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+

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

Estimating excess and baseline mortality

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

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

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

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

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 pneumonis-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.