for influenza-like illness in the 45–64, 65–74 and >=75
5
6
7 years age groups tend to coincide with same-age peaks in respiratory deaths, plus or minus 1 week
8
9
10 (e.g. 1995/1996, 1996/1997, 1998/1999 and 1999/2000).(18) Hence the potential bias in our
11
12 estimates of excess mortality is likely to be minimal because the weeks we might have missed by not
13
14 allowing for a lag will be close to the start or end of the period of influenza circulation and thus will
15
16 make up a small proportion of the total influenza attributable P&I deaths in a given winter. Our
17
18 estimates of long-term trends may be confounded by the trends in co-morbidities linked to smoking
19
20 or by long-term patterns in other co-morbidities associated with respiratory mortality, which we have
21
22 not accounted for. While it would have been possible to test for a change in slope of the long-term
23
24 trend with a piecewise linear approximation, we did not do this because issues of confounding by
25
26 these types of time-varying covariates, which we are only able to speculate about, would limit the
27
28 interpretability of any coefficient. Finally, the separate vaccine coverage estimates we present for the
29
30 65-74 and 75+ age groups from 2000/01 onwards are sensitive to our assumption of a constant ratio
31
32 of vaccine coverage in the 65-74 to 75+ age groups from 2000/01 onwards (described in the
33
34 supplementary file). The assumption of a constant ratio is unlikely to be true and as such we have
35
36 probably underestimated coverage in the 65-74 age group and overestimated it in the 75+ age group;
37
38 the increase in coverage in 2000/01 was probably disproportionately accounted for by an increase in
39
40 coverage in the 65-74 age group, newly targeted as fully “at risk” from the 2000/01 influenza season.
41
42 Our main findings are unaffected by this because we focus on results from regression models of the
43
44 effect of change in vaccination policy as a binary variable.
45
46
47
48
49
50
51
52
53
54

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

56
57 Using as a reference the previous estimates which exist of excess respiratory mortality in
58
59
60

1
2 England & Wales, our estimates appear to be a valid reflection of variability between years and
3
4 between age groups in influenza-attributable mortality. Findings as to vaccine impact from other
5
6 settings have been mixed, thus our observation of perhaps some limited impact is not inconsistent
7
8 with reports from other settings which analysed the impact of similar levels of vaccine coverage to
9
10 that achieved in the UK. Previous estimates of excess, all-age respiratory mortality for the influenza
11
12 years 1975/76, 1976/77 and 1977/78 are higher than our excess P&I estimates for these years but the
13
14 relative magnitude of the excess mortality between these years matches our estimates well.
15
16 (supplementary table 1). The absolute value of the previous estimates is higher than ours because the
17
18 authors included bronchitis deaths and analysed all-ages combined, not just the elderly. For the
19
20 influenza years 1994/95 to 1999/2000, published estimates of average influenza-attributable
21
22 respiratory mortality by age group (45-64, 65-74 and 75+) are higher than our averages for the same
23
24 age groups over the same period but ratios between different age groups are similar to our estimates.
25
26 Differences in the magnitude of estimates from the two methods will be because they include
27
28 bronchitis deaths and but also because the rate difference-type method used by Fleming and
29
30 colleagues tends to produce higher estimates of excess than the Serfling-type method we used, due
31
32 to a lower reference mortality and the mortality rate in the “influenza-active periods” being entirely
33
34 attributed to influenza.(55) There has been much interest in measuring the impact of influenza
35
36 vaccination campaigns in other settings.(14, 15, 17, 56) Excess all-cause mortality declined in Dutch
37
38 elderly after the introduction of universal yearly vaccination of those aged 65 and over which saw
39
40 yearly coverage reach 80%.(14) Excess all-cause mortality and influenza-related hospitalisations and
41
42 GP visits declined more in Ontario than in other Canadian provinces after the introduction of universal
43
44 yearly vaccination for all Ontario residents.(56) Analyses of the impact of rising vaccine coverage of
45
46 the elderly on excess all-cause mortality in the US, Italy and in Catalonia did not detect impact
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 northern 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

1
2 influenza circulating in 2000-2005 than previously since the decline in rates of infectious and parasitic
3
4 diseases rates then still needs explaining. It may in part be that there was progressively lower use of
5
6 GP services in the 2000-2005 period. Rates of laboratory reported influenza infections for all-ages,
7
8 reported to the HPA CfI, were certainly lower in 2000-2005 than in the decade prior, and were similar
9
10 to rates observed around 1980 when excess mortality also appeared to be low for several consecutive
11
12 years. It is difficult to interpret long-term trends in laboratory reports of influenza infections because
13
14 of changing testing practices and changing volumes of test requisitions over the time period. For
15
16 example, between 1975 and 1992, the number of laboratory reports of viral infections doubled (57);
17
18 this is unlikely to reflect a doubling of viral infections over this period. If more tests were requisitioned
19
20 in 2000-2005 than in the years around 1980 similar rates of positive reports in the two periods would
21
22 suggest less viral activity in 2000-2005 than around 1980. However, it is hard to see how less influenza
23
24 in circulation later than earlier in the study period could explain a turning point in baseline mortality
25
26 in the 65-74 and 75+ age groups approximately coincident with policy changes to specifically target
27
28 these age groups for vaccination. We think the observation of a turning point in baseline mortality
29
30 reflects partly a non-specific impact of influenza vaccination on respiratory mortality in the elderly
31
32 that is not directly attributable to influenza as well as partly a specific impact of influenza vaccination
33
34 given that analysing excess mortality necessarily means some truly influenza-attributable mortality
35
36 (i.e. that which does not breach the epidemic threshold) contributes to baseline. A further possible
37
38 alternative explanation for the apparent, small influenza vaccine impact we have observed is that this
39
40 is really an impact of pneumococcal vaccination. This is unlikely to be true; to the end of the 2004/05
41
42 influenza year, less than 30% of people 65 years of age and over had received the recommended 23-
43
44 valent pneumococcal polysaccharide vaccine.(58) Pneumococcal conjugate vaccination of infants and
45
46 children, which might be expected to provide indirect protection to the elderly, has only been
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2 routinely recommended since 2006. It is possible that there is some other factor which also changed
3
4 over the time period and which explains part of the mortality impact we observed (e.g. trends in co-
5
6 morbidity linked to smoking).
7
8

9 10 **Unanswered questions and future research**

11
12 Influenza vaccine impact can be difficult to measure due to its reliance on surveillance data
13
14 which are generally not collected in a consistent way over time, and because of the variable nature of
15
16 influenza activity over time. One way of adding to the evidence base is to look at vaccine
17
18 effectiveness. In order to strengthen the evidence base for influenza vaccine effectiveness in the
19
20 elderly, further good quality cohort and case-control studies across multiple influenza seasons with
21
22 varying degrees of match between vaccine and circulating variants, and adequate control for negative
23
24 confounding by indication (sicker elderly being preferentially offered vaccination) and positive
25
26 confounding by healthier older people putting themselves forward for vaccination, are required. It
27
28 remains unclear to what extent our findings are due to there being less influenza around 2000-2005
29
30 than before this time or to confounding by factors such as trends in co-morbidities linked to smoking.
31
32 Analyses including more recent influenza seasons, which experienced a pandemic (2009/10) and a
33
34 severe influenza season dominated by H1N1pdm09 virus (2010/11) and which saw vaccine uptake of
35
36 the elderly further increase, will help to answer these questions and to monitor whether the modest
37
38 mortality impact we observed in the 6 years after age group-based targeting of vaccination began has
39
40 been sustained. This analysis will be complicated by the presence of pneumococcal vaccination of
41
42 infants and the elderly, making teasing apart the effects of how much influenza circulated during the
43
44 time period, the impact of influenza vaccination and the impact of pneumococcal vaccination a
45
46 challenge. A way of addressing this would be to calculate attack rates based on serological data now
47
48 being collected by the HPA CfI.
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2 relationships or activities that could appear to have influenced the submitted work.
3
4

5 **Contributors**

6
7
8 AGM, PM and JCW conceived of the study, AGM conducted the analysis, led on the
9
10 interpretation and wrote the paper; JCW, PM and CAR contributed to interpretation and to
11
12 subsequent drafts of the paper. All authors approved the final version to be published. AGM is the
13
14 guarantor for the study. P&I data were provided by Cleo Rooney and Emma Gordon from the Office
15
16 for National Statistics. Laboratory data were provided by Carol Joseph and Joy Field of the Health
17
18 Protection Agency Centre for Infections. GP consultation data were provided by Douglas Fleming and
19
20 Alex Elliot of the Royal College of General Practitioners.
21
22
23

24 **Acknowledgements**

25
26
27
28
29 We are very grateful to the reviewers' whose comments greatly improved this paper.
30
31
32
33

34 **Funding**

35
36
37 This work was supported by a Researcher Development Award to AGM from the National
38
39 Institute of Health Research, UK [fellowship grant number RDA06/068]. The funder had no role in the
40
41 study design, in the collection, analysis, or interpretation of data, in the writing of the report or in the
42
43 decision to submit the article for publication. We the authors are independent from the funders.
44
45
46

47 **Access**

48
49
50 AGM had full access to all of the data in the study and takes responsibility for the integrity of
51
52 the data and the accuracy of the data analysis.
53
54

55 **Data sharing**

1
2 There are no additional data available.
3
4

5 **Ethics**

6
7
8 This study was approved by the ethics committee of the London School of Hygiene & Tropical
9
10 Medicine (approval number 5109).
11

12 **Licence**

13
14
15
16 The Corresponding Author has the right to grant on behalf of all authors and does grant on
17
18 behalf of all authors, an exclusive licence on a worldwide basis to the BMJ Publishing Group Ltd and
19
20 its Licensees to permit this article (if accepted) to be published in BMJ editions and any other BMJPG
21
22 products and sublicences to exploit all subsidiary rights, as set out in our licence (
23
24 <http://resources.bmj.com/bmj/authors/checklists-forms/licence-for-publication>).
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2 **Table title**
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Tab: Influenza seasons in England & Wales, 1974/75-2004/05: dominant variant, antigenic drift events in evolution 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.

For peer review only

1
2 **Figure legends**
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2 **Fig 1:** Excess mortality in the a) 65-74 and b) 75+ age groups in each influenza season in England &
3 Wales, stratified by the dominant influenza virus in circulation (black 'x' = A/H3N2 viruses were
4 dominant or co-dominant; grey '+' = A/H1N1 or B viruses were dominant). Vaccine coverage in the
5 respective age group from published data is also shown (dots and asterisks, right axis). Asterisks
6 indicate that vaccine coverage in these years was inferred from observed vaccine coverage in the 65+
7 age group and the average ratio of coverage in the 65+ to 65-74 (or 75+) age group.
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2 **Fig 2:** Summary of estimated vaccine impact from $\log(\text{excess} + 1)$ regression models of the binary
3 effect of the switch to age group-based targeting of yearly influenza vaccination to all those 65 years
4 of age and older (from 2000/01 onwards) compared to before 2000/01. Coefficients are shown on the
5 original scale and are therefore multiplicative. Squares are the 65-74 age group, circles the 75+ age
6 group and triangles the 45-64 age group. Filled symbols represent seasons dominated by influenza
7 A/H3N2 viruses, open symbols seasons dominated by influenza A/H1N1 or B viruses.
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2 **Fig 3:** Model fit: The observed time series of weekly P&I deaths in the a) 65-74 sand b) 75+ age group
3 in England & Wales between 1975 and 2005 (light dotted line on each plot). The fitted curve from the
4 log-linear Simonsen-like model fitted excluding December to April and accounting for seasonality,
5 long-term trend and artefacts is overlaid (dark line). Vaccine coverage (in the 65-74 and 75+ age
6 groups) adapted from published data is shown on the right axis of each plot (dots and asterisks).
7 Asterisks indicate that vaccine coverage in these years was inferred from observed vaccine coverage
8 in the 65+ age group and the average ratio of coverage in the 65-74 (or 75+) to 65+ age group. The
9 fitted curve can be deconstructed into its constituent parts. Thus c) and d) show just the long-term
10 trend (i.e. cubic spline) component of the fitted curve (dark lines), with its 95% confidence interval
11 (light lines), for the 65-74 and 75+ age groups, respectively. Doing this allows a better visualisation of
12 the shape of the long-term trend.
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

References

1. Department of Health: From the Chief Medical Officer, the Chief Nursing Officer and the Chief Pharmaceutical Officer. Influenza immunisation. PL/CMO/2000/3. London: Department of Health, 2000.
2. Joseph C, Goddard N, Gelb D. Influenza vaccine uptake and distribution in England and Wales using data from the General Practice Research Database, 1989/90-2003/04. *J Public Health (Oxf)* 2005;**27**:371-7.
3. Butt S, Zhang N, Joseph CA. Vaccination uptake among the 65 years and over and under 65 years at risk in England 2006-07. London: Health Protection Agency Centre for Infections, 2007.
4. Begum F, Pebody R. Seasonal influenza vaccine uptake amongst GP patient groups in England. London: Department of Health, 2012.
5. Fedson DS, Nichol KL. Influenza vaccination: policy versus evidence: no gap between policy and evidence. *BMJ* 2006;**333**:1020.
6. Jefferson T. Influenza vaccination: policy versus evidence. *BMJ* 2006;**333**:912-5.
7. Mangtani P, Hall AJ, Armstrong BG. Influenza vaccination: the case for a gap in the evidence is flawed. *BMJ* 2006;**333**.
8. Simonsen L, Viboud C, Taylor R. Influenza vaccination in elderly people. *Lancet* 2005;**366**:2086.
9. Jefferson T, Di Pietrantonj C, Al-Ansary LA, et al. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev* 2010:CD004876.
10. Osterholm MT, Kelley NS, Sommer A, et al. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;**12**:36-44.
11. Govaert TM, Thijs CT, Masurel N, et al. The efficacy of influenza vaccination in elderly

- 1
2 individuals. A randomized double-blind placebo-controlled trial. *JAMA* 1994;**272**:1661-5.
3
4
5 12. Mangtani P, Cumberland P, Hodgson CR, et al. A cohort study of the effectiveness of influenza
6
7 vaccine in older people, performed using the United Kingdom general practice research database. *J*
8
9 *Infect Dis* 2004;**190**:1-10.
10
11
12 13. Ortqvist A, Granath F, Askling J, et al. Influenza vaccination and mortality: prospective cohort
13
14 study of the elderly in a large geographical area. *Eur Respir J* 2007;**30**:414-22.
15
16
17 14. Jansen AGSC, Sanders EAM, Nichol KL, et al. Decline in influenza-associated mortality among
18
19 Dutch elderly following the introduction of a nationwide vaccination program. *Vaccine* 2008;**26**:5567-
20
21 74.
22
23
24 15. Simonsen L, Reichert TA, Viboud C, et al. Impact of influenza vaccination on seasonal mortality
25
26 in the US elderly population. *Arch Intern Med* 2005;**165**:265-72.
27
28
29 16. Rizzo C, Viboud C, Montomoli E, et al. Influenza-related mortality in the Italian elderly: no
30
31 decline associated with increasing vaccination coverage. *Vaccine* 2006;**24**:6468-75.
32
33
34 17. Muñoz MP, Soldevila N, Martínez A, et al. Influenza vaccine coverage, influenza-associated
35
36 morbidity and all-cause mortality in Catalonia (Spain). *Vaccine* 2011;**29**:5047-52.
37
38
39 18. Fleming DM, Cross KW, Pannell RS. Influenza and its relationship to circulatory disorders.
40
41 *Epidemiol Infect* 2005;**133**:255-62.
42
43
44 19. Hardelid P, Pebody R, Andrews N. Mortality caused by influenza and respiratory syncytial virus
45
46 by age group in England and Wales 1999–2010. *Influenza Other Respi Viruses* 2013;**7**:35-45.
47
48
49 20. Pitman RJ, Melegaro A, Gelb D, et al. Assessing the burden of influenza and other respiratory
50
51 infections in England and Wales. *J Infect* 2007;**54**:530-8.
52
53
54 21. Serfling RE. Methods of current statistical analysis of excess pneumonitis-influenza death. *Public*
55
56 *Health Rep* 1963;**78**:494-506.
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
22. Fleming D, Wood M. The clinical diagnosis of influenza. *Curr Med Res Opin* 2002;**18**:338-41.
 23. Barker WH, Mullooly JP. Underestimation of the role of pneumonia and influenza in causing excess mortality. *Am J Public Health* 1981;**71**:643-5.
 24. Housworth J, Langmuir AD. Excess mortality from epidemic influenza, 1957-1966. *Am J Epidemiol* 1974;**100**:40-8.
 25. Janssen F, Kunst AE. ICD coding changes and discontinuities in trends in cause-specific mortality in six European countries, 1950-99. *Bull World Health Organ* 2004;**82**:904-13.
 26. Devis T, Rooney C. Death certification and the epidemiologist. *Health Stat Quarterly* 1999;**01**:21-33.
 27. Rooney C, Griffiths C, Cook L. The implementation of ICD-10 for cause of death coding - some preliminary results from the bridge coding study. *Health Stat Quarterly* 2002;**13**:31-41.
 28. Brock A, Griffiths C, Rooney C. The impact of introducing ICD-10 on analysis of respiratory mortality trends in England and Wales. *Health Stat Quarterly* 2006;**29**:9-17.
 29. Met Office Hadley Centre Central England Temperature Data: Monthly HadCET mean [database on the Internet]. [Accessed 18 June 2008]. Available from: www.metoffice.gov.uk/research/hadleycentre/CR_data/Daily/HadCET_act.txt.
 30. Smith DJ, Lapedes AS, de Jong JC, et al. Mapping the Antigenic and Genetic Evolution of Influenza Virus. *Science* 2004;**305**:371-6.
 31. Fleming DM. The contribution of influenza to combined acute respiratory infections, hospital admissions, and deaths in winter. *Commun Dis Public Health* 2000;**3**:32-8.
 32. Pereira MS, Chakraverty P. Influenza in the United Kingdom 1977-1981. *J Hyg (Lond)* 1982;**88**:501-12.
 33. Pereira M, Assaad FA, Delon PJ. Influenza surveillance. *Bull World Health Organ* 1978;**56**:192-

- 1
2 203.
3
4
5 34. Chakraverty P, Cunningham P, Shen GZ, et al. Influenza in the United Kingdom 1982-85. *J Hyg*
6
7 (*Lond*) 1986;**97**:347-58.
8
9
10 35. Smith DJ, Forrest S, Ackley DH, et al. Variable efficacy of repeated annual influenza
11
12 vaccination. *Proc Natl Acad Sci U S A* 1999;**96**:14001-6.
13
14 36. Fleming DM, Zambon M, Bartelds AI, et al. The duration and magnitude of influenza
15
16 epidemics: a study of surveillance data from sentinel general practices in England, Wales and the
17
18 Netherlands. *Eur J Epidemiol* 1999;**15**:467-73.
19
20
21
22 37. Recommended composition of influenza virus vaccines for use in the 1989-1990 season. *Wkly*
23
24 *Epidemiol Rec* 1989;**64**:53-60.
25
26
27 38. Recommended composition of influenza virus vaccines for use in the 1990-1991 season. *Wkly*
28
29 *Epidemiol Rec* 1990;**65**:53-6.
30
31
32 39. Joseph CA, Dedman D, Fern K, et al. Influenza surveillance in England and Wales: November
33
34 1991-June 1992. *Commun Dis Rep CDR Rev* 1992;**2**:R149-52.
35
36
37 40. Dedman D, Joseph CA, Chakraverty P, et al. Influenza surveillance, England and Wales: October
38
39 1992-June 1993. *Commun Dis Rep CDR Rev* 1993;**3**:R184-6.
40
41
42 41. Dedman DJ, Joseph CA, Chakraverty P, et al. Influenza surveillance, England and Wales:
43
44 October 1993 to June 1994. *Commun Dis Rep CDR Rev* 1994;**4**:R164-8.
45
46
47 42. Hutchinson EJ, Joseph CA, Chakraverty P, et al. Influenza surveillance in England and Wales:
48
49 October 1994 to June 1995. *Commun Dis Rep CDR Rev* 1995;**5**:R200-4.
50
51
52 43. Hutchinson EJ, Joseph CA, Zambon M, et al. Influenza surveillance in England and Wales:
53
54 October 1995 to June 1996. *Commun Dis Rep CDR Rev* 1996;**6**:R163-9.
55
56
57 44. Dedman DJ, Joseph CA, Zambon M, et al. Influenza surveillance in England and Wales: October
58
59
60

1
2 1996 to June 1997. *Commun Dis Rep CDR Rev* 1997;**7**:R212-9.

3
4 45. Dedman DJ, Zambon M, Buynder PV, et al. Influenza surveillance in England and Wales:
5
6 October 1997 to June 1998. *Commun Dis Public Health* 1998;**1**:244-51.

7
8 46. Whiting P, Joseph CA, Zambon M, et al. Influenza activity in England and Wales: October 1998
9
10 to June 1999. *Commun Dis Public Health* 1999;**2**:273-9.

11
12 47. Goddard NL, Joseph CA, Zambon M, et al. Influenza surveillance in England and Wales:
13
14 October 1999 to May 2000. *Commun Dis Public Health* 2000;**3**:261-6.

15
16 48. Goddard NL, Joseph CA, Zambon M, et al. Influenza surveillance in the United Kingdom:
17
18 October 2000 to May 2001. *Commun Dis Rep CDR Suppl* 2001:1-7.

19
20 49. Crofts JP, Goddard NL, Joseph CA, et al. Influenza surveillance in the United Kingdom: October
21
22 2001 to May 2002. *Commun Dis Rep CDR Suppl* 2002:1-7.

23
24 50. Crofts JP, Joseph CA, Zambon M, et al. Influenza surveillance in the United Kingdom: October
25
26 2002 to May 2003. *Commun Dis Rep CDR Suppl* 2004;**14**:1-9.

27
28 51. Cooke MK, Crofts JP, Joseph CA, et al. Influenza and other respiratory viruses surveillance in
29
30 the United Kingdom: October 2003 to May 2004. *Commun Dis Rep CDR Suppl* 2005;**15**:1-8.

31
32 52. Zhao H, Cooke MK, Joseph CA, et al. Surveillance of influenza and other respiratory viruses in
33
34 the United Kingdom: October 2004 to May 2005. *Commun Dis Rep CDR Suppl* 2006;**16**:1-8.

35
36 53. Thompson WW, Shay DK, Weintraub E, et al. Mortality Associated With Influenza and
37
38 Respiratory Syncytial Virus in the United States. *JAMA* 2003;**289**:179-86.

39
40 54. Perry M. Climate memorandum no 21: A spatial analysis of trends in the UK climate since 1914
41
42 using gridded datasets. London: Met Office, 2006.

43
44 55. Thompson WW, Weintraub E, Dhankhar P, et al. Estimates of US influenza-associated deaths
45
46 made using four different methods. *Influenza Other Respi Viruses* 2009;**3**:37-49.

- 1
2 56. Kwong JC, Stukel TA, Lim J, et al. The Effect of Universal Influenza Immunization on Mortality
3
4 and Health Care Use. *PLoS Med* 2008;**5**:e211.
5
6
7 57. Grant AD, Eke B. Application of information technology to the laboratory reporting of
8
9 communicable disease in England and Wales. *Commun Dis Rep CDR Rev* 1993;**3**:R75-8.
10
11 58. Health Protection Agency Centre for Infections. Pneumococcal Vaccination Uptake Monitoring
12
13 on behalf of the Department of Health. [Accessed 18 Sept 2012]; Available from:
14
15 <http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/Pneumococcal/PPVUptake/>.
16
17
18
19 59. Baguelin M, Jit M, Miller E, et al. Health and economic impact of the seasonal influenza
20
21 vaccination programme in England. *Vaccine* 2012;**30**:3459-62.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

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

Department of Infectious Disease Epidemiology, Faculty of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK Andrea G Mann Lecturer

Department of Infectious Disease Epidemiology, Faculty of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK Punam Mangtani Clinical Senior Lecturer

Department of Zoology, University of Cambridge, Downing Street, Cambridge, UK, CB2 3EJ and Fogarty International Center, National Institutes of Health, Bethesda, 20892-2220, USA Colin A Russell Research Fellow

Department of Non-Communicable Disease Epidemiology, Faculty of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK and Statistical Platforms and Technologies, GlaxoSmithKline, Medicines Research Centre, Mailstop 1S101, Gunnels Wood Road, Stevenage, SG1 2NY, UK John C Whittaker Professor

Correspondence to: A G Mann andrea.mann@lshtm.ac.uk

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

Key words: influenza; mortality; aged; mass vaccination; trends

Word count: [48165026](#)

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](#)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](#) [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

1
2
3
4
5
6
7
8 targeting began compared to before but [the confidence interval for the 65-74 age groups](#) includes no
9 difference. Trend in baseline pneumonia and influenza mortality shows an apparent downwards
10 turning point around 2000 for the 65-74 age group and from the mid-1990s in the 75+ age group.
11
12

13 Conclusions

14
15
16 There is weakly supportive evidence that the marked increases in vaccine coverage accompanying the
17 switch from risk-based to age group-based targeting of the elderly for yearly influenza vaccination in
18 England & Wales was associated with lower levels of pneumonia and influenza mortality in older
19 people in the first 6 years after age group-based targeting began. The possible impact of these policy
20 changes is observed both as weak evidence for lower average excess mortality and as a turning point
21 in baseline mortality coincident with the changes. [Further work is required to exclude residual](#)
22 [confounding.](#)
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4
5
6
7
8 the elderly which occur secondary to influenza often result from pneumonia.(22, 23) P&I mortality
9 rates are a more specific measure of influenza activity than rates of all-cause mortality.(24)

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

23
24 The Health Protection Agency Centre for Infections (HPA CfI) provided an extract of all
25 individual reports of laboratory-confirmed influenza A infections between 1975 to 2005 from their
26 LabBase2 database. These reports, based on virus isolation and PCR, were reported voluntarily by
27 National Health Service (NHS) and HPA laboratories in England & Wales. Records included individuals'
28 age, sex and the earliest specimen date.

29
30 The statistical methods used are summarized below, with full details provided in the
31 supplementary material. Vaccine coverage estimates for 1989/90 to 2004/05 were adapted from
32 published sources. Published estimates of vaccine coverage were available by age group and
33 separately for persons considered at high or low risk of influenza complications.(2, 3) Separate

1
2
3
4
5
6
7
8 estimates by risk group were combined proportionately according to the number of each group
9 vaccinated to give coverage for that age group regardless of risk group.
10

11
12 There are numerous approaches in the literature to quantifying excess mortality as a measure
13 of influenza severity and no gold standard approach. We elected to modify the method of Simonsen
14 and colleagues,(15) used in their paper analysing influenza vaccine impact in the US, to examine both
15 excess mortality and the long-term trend in non-excess mortality in relation to changes in vaccine
16 policy and coverage. The Simonsen method is a modification of Serfling's cyclical regression
17 approach,(21) where non-epidemic data are modeled to estimate expected mortality and mortality
18 greater than expected is labelled as excess, but improves on the specificity of Serfling's model in that
19 epidemic periods in the data are informed by a specific measure of influenza.
20
21

22
23 An influenza year was defined as week 26 of one year to week 25 of the next because the
24 timing of influenza circulation during a given winter usually spans two calendar years (i.e. extends
25 from October of one year to March of the next year). Mortality and laboratory data were collapsed
26 into weekly counts for analysis. In order to differentiate excess from baseline mortality we used
27 laboratory data to estimate which were the epidemic weeks in the time series. We then fitted models
28 to the mortality time series to determine both excess and baseline mortality with reference to these
29 epidemic weeks. Excess mortality was the sum of observed minus predicted deaths in weeks when
30 laboratory data breached their epidemic threshold, by influenza year. Baseline trend in mortality
31 incidence was approximated by fitting the mortality model to the death counts not labelled as excess.
32 This model fit was then deconstructed and just the spline (i.e. trend) component was plotted in order
33 to graphically assess its shape for changes, or turning points, in the direction of the trend coincident
34 with policy changes. In the same way, estimates of excess mortality were plotted over time to look for
35 evidence of turning points in the trend. Estimates of excess mortality and plots of baseline trends
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52

53 7
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8 were determined separately for the age groups 65-74, 75+ and 45-64 (the latter age group being
9 “unexposed” to a change in vaccine policy or coverage over the period). Any estimates of negative
10 excess mortality were recoded to 0. No model was stratified by sex because an initial exploration of
11 the data suggested similar trends by sex in the study period. A sensitivity analysis was carried out
12 defining epidemic periods based on counts of combined laboratory-confirmed influenza A and
13 influenza B virus infections (as opposed to the main analysis where this was done using counts of
14 influenza A infections only).

21
22 To quantify vaccine impact on excess mortality, we fitted age group-specific ~~linear~~-regression
23 models of excess mortality for each influenza year against a) a dummy variable having a value of 0 for
24 1989/90 to 1999/00 and 1 for 2000/01 to 2004/05 to capture the start of the policy targeting all those
25 65+ for yearly influenza vaccination (exposure of interest), b) the minimum monthly temperature
26 observed in each influenza year,(29) c) whether the influenza season experienced a large antigenic
27 drift event or not,(30) and d) whether the influenza season was characterised by a mismatch between
28 vaccine and circulating H3N2 viruses or not (references in Table). [Excess deaths are right skewed so](#)
29 [we transformed using log\(excess + 1\) to obtain a good approximation to normality](#). Models were
30 fitted separately for influenza A/H3N2 virus-dominated influenza seasons and for influenza seasons
31 dominated by other influenza virus subtypes. This was done to allow for greater mortality, and thus
32 potentially greater vaccine impact, in influenza seasons dominated by influenza A/H3N2 viruses than
33 those dominated by influenza A/H1N1 or B viruses.(31) Vaccine mismatch was not included in models
34 where the outcome was excess mortality in non-influenza A/H3N2 virus-dominated seasons because
35 both mismatch seasons were seasons when influenza A/H3N2 viruses dominated. Separate sensitivity
36 analyses were carried out a) defining the vaccine coverage dummy variable with reference to 1998/99
37 rather than 2000/01 (because 1998/99 was the first influenza year of age group-based targeting of
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8 vaccination (to those 75+) and b) modelling vaccination as a linear term, using derived estimates of
9 coverage by age group in each influenza year, rather than as a dummy variable.
10

11 To establish the extent of circulation of influenza in the community over the influenza years
12 studied, weekly rates of consultation for influenza-like illness (ILI), and for infectious and parasitic
13 diseases (which excludes ILI), with sentinel general practices in England & Wales for 0-4 and 5-14
14 years olds were plotted over time (data provided by the Royal College of General Practitioners weekly
15 returns service). We also plotted weekly, all-age rates of laboratory-reported influenza A and B
16 infections over time.
17
18
19
20
21
22

23 Models were fitted in R (R version 2.12.1 (2010-12-16), Copyright 2010 The R Foundation for
24 Statistical Computing).
25
26

27 **Results**

28
29 Weekly deaths registered to underlying P&I in those 65 years of age and older in England &
30 Wales in the period from 1975/76 to 2004/05 ranged from 34 deaths per 1,000,000 person weeks (in
31 week 36 of 1984) to 481 deaths per 1,000,000 person weeks (in week 7 of 1976).
32
33
34
35

36 **Excess mortality**

37
38 Excess mortality for the 65-74 age group ranged from 0 to just over 2000 deaths per influenza
39 year in the study period (Table). For the 75+ age group, the range was from 0 to over 14,000 deaths
40 per influenza year. Mortality attributable to epidemic influenza was highly variable year to year. For
41 neither age group does there appear to have been a turning point in the trend in excess mortality
42 coinciding with the 2000/01 season, when the policy of targeting all persons aged 65 and over for
43 yearly influenza vaccination was enacted (Figure 1). Similarly, there was no turning point in the trend
44 in excess mortality in the 75+ age group around 1998/99 when this age group became fully targeted
45 for yearly influenza vaccination. The direction of the trend in excess mortality over the whole time
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8 period appears to be downwards or flat. Trend in excess mortality in the 45-64 age group is

9
10 approximately flat in the same period (Supplementary Figure 1). [Mean excess mortality was lower](#)
11 [after the policy change for both the 65-74 and 75+ age groups but was also lower after 2000/01 than](#)
12 [before among 45-64 year olds \(Supplementary table 2\).](#)
13
14

15 16 **Vaccine impact from ~~linear~~ multivariable regression**

17
18 Point estimates for the ~~average multiplicative effect that the policy change had on~~
19 ~~difference~~
20 ~~between~~ excess mortality after 2000 compared to before, adjusting for cold weather and antigenic
21 drift in influenza A/H3N2 viruses and stratified by dominant circulating virus subtype, are in the
22 direction of lower excess mortality after 2000 than before for both the 65-74 and 75+ age groups,
23 except for mortality in seasons dominated by influenza A/H1N1 or B viruses for the ~~65-74~~
24 ~~75+~~ age
25 group [for which the coefficient suggested higher mortality after the policy change but with a very](#)
26 [wide confidence interval which was similar after 2000 to before](#) (Figure 2). ~~However, confidence~~
27 ~~intervals include no difference.~~ Point estimates indicate ~~a modest~~
28 ~~greater~~ impact in influenza A/H3N2
29 virus-dominated seasons, [which is unlikely to be due to chance for the 75+ age group, while in](#)
30 [seasons dominated by than in influenza A/H1N1 or B viruses confidence intervals are wide and include](#)
31 [no effect](#)
32 ~~rus-dominated seasons~~. These findings are robust to modelling the vaccine policy change as
33 occurring in 1998/99 instead of 2000/01 (data not shown). For the 45-64 age group, point estimates
34 suggest lower excess mortality after 2000 than before for seasons dominated by influenza A/H3N2
35 viruses, ~~but the confidence interval again includes the null~~ (Figure 2). For each of the three age
36 groups, modelling the effect of change in vaccine coverage as a linear instead of binary (dummy)
37 variable results in point estimates suggesting lower excess mortality per unit increase in vaccine
38 coverage but with wide confidence intervals including the null (data not shown).
39
40
41
42
43
44
45
46
47
48
49
50

51 **Trends in baseline mortality**

1
2
3
4
5
6
7
8 Long-term trends in mortality not labelled as excess, analysed as a proxy for baseline P&I
9 mortality, are complex, with three to four periods during which different trends were observed. For
10 the 65-74 age group, rates in the study period were highest until the late 1970s, declined to
11 approximately 1990, plateaued to 2000 and fell after 2000 (Figure 3). For the 75+ age group, rates
12 increased to the late 1970s, declined to the mid-1980s, plateaued to the mid-1990s and then fell. The
13 45-64 age group showed a broadly similar baseline trend to that of the 65-74 age group, though the
14 trend was more tortuous due to smaller numbers (Supplementary figure 2). Residuals from fitted
15 models were normally distributed with mean approximately 0 and standard deviation approximately
16 1 with some residual autocorrelation (data not shown). Findings are robust to defining epidemic
17 periods using laboratory reports of influenza A infections alone or to using both influenza A and B
18 infections for this purpose.
19

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

31 During the period 2000-2005, ILI consultations for 0-4 and 5-14 year olds were lower than
32 historically (supplementary fig 3). However, over the same time period consultations for infectious
33 and parasitic diseases (which excludes ILI) also appeared to decline, especially in the 5-14 year age
34 group (supplementary fig 4). Rates of laboratory reported influenza infections were lower in 2000-
35 2005 than in the decade prior. (supplementary fig 5). Rates in 2000-2005 were similar to those
36 observed around 1980 (figure 3).
37

44 Discussion

46 Statement of principal findings

48 There is weakly supportive evidence that the switch from risk-based to age group-based
49 targeting of influenza vaccination for older people was associated with lower influenza-related
50 mortality in the 4-6 years following this policy change. Results from our multivariable ~~linear~~ regression
51
52

11

1
2
3
4
5
6
7
8 suggest that this policy change had a weak, positive impact on excess mortality in both the 65-74 and
9
10 75+ age groups. There is no indication of a downwards turning point in the trend in excess mortality
11
12 around 2000/01 (when all those 65+ began to be targeted for vaccination) or 1998/99 (when those
13
14 75+ began to be targeted). [There were fewer excess deaths, on average, in seasons after the policy](#)
15
16 [change than before \(including in the 45-64 age group\)](#) which argues against a strong, specific impact
17
18 of [this the](#) policy change on excess mortality [in either age group](#). Trends in baseline, as opposed to
19
20 excess, mortality do show a suggestion of a downwards turning point in the mid-1990s for the 75+
21
22 age group and around 2000 for the 65-74 age group, coinciding approximately with the timing of the
23
24 changes to specifically target these age groups for vaccination. Results obtained by fitting the various
25
26 models to data for the 45-64 age group, in whom vaccine coverage was largely static over the study
27
28 period, are in a similar direction but are of a smaller magnitude than the apparent impact in the 65-74
29
30 and 75+ age groups, suggesting there may have been other factors acting to bring down P&I mortality
31
32 at the time of the policy changes. Thus our analysis is consistent with a small mortality impact in the
33
34 65-74 and 75+ age groups during the six years after policies to wholly target these age groups for
35
36 yearly influenza vaccination were enacted.

37 **Strengths and weaknesses of the study**

38
39 There are a number of strengths to the work undertaken, as well as several limitations. The
40
41 key strengths are that we estimated excess mortality and long-term trend in mortality over a long
42
43 period (30 years). We carefully controlled for changes to death coding and laboratory practices which
44
45 occurred over this time period. The analytical approach we used, which is similar to one used by many
46
47 others,(15, 16) of modelling seasonality and trend using splines in addition to sinusoidal terms (full
48
49 details provided in the supplementary material), is a highly flexible method of fitting complex patterns
50
51 and trends that is especially helpful when modelling a long time series. The outcome we chose to
52

1
2
3
4
5
6
7
8 model (deaths from underlying P&I) is the most specific option available which allows sufficient
9 numbers of deaths for analysis. This choice maximised our ability to discern high mortality impact
10 influenza years from those less so, and thus to detect vaccine impact. Analysing underlying P&I of
11 course means our estimates of excess mortality underestimate the burden of mortality due to all
12 respiratory disease (which includes bronchitis), cardiovascular disease and other causes of death
13 which may be linked to influenza. (19, 20) However, it was not the aim of this work to estimate the
14 total mortality burden due to influenza. Further adding to the specificity of our outcome was our
15 designation of epidemic periods in the mortality data with reference to the time series of laboratory-
16 confirmed influenza A infections. Better still might have been to use influenza A/H3N2 infections, the
17 subtype most often associated with influenza years when there is substantial mortality,(53) but the
18 laboratory data available for this analysis were not broken down by subtype. The limitations of our
19 work include that our estimate of the extent of variability in excess mortality across influenza years is
20 likely to be an underestimate because our model failed to explain all variability in the mortality data
21 (as evidenced by a small amount of autocorrelation in residuals, data not shown). This may be
22 because we did not include temperature or other climatic variables in the models estimating excess
23 mortality. We did adjust for temperature in [linear-multivariable](#) regression models of vaccine impact
24 on excess mortality and as such our analysis of vaccine impact should not be confounded by
25 temperature. However, our results regarding long-term trends in non-excess mortality may be
26 confounded by temperature as there is evidence that minimum winter temperatures have increased
27 since the early 1960s.(54) In using laboratory data to inform epidemic periods in the mortality data,
28 we made no allowance for a lag between the increase, or peak, in incidence of laboratory-reported
29 infections and the timing of excess deaths associated with these infections. This is likely to have led us
30 to underestimate excess mortality, assuming the peak in deaths rarely precedes and generally

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

1
2
3
4
5
6
7
8 coincides or follows the peak in laboratory reports. However, the rise in influenza activity in the
9
10 community in terms of GP consultations generally coincides with the rise in numbers of laboratory
11
12 reports of influenza infections,(36) and, during influenza years dominated by circulation of influenza A
13
14 viruses, peak weekly GP consultation rates for influenza-like illness in the 45–64, 65–74 and >=75
15
16 years age groups tend to coincide with same-age peaks in respiratory deaths, plus or minus 1 week
17
18 (e.g. 1995/1996, 1996/1997, 1998/1999 and 1999/2000).(18) Hence the potential bias in our
19
20 estimates of excess mortality is likely to be minimal because the weeks we might have missed by not
21
22 allowing for a lag will be close to the start or end of the period of influenza circulation and thus will
23
24 make up a small proportion of the total influenza attributable P&I deaths in a given winter. Our
25
26 estimates of long-term trends may be confounded by the trends in co-morbidities linked to smoking
27
28 or by long-term patterns in other co-morbidities associated with respiratory mortality, which we have
29
30 not accounted for. [While it would have been possible to test for a change in slope of the long-term](#)
31
32 [trend with a piecewise linear approximation, we did not do this because issues of confounding by](#)
33
34 [these types of time-varying covariates, which we are only able to speculate about, would limit the](#)
35
36 [interpretability of any coefficient.](#) Finally, the separate vaccine coverage estimates we present for the
37
38 65-74 and 75+ age groups from 2000/01 onwards are sensitive to our assumption of a constant ratio
39
40 of vaccine coverage in the 65-74 to 75+ age groups from 2000/01 onwards (described in the
41
42 supplementary file). The assumption of a constant ratio is unlikely to be true and as such we have
43
44 probably underestimated coverage in the 65-74 age group and overestimated it in the 75+ age group;
45
46 the increase in coverage in 2000/01 was probably disproportionately accounted for by an increase in
47
48 coverage in the 65-74 age group, newly targeted as fully “at risk” from the 2000/01 influenza season.
49
50 Our main findings are unaffected by this because we focus on results from [linear-regression](#) models of
51
52 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

1
2
3
4
5
6
7
8 yearly vaccination for all Ontario residents.⁽⁵⁶⁾ Analyses of the impact of rising vaccine coverage of
9 the elderly on excess all-cause mortality in the US, Italy and in Catalonia did not detect impact
10 perhaps because, in the case of the US and Italy, coverage did not reach high enough levels for long
11 enough during the study period, or because, as in Catalonia, there were limited data available, prior
12 to coverage exceeding 60%, to provide a baseline against which to estimate impact.⁽¹⁵⁻¹⁷⁾ Because
13 ratios of our estimates of excess P&I between adjacent seasons, and between age groups, are
14 consistent with previous work using different models, we are confident that our impression of the
15 relative magnitude of P&I mortality between age groups and from one influenza year to the next are a
16 true reflection of patterns in influenza mortality during the study period. Our having observed some
17 evidence for vaccine impact on excess mortality in the 6 years after implementation of age group-
18 based influenza vaccination is consistent with findings from other temperate northern hemisphere
19 settings which have attained similar levels of vaccine coverage in the elderly, where some studies
20 have demonstrated impact and others have not.

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

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

1
2
3
4
5
6
7
8 and parasitic diseases (which excludes respiratory disease) were lower in the 2000-2005 period than
9 earlier in the study period. It is difficult to interpret lower ILI rates as strong evidence for less
10 influenza circulating in 2000-2005 than previously since the decline in rates of infectious and parasitic
11 diseases rates then still needs explaining. It may in part be that there was progressively lower use of
12 GP services in the 2000-2005 period. Rates of laboratory reported influenza infections for all-ages,
13 reported to the HPA CfI, were certainly lower in 2000-2005 than in the decade prior, and were similar
14 to rates observed around 1980 when excess mortality also appeared to be low for several consecutive
15 years. It is difficult to interpret long-term trends in laboratory reports of influenza infections because
16 of changing testing practices and changing volumes of test requisitions over the time period. For
17 example, between 1975 and 1992, the number of laboratory reports of viral infections doubled (57);
18 this is unlikely to reflect a doubling of viral infections over this period. If more tests were requisitioned
19 in 2000-2005 than in the years around 1980 similar rates of positive reports in the two periods would
20 suggest less viral activity in 2000-2005 than around 1980. However, it is hard to see how less influenza
21 in circulation later than earlier in the study period could explain a turning point in baseline mortality
22 in the 65-74 and 75+ age groups approximately coincident with policy changes to specifically target
23 these age groups for vaccination. We think the observation of a turning point in baseline mortality
24 reflects partly a non-specific impact of influenza vaccination on respiratory mortality in the elderly
25 that is not directly attributable to influenza as well as partly a specific impact of influenza vaccination
26 given that analysing excess mortality necessarily means some truly influenza-attributable mortality
27 (i.e. that which does not breach the epidemic threshold) contributes to baseline. A further possible
28 alternative explanation for the apparent, small influenza vaccine impact we have observed is that this
29 is really an impact of pneumococcal vaccination. This is unlikely to be true; to the end of the 2004/05
30 influenza year, less than 30% of people 65 years of age and over had received the recommended 23-

1
2
3
4
5
6
7
8 valent pneumococcal polysaccharide vaccine.(58) Pneumococcal conjugate vaccination of infants and
9
10 children, which might be expected to provide indirect protection to the elderly, has only been
11
12 routinely recommended since 2006. It is possible that there is some other factor which also changed
13
14 over the time period and which explains part of the mortality impact we observed (e.g. trends in co-
15
16 morbidities linked to smoking).

17 18 **Unanswered questions and future research**

19
20 Influenza vaccine impact can be difficult to measure due to its reliance on surveillance data
21
22 which are generally not collected in a consistent way over time, and because of the variable nature of
23
24 influenza activity over time. One way of adding to the evidence base is to look at vaccine
25
26 effectiveness. In order to strengthen the evidence base for influenza vaccine effectiveness in the
27
28 elderly, further good quality cohort and case-control studies across multiple influenza seasons with
29
30 varying degrees of match between vaccine and circulating variants, and adequate control for negative
31
32 confounding by indication (sicker elderly being preferentially offered vaccination) and positive
33
34 confounding by healthier older people putting themselves forward for vaccination, are required. It
35
36 remains unclear to what extent our findings are due to there being less influenza around 2000-2005
37
38 than before this time or to confounding by factors such as trends in co-morbidities linked to smoking.

39
40 Analyses including more recent influenza seasons, [which experienced a pandemic \(2009/10\) and a](#)
41
42 [severe influenza season dominated by H1N1pdm09 virus \(2010/11\) and which saw vaccine uptake of](#)
43
44 [the elderly further increase](#), will help to answer these questions and to monitor whether the modest
45
46 mortality impact we observed in the 6 years after age group-based targeting of vaccination began has
47
48 been sustained. This analysis will be complicated by the presence of pneumococcal vaccination of
49
50 infants and the elderly, making teasing apart the effects of how much influenza circulated during the
51
52 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

1
2
3
4
5
6
7
8 currently employed by, and holds stock options with, GlaxoSmithKline but that the relationship of
9
10 JCW to GSK had no influence on the work or on the decision to publish it; that there are no other
11
12 relationships or activities that could appear to have influenced the submitted work.
13

14 **Contributors**

15
16 AGM, PM and JCW conceived of the study, AGM conducted the analysis, led on the
17
18 interpretation and wrote the paper; JCW, PM and CAR contributed to interpretation and to
19
20 subsequent drafts of the paper. All authors approved the final version to be published. AGM is the
21
22 guarantor for the study. P&I data were provided by Cleo Rooney and Emma Gordon from the Office
23
24 for National Statistics. Laboratory data were provided by Carol Joseph and Joy Field of the Health
25
26 Protection Agency Centre for Infections. GP consultation data were provided by Douglas Fleming and
27
28 Alex Elliot of the Royal College of General Practitioners.
29

30 **Acknowledgements**

31
32 [We are very grateful to the reviewers' whose comments greatly improved this paper.](#)
33
34
35
36

37 **Funding**

38
39 This work was supported by a Researcher Development Award to AGM from the National
40
41 Institute of Health Research, UK [fellowship grant number RDA06/068]. The funder had no role in the
42
43 study design, in the collection, analysis, or interpretation of data, in the writing of the report or in the
44
45 decision to submit the article for publication. We the authors are independent from the funders.
46
47

48 **Access**

49
50 AGM had full access to all of the data in the study and takes responsibility for the integrity of
51
52 the data and the accuracy of the data analysis.
53

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).

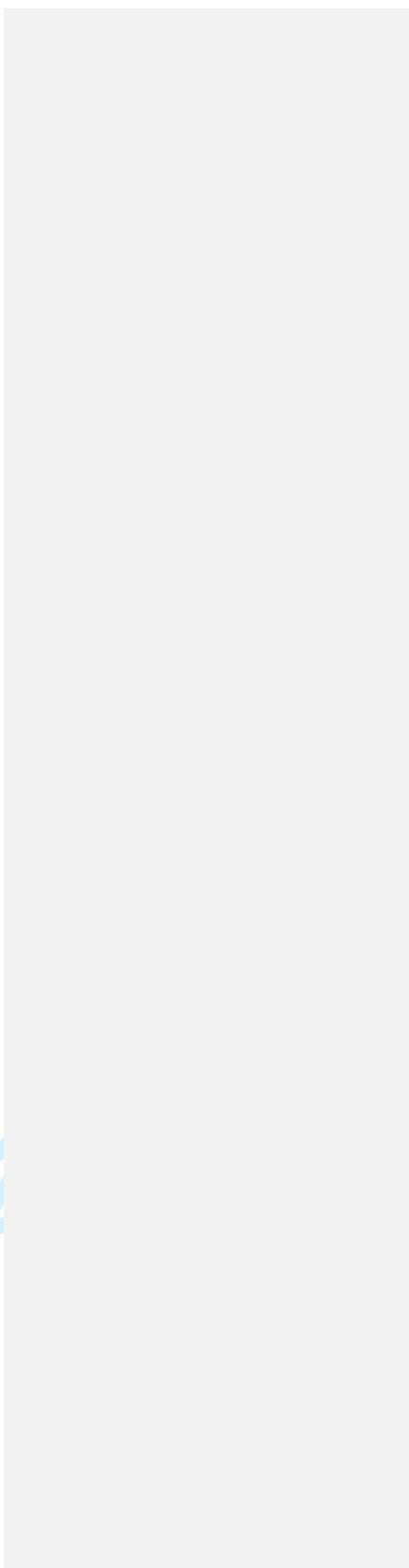
Licence

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in BMJ editions and any other BMJPG products and sublicences to exploit all subsidiary rights, as set out in our licence (<http://resources.bmj.com/bmj/authors/checklists-forms/licence-for-publication>).

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table title

For peer review only



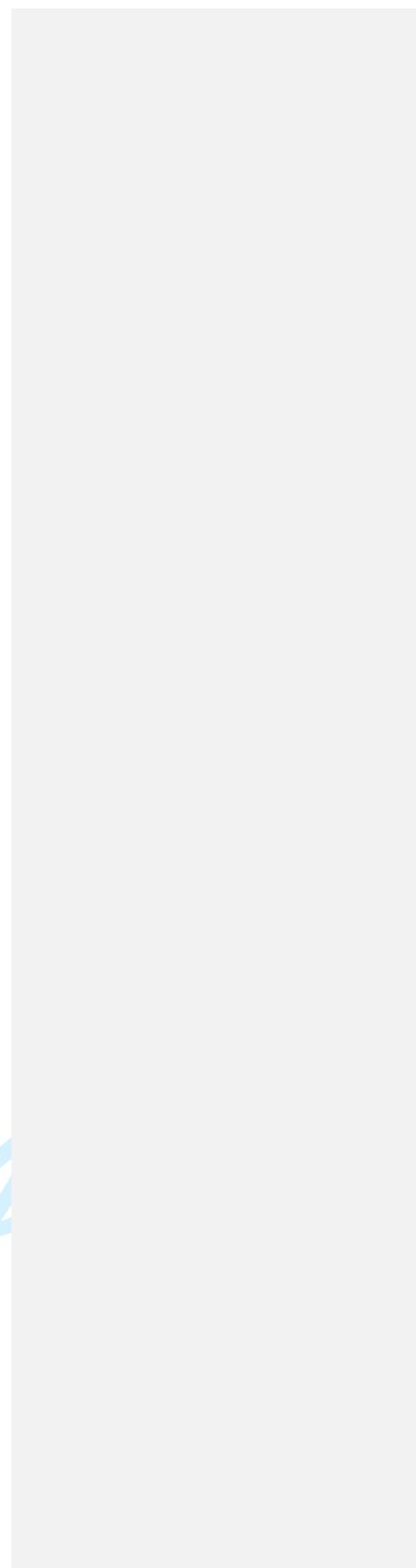
1
2
3
4
5
6
7
8 **Tab:** Influenza seasons in England & Wales, 1974/75-2004/05: dominant variant, antigenic drift events
9 in evolution of influenza A/H3N2 viruses,vaccine mismatch, vaccine coverage and numbers of excess
10 P&I deaths by age group. Bolding means H3N2 dominant and vaccine variants are from different
11 antigenic clusters.
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure legends

For peer review only

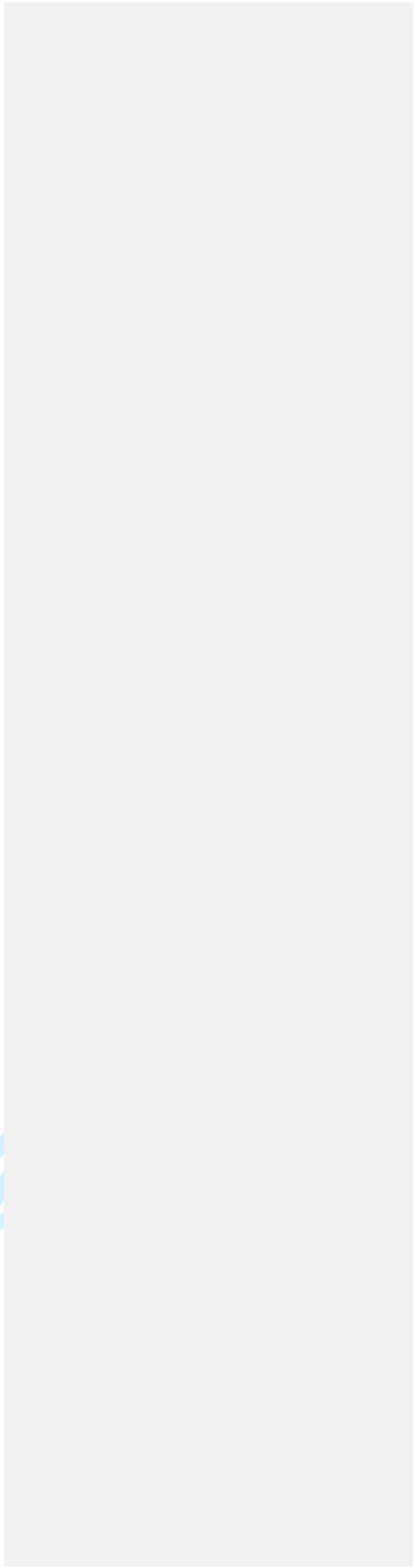


1
2
3
4
5
6
7
8 **Fig 1:** Excess mortality in the a) 65-74 and b) 75+ age groups in each influenza season in England &
9 Wales, stratified by the dominant influenza virus in circulation (black 'x' = A/H3N2 viruses were
10 dominant or co-dominant; grey '+' = A/H1N1 or B viruses were dominant). ~~Best fitting trend lines in~~
11 ~~excess mortality, with 95% CIs, are overlaid.~~ Vaccine coverage in the respective age group from
12 published data is also shown (dots and asterisks, right axis). Asterisks indicate that vaccine coverage in
13 these years was inferred from observed vaccine coverage in the 65+ age group and the average ratio
14 of coverage in the 65+ to 65-74 (or 75+) age group.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

For peer review only

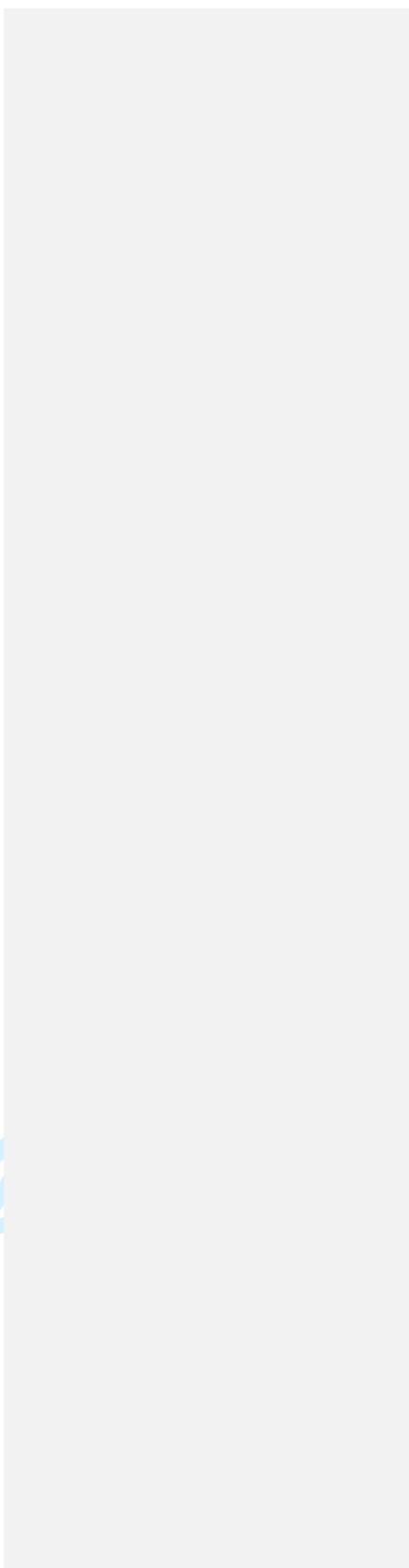


1
2
3
4
5
6
7
8 **Fig 3:** Model fit: The observed time series of weekly P&I deaths in the a) 65-74 and b) 75+ age group
9 in England & Wales between 1975 and 2005 (light dotted line on each plot). The fitted curve from the
10 log-linear Simonsen-like model fitted excluding December to April and accounting for seasonality,
11 long-term trend and artefacts is overlaid (dark line). Vaccine coverage (in the 65-74 and 75+ age
12 groups) adapted from published data is shown on the right axis of each plot (dots and asterisks).
13 Asterisks indicate that vaccine coverage in these years was inferred from observed vaccine coverage
14 in the 65+ age group and the average ratio of coverage in the 65-74 (or 75+) to 65+ age group. The
15 fitted curve can be deconstructed into its constituent parts. Thus c) and d) show just the long-term
16 trend (i.e. cubic spline) component of the fitted curve (dark lines), with its 95% confidence interval
17 (light lines), for the 65-74 and 75+ age groups, respectively. Doing this allows a better visualisation of
18 the shape of the long-term trend.
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table

For peer review only



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

References

1. Department of Health: From the Chief Medical Officer, the Chief Nursing Officer and the Chief Pharmaceutical Officer. Influenza immunisation. PL/CMO/2000/3. London: Department of Health, 2000.
2. Joseph C, Goddard N, Gelb D. Influenza vaccine uptake and distribution in England and Wales using data from the General Practice Research Database, 1989/90-2003/04. *J Public Health (Oxf)* 2005;**27**:371-7.
3. Butt S, Zhang N, Joseph CA. Vaccination uptake among the 65 years and over and under 65 years at risk in England 2006-07. London: Health Protection Agency Centre for Infections, 2007.
4. Begum F, Pebody R. Seasonal influenza vaccine uptake amongst GP patient groups in England. London: Department of Health, 2012.
5. Fedson DS, Nichol KL. Influenza vaccination: policy versus evidence: no gap between policy and evidence. *BMJ* 2006;**333**:1020.
6. Jefferson T. Influenza vaccination: policy versus evidence. *BMJ* 2006;**333**:912-5.
7. Mangtani P, Hall AJ, Armstrong BG. Influenza vaccination: the case for a gap in the evidence is flawed. *BMJ* 2006;**333**.
8. Simonsen L, Viboud C, Taylor R. Influenza vaccination in elderly people. *Lancet* 2005;**366**:2086.
9. Jefferson T, Di Pietrantonj C, Al-Ansary LA, et al. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev* 2010:CD004876.
10. Osterholm MT, Kelley NS, Sommer A, et al. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;**12**:36-44.
11. Govaert TM, Thijs CT, Masurel N, et al. The efficacy of influenza vaccination in elderly

- 1
2
3
4
5
6
7
8 individuals. A randomized double-blind placebo-controlled trial. *JAMA* 1994;**272**:1661-5.
- 9
10 12. Mangtani P, Cumberland P, Hodgson CR, et al. A cohort study of the effectiveness of influenza
11 vaccine in older people, performed using the United Kingdom general practice research database. *J*
12 *Infect Dis* 2004;**190**:1-10.
- 13
14 13. Ortqvist A, Granath F, Askling J, et al. Influenza vaccination and mortality: prospective cohort
15 study of the elderly in a large geographical area. *Eur Respir J* 2007;**30**:414-22.
- 16
17 14. Jansen AGSC, Sanders EAM, Nichol KL, et al. Decline in influenza-associated mortality among
18 Dutch elderly following the introduction of a nationwide vaccination program. *Vaccine* 2008;**26**:5567-
19 74.
- 20
21 15. Simonsen L, Reichert TA, Viboud C, et al. Impact of influenza vaccination on seasonal mortality
22 in the US elderly population. *Arch Intern Med* 2005;**165**:265-72.
- 23
24 16. Rizzo C, Viboud C, Montomoli E, et al. Influenza-related mortality in the Italian elderly: no
25 decline associated with increasing vaccination coverage. *Vaccine* 2006;**24**:6468-75.
- 26
27 17. Muñoz MP, Soldevila N, Martínez A, et al. Influenza vaccine coverage, influenza-associated
28 morbidity and all-cause mortality in Catalonia (Spain). *Vaccine* 2011;**29**:5047-52.
- 29
30 18. Fleming DM, Cross KW, Pannell RS. Influenza and its relationship to circulatory disorders.
31 *Epidemiol Infect* 2005;**133**:255-62.
- 32
33 19. Hardelid P, Pebody R, Andrews N. Mortality caused by influenza and respiratory syncytial virus
34 by age group in England and Wales 1999–2010. *Influenza Other Respi Viruses* 2013;**7**:35-45.
- 35
36 20. Pitman RJ, Melegaro A, Gelb D, et al. Assessing the burden of influenza and other respiratory
37 infections in England and Wales. *J Infect* 2007;**54**:530-8.
- 38
39 21. Serfling RE. Methods of current statistical analysis of excess pneumonitis-influenza death. *Public*
40 *Health Rep* 1963;**78**:494-506.
- 41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6
7
8 22. Fleming D, Wood M. The clinical diagnosis of influenza. *Curr Med Res Opin* 2002;**18**:338-41.
- 9
10 23. Barker WH, Mullooly JP. Underestimation of the role of pneumonia and influenza in causing
11 excess mortality. *Am J Public Health* 1981;**71**:643-5.
- 12
13 24. Housworth J, Langmuir AD. Excess mortality from epidemic influenza, 1957-1966. *Am J*
14 *Epidemiol* 1974;**100**:40-8.
- 15
16 25. Janssen F, Kunst AE. ICD coding changes and discontinuities in trends in cause-specific
17 mortality in six European countries, 1950-99. *Bull World Health Organ* 2004;**82**:904-13.
- 18
19 26. Devis T, Rooney C. Death certification and the epidemiologist. *Health Stat Quarterly*
20 1999;**01**:21-33.
- 21
22 27. Rooney C, Griffiths C, Cook L. The implementation of ICD-10 for cause of death coding - some
23 preliminary results from the bridge coding study. *Health Stat Quarterly* 2002;**13**:31-41.
- 24
25 28. Brock A, Griffiths C, Rooney C. The impact of introducing ICD-10 on analysis of respiratory
26 mortality trends in England and Wales. *Health Stat Quarterly* 2006;**29**:9-17.
- 27
28 29. Met Office Hadley Centre Central England Temperature Data: Monthly HadCET mean
29 [database on the Internet]. [Accessed 18 June 2008]. Available from:
30 www.metoffice.gov.uk/research/hadleycentre/CR_data/Daily/HadCET_act.txt.
- 31
32 30. Smith DJ, Lapedes AS, de Jong JC, et al. Mapping the Antigenic and Genetic Evolution of
33 Influenza Virus. *Science* 2004;**305**:371-6.
- 34
35 31. Fleming DM. The contribution of influenza to combined acute respiratory infections, hospital
36 admissions, and deaths in winter. *Commun Dis Public Health* 2000;**3**:32-8.
- 37
38 32. Pereira MS, Chakraverty P. Influenza in the United Kingdom 1977-1981. *J Hyg (Lond)*
39 1982;**88**:501-12.
- 40
41 33. Pereira M, Assaad FA, Delon PJ. Influenza surveillance. *Bull World Health Organ* 1978;**56**:192-
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6
7
8 203.
9
10 34. Chakraverty P, Cunningham P, Shen GZ, et al. Influenza in the United Kingdom 1982-85. *J Hyg*
11 *(Lond)* 1986;**97**:347-58.
12
13
14 35. Smith DJ, Forrest S, Ackley DH, et al. Variable efficacy of repeated annual influenza
15 vaccination. *Proc Natl Acad Sci U S A* 1999;**96**:14001-6.
16
17
18 36. Fleming DM, Zambon M, Bartelds AI, et al. The duration and magnitude of influenza
19 epidemics: a study of surveillance data from sentinel general practices in England, Wales and the
20 Netherlands. *Eur J Epidemiol* 1999;**15**:467-73.
21
22
23
24 37. Recommended composition of influenza virus vaccines for use in the 1989-1990 season. *Wkly*
25 *Epidemiol Rec* 1989;**64**:53-60.
26
27
28 38. Recommended composition of influenza virus vaccines for use in the 1990-1991 season. *Wkly*
29 *Epidemiol Rec* 1990;**65**:53-6.
30
31
32 39. Joseph CA, Dedman D, Fern K, et al. Influenza surveillance in England and Wales: November
33 1991-June 1992. *Commun Dis Rep CDR Rev* 1992;**2**:R149-52.
34
35
36 40. Dedman D, Joseph CA, Chakraverty P, et al. Influenza surveillance, England and Wales: October
37 1992-June 1993. *Commun Dis Rep CDR Rev* 1993;**3**:R184-6.
38
39
40 41. Dedman DJ, Joseph CA, Chakraverty P, et al. Influenza surveillance, England and Wales:
41 October 1993 to June 1994. *Commun Dis Rep CDR Rev* 1994;**4**:R164-8.
42
43
44 42. Hutchinson EJ, Joseph CA, Chakraverty P, et al. Influenza surveillance in England and Wales:
45 October 1994 to June 1995. *Commun Dis Rep CDR Rev* 1995;**5**:R200-4.
46
47
48 43. Hutchinson EJ, Joseph CA, Zambon M, et al. Influenza surveillance in England and Wales:
49 October 1995 to June 1996. *Commun Dis Rep CDR Rev* 1996;**6**:R163-9.
50
51
52 44. Dedman DJ, Joseph CA, Zambon M, et al. Influenza surveillance in England and Wales: October
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8 1996 to June 1997. *Commun Dis Rep CDR Rev* 1997;**7**:R212-9.

9
10 45. Dedman DJ, Zambon M, Buynder PV, et al. Influenza surveillance in England and Wales:
11 October 1997 to June 1998. *Commun Dis Public Health* 1998;**1**:244-51.

12
13 46. Whiting P, Joseph CA, Zambon M, et al. Influenza activity in England and Wales: October 1998
14 to June 1999. *Commun Dis Public Health* 1999;**2**:273-9.

15
16 47. Goddard NL, Joseph CA, Zambon M, et al. Influenza surveillance in England and Wales:
17 October 1999 to May 2000. *Commun Dis Public Health* 2000;**3**:261-6.

18
19 48. Goddard NL, Joseph CA, Zambon M, et al. Influenza surveillance in the United Kingdom:
20 October 2000 to May 2001. *Commun Dis Rep CDR Suppl* 2001:1-7.

21
22 49. Crofts JP, Goddard NL, Joseph CA, et al. Influenza surveillance in the United Kingdom: October
23 2001 to May 2002. *Commun Dis Rep CDR Suppl* 2002:1-7.

24
25 50. Crofts JP, Joseph CA, Zambon M, et al. Influenza surveillance in the United Kingdom: October
26 2002 to May 2003. *Commun Dis Rep CDR Suppl* 2004;**14**:1-9.

27
28 51. Cooke MK, Crofts JP, Joseph CA, et al. Influenza and other respiratory viruses surveillance in
29 the United Kingdom: October 2003 to May 2004. *Commun Dis Rep CDR Suppl* 2005;**15**:1-8.

30
31 52. Zhao H, Cooke MK, Joseph CA, et al. Surveillance of influenza and other respiratory viruses in
32 the United Kingdom: October 2004 to May 2005. *Commun Dis Rep CDR Suppl* 2006;**16**:1-8.

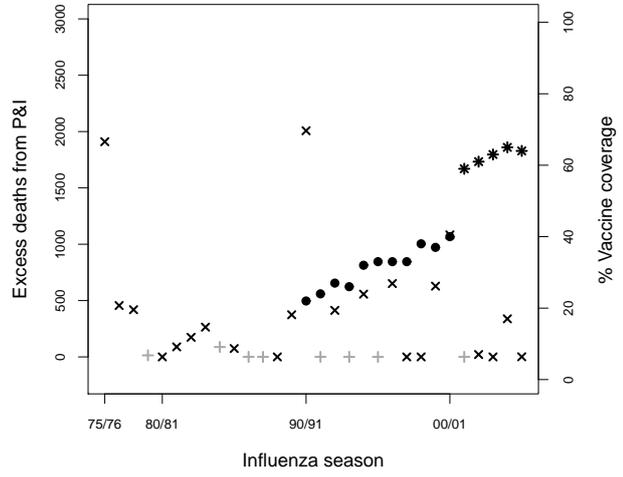
33
34 53. Thompson WW, Shay DK, Weintraub E, et al. Mortality Associated With Influenza and
35 Respiratory Syncytial Virus in the United States. *JAMA* 2003;**289**:179-86.

36
37 54. Perry M. Climate memorandum no 21: A spatial analysis of trends in the UK climate since 1914
38 using gridded datasets. London: Met Office, 2006.

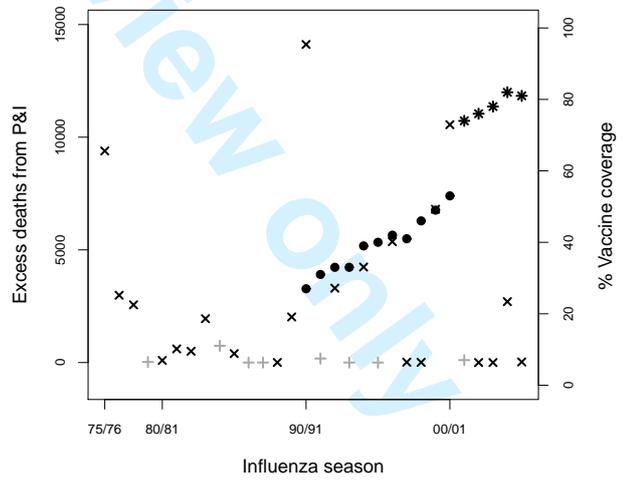
39
40 55. Thompson WW, Weintraub E, Dhankhar P, et al. Estimates of US influenza-associated deaths
41 made using four different methods. *Influenza Other Respi Viruses* 2009;**3**:37-49.

- 1
2
3
4
5
6
7
8
9 56. Kwong JC, Stukel TA, Lim J, et al. The Effect of Universal Influenza Immunization on Mortality
10 and Health Care Use. *PLoS Med* 2008;**5**:e211.
11
12 57. Grant AD, Eke B. Application of information technology to the laboratory reporting of
13 communicable disease in England and Wales. *Commun Dis Rep CDR Rev* 1993;**3**:R75-8.
14
15 58. Health Protection Agency Centre for Infections. Pneumococcal Vaccination Uptake Monitoring
16 on behalf of the Department of Health. [Accessed 18 Sept 2012]; Available from:
17
18 <http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/Pneumococcal/PPVUptake/>.
19
20
21
22 59. Baguelin M, Jit M, Miller E, et al. Health and economic impact of the seasonal influenza
23 vaccination programme in England. *Vaccine* 2012;**30**:3459-62.
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

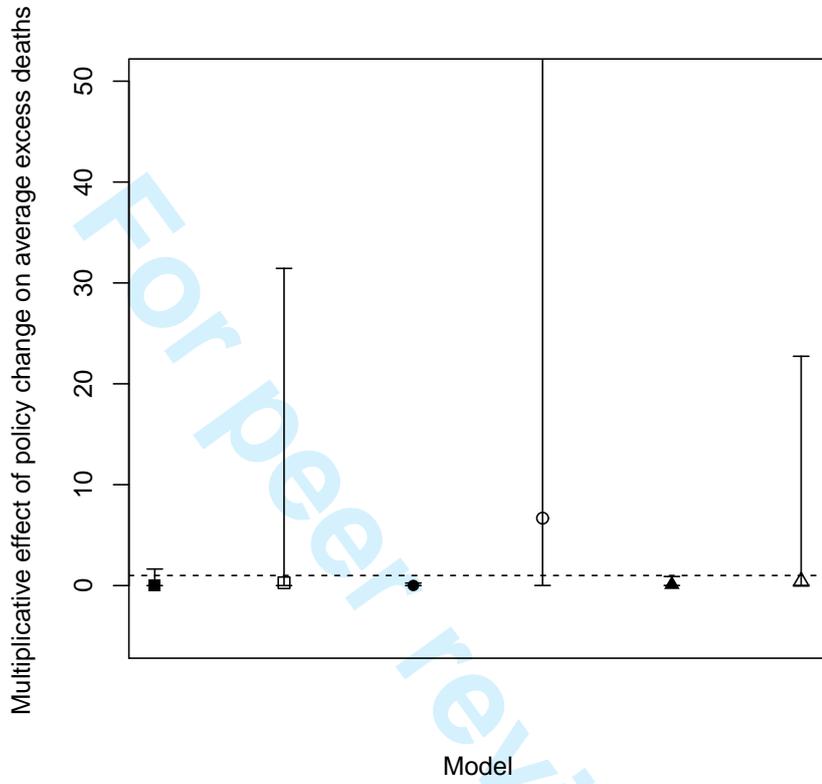


(a) 65-74 yrs



(b) 75+ yrs

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



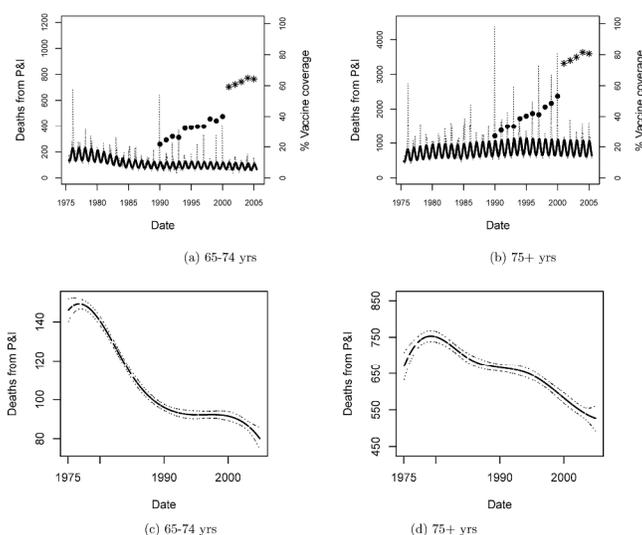


Fig 3: Model fit: The observed time series of weekly P&I deaths in the a) 65-74 and b) 75+ age group in England & Wales between 1975 and 2005 (light dotted line on each plot). The fitted curve from the log-linear Simonsen-like model fitted excluding December to April and accounting for seasonality, long-term trend and artefacts is overlaid (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

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

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+

1
2
3 age group from 2000/01-2004/05 was therefore derived by calculating the coverage for
4
5 those 65+ (regardless of risk group), using the method described above for the 45-64 age
6
7 group, for all years and determining the average ratio of coverage in the 75+ age group to
8
9 65+ age group for years when coverage in those 75+ was reported (1989/90-1999/00).
10
11 Multiplying coverage in the 65+ age group for 2000/01 by this average ratio gave estimated
12
13 coverage in the 75+ age group for 2000/01 (and so on for 2001/02-2004/05). The same
14
15 procedure was followed to estimate coverage for the 65-74 age group.
16
17
18
19

20 21 **Estimating excess and baseline mortality**

22
23 There are numerous approaches in the literature to quantifying excess mortality as a
24
25 measure of influenza severity and no gold standard approach. The different methods
26
27 produce different estimates of excess mortality when fitted to the same data.(3) We elected
28
29 to modify the method of Simonsen and colleagues,(4) used in their paper analysing
30
31 influenza vaccine impact in the US, to examine both excess mortality and the long-term
32
33 trend in non-excess mortality in relation to changes in vaccine policy and coverage. The
34
35 Simonsen method is a modification of Serfling's cyclical regression approach,(5) where non-
36
37 epidemic data are modeled to estimate expected mortality and mortality greater than
38
39 expected is labelled as excess, but improves on the specificity of Serfling's model in that
40
41 epidemic periods in the data are informed by a specific measure of influenza. We adapted
42
43 Simonsen's approach to the specifics of our data in two ways. We fitted log-linear negative
44
45 binomial, instead of Poisson, models to allow for overdispersion apparent in the P&I data
46
47 from England & Wales. Also, we used all-age laboratory reports for influenza A to inform
48
49 epidemic periods in the data instead of laboratory-confirmed influenza deaths because
50
51 there are too few laboratory-confirmed influenza deaths in England & Wales to allow them
52
53 to be modelled (a given year may have only 25 laboratory-confirmed influenza deaths
54
55
56
57
58
59
60

1
2
3 (Emma Gordon, personal communication)). Our modelling approach differed from
4
5
6 Simonsen's in two additional ways. Firstly, we controlled for the changing size of the
7
8 population at risk via the offset term rather than fitting models in fine age bands and
9
10 calculating age-standardized sums of excess deaths. Second, we directly modelled long-term
11
12 trend using cubic splines (with default knot points) rather than first removing trend from the
13
14 data with a smoothing spline. This was done so that we could pull out the long-term trend
15
16 component of the fitted model to plot and visualise in its own right. Our approach to
17
18 analysis is described in full below.
19
20
21
22

23
24 An influenza year was defined as week 26 of one year to week 25 of the next
25
26 because the timing of influenza circulation during a given winter usually spans two calendar
27
28 years (i.e. extends from October of one year to March of the next year). Mortality and
29
30 laboratory data were collapsed into weekly counts for analysis. In order to differentiate
31
32 excess from baseline mortality we used laboratory data to estimate which were the
33
34 epidemic weeks in the time series. We then fitted models to the mortality time series to
35
36 determine both excess and baseline mortality with reference to these epidemic weeks.
37
38 Specifically, in the first instance we fitted a negative binomial model to all-age weekly
39
40 counts of laboratory-confirmed influenza A infections excluding counts from the period
41
42 when influenza is most likely to be circulating in the community (December to April, week
43
44 numbers 48 of one calendar year to 18 of the next (4)). This negative binomial model
45
46 included the following terms: as an offset the decennial census population of England &
47
48 Wales from census years and an inter-census estimate from years between censuses,(6)
49
50 cubic splines with 6 degrees of freedom to model trend, 1 Fourier term (ie. 1 sine and 1
51
52 cosine term) with period 52.2 weeks to model seasonality, and dummy variables to account
53
54 for minor artefacts. (An initial exploration of options to model trend as linear, quadratic or
55
56
57
58
59
60

1
2
3 with a cubic spline with up to 20 degrees of freedom (df) was undertaken to determine how
4 to fit trend (data not shown)). A time series of counts was predicted from this model when
5 refitted to the full time series of influenza A counts (i.e. not excluding Dec – Apr). The
6 epidemic threshold for each week was defined as the upper 95% confidence bound on the
7 predicted laboratory count for that week. We then fitted the same negative binomial model
8 (except with trend modeled using a cubic spline with 5 df, informed based on our earlier
9 model selection exercise) to the time series of death counts with December to April deleted.
10 We again predicted the time series of counts from this model refitted to the full time series
11 (i.e. without Dec-Apr excluded). Excess mortality was the sum of observed minus predicted
12 deaths in weeks when laboratory data breached their epidemic threshold, by influenza year.
13 Baseline trend in mortality incidence was approximated by fitting the negative binomial
14 model above to the death counts not labelled as excess. This model fit was then
15 deconstructed and just the spline (i.e. trend) component was plotted in order to graphically
16 assess its shape. Estimates of excess mortality and plots of baseline trends were determined
17 separately for the age groups 65-74, 75+ and 45-64 (the latter age group being “unexposed”
18 to a change in vaccine policy or coverage over the period). Any estimates of negative excess
19 mortality were recoded to 0. No model was stratified by sex because an initial exploration of
20 the data suggested similar trends by sex in the study period. A sensitivity analysis was
21 carried out defining epidemic periods based on counts of combined laboratory-confirmed
22 influenza A and influenza B virus infections (as opposed to the main analysis where this was
23 done using counts of influenza A infections only).
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

1. Butt S, Zhang N, Joseph CA. Vaccination uptake among the 65 years and over and under 65 years at risk in England 2006-07. London: Health Protection Agency Centre for Infections, 2007.
2. Joseph C, Goddard N, Gelb D. Influenza vaccine uptake and distribution in England and Wales using data from the General Practice Research Database, 1989/90-2003/04. *J Public Health (Oxf)*. 2005;27(4):371-7.
3. Thompson WW, Weintraub E, Dhankhar P, Cheng PY, Brammer L, Meltzer MI, et al. Estimates of US influenza-associated deaths made using four different methods. *Influenza Other Respi Viruses*. 2009;3(1):37-49.
4. Simonsen L, Reichert TA, Viboud C, Blackwelder WC, Taylor RJ, Miller MA. Impact of influenza vaccination on seasonal mortality in the US elderly population. *Arch Intern Med*. 2005;165(3):265-72.
5. Serfling RE. Methods of current statistical analysis of excess pneumonitis-influenza death. *Public Health Rep*. 1963;78(6):494-506.
6. Mid-year population estimates [database on the Internet]. [cited November 21st 2007]. Available from: <http://www.statistics.gov.uk/statbase/explorer.asp?CTG=3&SL=4819,4824,3880&D=4426&DCT=0&DT=32#4426>.
7. Met Office Hadley Centre Central England Temperature Data: Monthly HadCET mean [database on the Internet]. [cited 18 June 2008]. Available from: www.metoffice.gov.uk/research/hadleycentre/CR_data/Daily/HadCET_act.txt.
8. Smith DJ, Lapedes AS, de Jong JC, Bestebroer TM, Rimmelzwaan GF, Osterhaus ADME, et al. Mapping the Antigenic and Genetic Evolution of Influenza Virus. *Science*. 2004;305(5682):371-6.
9. Fleming DM. The contribution of influenza to combined acute respiratory infections, hospital admissions, and deaths in winter. *Commun Dis Public Health*. 2000;3(1):32-8.

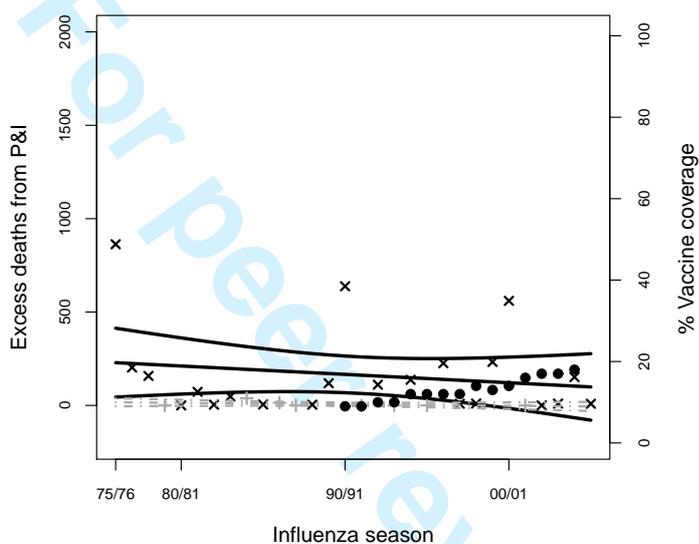
SUPPLEMENTARY FIGURES

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

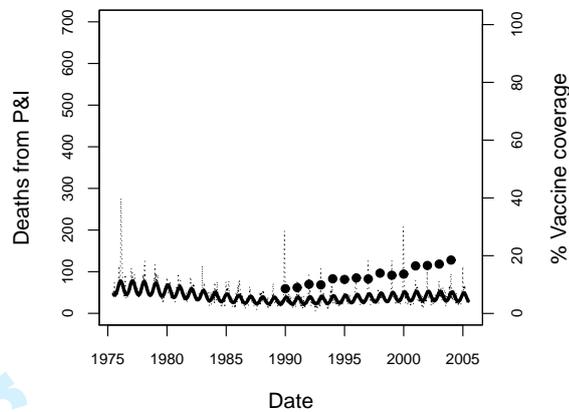
Authors: Andrea G. Mann, Punam Mangtani, Colin A. Russell, John C. Whittaker

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

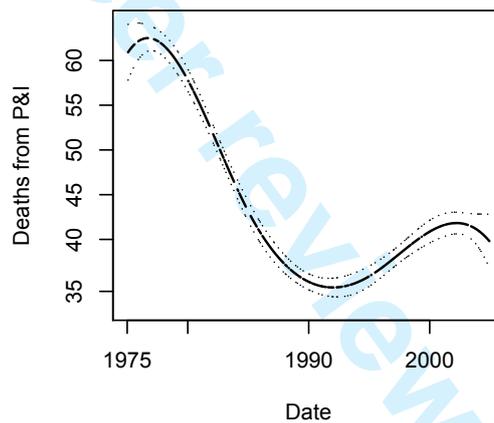


(a)

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 overlaid. Vaccine coverage in the 45-64 age group from published data is also shown (dots, right axis).



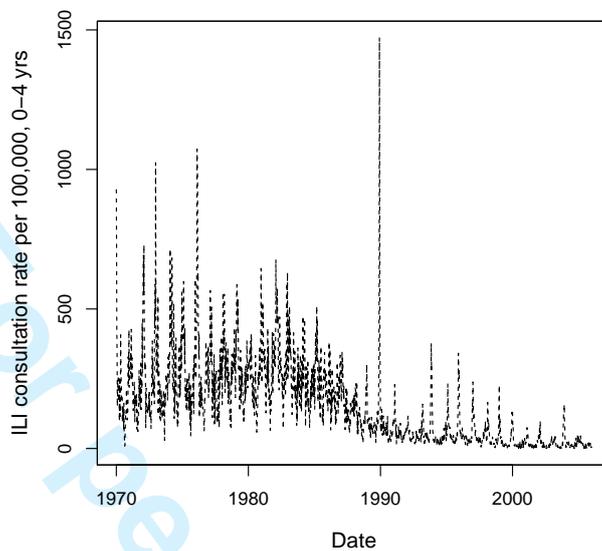
(a)



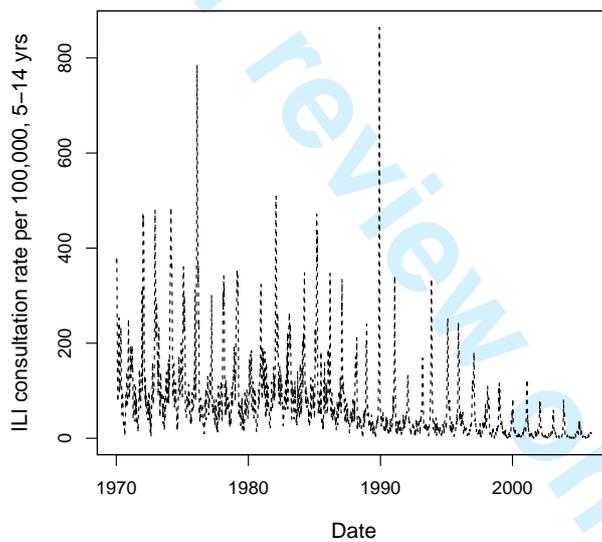
(b)

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 overlaid (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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

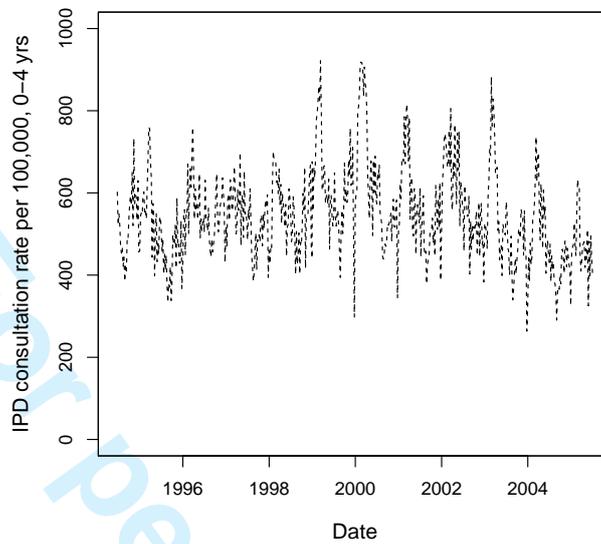


(a)

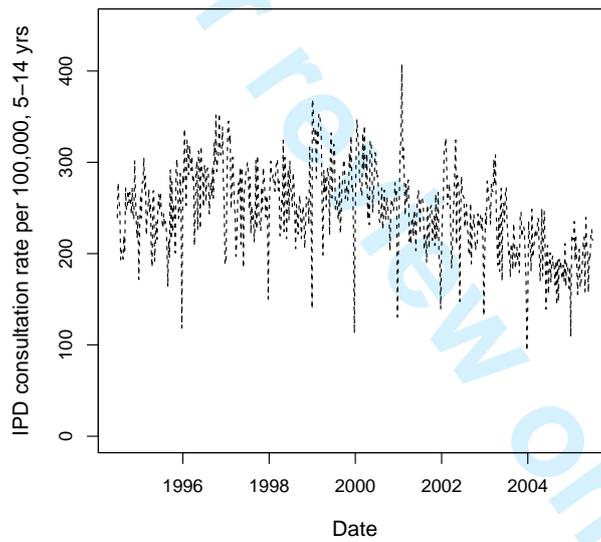


(b)

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.

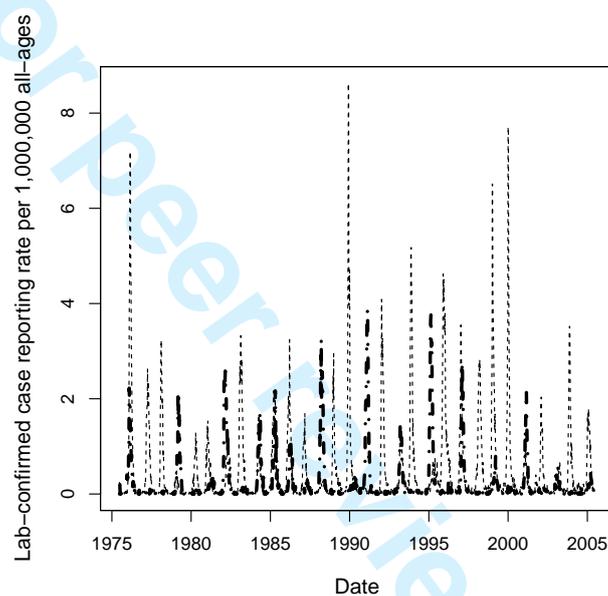


Figure 5: The weekly rate of laboratory reports for influenza A (light dotted line) and influenza B (dark dotted line) per 1,000,000 population, voluntarily reported to the Health Protection Agency Centre for Infections, England & Wales.

SUPPLEMENTARY TABLES

Article title: The impact of targeting all elderly persons in England & Wales for yearly influenza vaccination: excess mortality due to pneumonia or influenza 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 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 <u>before</u> policy change*	Range of number of excess deaths per influenza season <u>before</u> policy change*	Mean number of excess deaths per influenza season <u>after</u> policy change**	Range of number of excess deaths per influenza season <u>after</u> 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.