Reviewer's report

Title: Occurrence of invasive pneumococcal disease and number of excess cases due to influenza

Version: 1 Date: 19 October 2005

Reviewer: AJ Valleron

Reviewer's report:

General
This paper analyses the possible causal relationship between influenza and invasive pneumococcal disease (IPD). The material used to investigate this relationship is composed of 2 time series over more than 10 years. Then a statistical modelling is used to assess the existence of a temporal relationship between the 2 series, and estimate the best lag between the two series that can account for the observed cross correlations, and the part of the IPD incidence which could be attributed to influenza.

The title of the paper indicates that one of its goals is to assess the “number of <IPD> excess cases due to influenza”. However, it is well known that causal inference (“due to”) is difficult to achieve from the mere statistical analysis of the correlations between time series, even if more and more sophisticated statistical techniques are being used to try to overcome some of the difficulties. The biggest methodological efforts have been made in the analysis of the air pollution – mortality data, and – to a less extent- in the estimation of the deaths attributable to influenza (a subject closely related to this paper).

In this particular instance, a case control design where cases (IPD) and controls would be tested for influenza would allow o estimate the part of IPD attributable to influenza and bring directly the answer to the question posed :. It is true that this would imply 2 samples/subject (for example, one nasal swab for the test of influenza) while here the authors use existing data. However the limitations of this purely statistical approach must be kept in mind, and carefully discussed in the paper.

The statistical methods which are used here are not convincing on a key point : they do not demonstrate that the models presented (where influenza is assumed to play a role on IPD) are significantly better than a base model where IPD is not explained by influenza. If this demonstration is not done, the estimations of the lags and of the attributable parts are inappropriate. There are also a series of questions on the data analysed and the strategy of analysis (see below).

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Data

There is no information given in the paper on the quality and completeness of the IPD data, and of the influenza data.

Concerning influenza, the definition that the authors use of the influenza period should be justified, and the impact of this definition on the results should be assessed.. Influenza virus circulate long before the epidemics actually start (this is one of the mysteries of the influenza epidemics). I understand that the influenza period is defined here as the weeks when at least one influenza virus isolation was made. This certainly widens too much the window of the influenza period (and may explain why some are apparently so large). In my opinion the analysis should be restricted to the...
epidemic period. A figure showing how the influenza period (as defined here) is superposed to the clinical outbreaks (at least to the weekly influenza mortalities) would be useful. Also, a sensitivity analysis testing the impact of the choice of the beginning of the epidemic on the different results should also be made.

The authors have decided to express the influenza activity as a 1/0 variable (influenza epidemic present, or absent). Why do they not use more quantitative data (for example the weekly numbers of influenza isolates, and/or the influenza mortalities)? The visual comparison of the timings of the peaks of the two time series, and a descriptive statistical analysis (e.g. spectral analysis) would be useful. In particular there is apparently (fig. 1) an important synchrony in IPD counts, with a peak occurring regularly around the first week of January. This deserves a comment. Indeed, influenza epidemics occur annually but much less regularly. Therefore this simple observation puts a doubt on the nature of the correlation between IPD and influenza.

The authors do not take into account the nature of the predominantly circulating strain during each influenza season. This information is usually available. The analyses of the influenza time series have shown that the mortalities are attributable to influenza are more severe during the seasons when H3N2 is dominant.

Statistical analysis
The results concerning the "no influenza" model with no influenza terms at all, obtained for example by dropping from model 1 the terms expressing in the possible influence of influenza (e.g. βinf) are not presented. There is therefore no evidence in what is presented that Models 2 and 1 provide a significantly better fit that this "no influenza" model. As this "no influenza" model in nested in Model 1 (and in Model 2), the differences of likelihood of the 2 models are ch2 distributed and a test can be (must be) readily done. This is a crucial step in the analysis. If there is no significant information provided by models 1 and 2 (as compared to the "no influenza" model), the analysis ends at this point. The authors should do these tests (and present the results. Similarly, the results of Models 1 and 2 and of their "baseline" model could be compared with an Akaike test, as these are not nested.

With the information provided in the paper, the only models which can be compared are Models 1 and 2 as model 2 is nested in model 1 (as each yearly coefficient in Model 2 can be expressed as the sum of a "all years" coefficient (as in Model 1), plus a year specific coefficient). From the results shown in the table, I understand that the difference between Model 2 and Model 1 is far from been significant (2 (1831-1826,8 )= 8,4 < ch2 (5%, 10 ddl)). Therefore, even if I assume that Model 1 is significantly better than the "no influenza" model (previous paragraph), I do not see the rationale for using Model 2.

The "second" approach (2nd part of page 10) is not precisely described. I understand that a sinusoidal model (serf ling like) was used over the 11 years period, after dropping influenza periods and that, later, the mean values of –say- the 11 November values of the sinusoidal model are used to give a "baseline" November value (the grey curve of fig. 2A) and then that the excess IPD cases are computed each year by comparison with this "baseline" value. If this is the algorithm used, it should be explained more clearly... and I am surprised that the excess IPD was not simply calculated as the difference between the observed figure and the expected value from the sinusoidal model as is routinely done to evaluate the excess mortalities attributable to influenza.

Discussion
Even assuming that the relationship between the time series has been demonstrated and that the "best lag" is between 1 and 3 weeks, causal inference is impossible to achieve on statistical grounds alone. An in depth discussion about the causal physiopathological mechanism which could explain the results should be made.
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
A discussion of the recent paper by Talbot et al. (Am. J. of Medicine (2005) 118, 285-291 which addresses exactly the same problem is necessary.

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: Yes

Declaration of competing interests:
I declare that I have no competing interests