Influenza vaccination: the case for a gap in the evidence is flawed

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Send response to journal:
Re: Influenza vaccination: the case for a gap in the evidence is flawed

Jefferson's article attempts to use evidence, ours included, to question the seasonal influenza vaccination campaign, but raises a number of issues. Firstly the article is not one that follows established Cochrane procedures in that it provides incomplete evidence. Although noted in table 2, Thomas Jefferson does not discuss the high, over 70%, efficacy against laboratory confirmed illness from influenza by the trivalent inactivated vaccine in healthy adults and children in the Cochrane reviews or, in fact, other meta-analyses (e.g. reference 1appendix 20 page 249). In a trial in over 60 year olds vaccine efficacy was only slightly lower at 58% (95% CI 95% CI 26-77%))2. This last trial is not mentioned in the article but is key. As there is clear evidence of benefit against laboratory confirmed illness from influenza vaccination including in over 60 year olds, a trial now, with mortality as an endpoint, would not be ethical. Instead we have to rely on observational studies - which Thomas Jefferson dismisses. Such studies have an important role but we have to deal with the following constraints: the presence of both positive and negative confounding and the restriction to easily measured outcomes.

It is well known that vaccine recipients may be different to non- recipients in many ways. In some populations there may be a "healthy vaccine effect" with non-smokers and those with higher educational or social status more likely to have influenza vaccine3;4. This positive confounding would bias upwards any protective effect of the vaccine. Negative confounding "by indication", in which those identified as more frail are more likely to be offered the vaccine, would bias downwards any protective effect of the vaccine. The predominance of negative confounding explains some of the crude estimates of effect showing no effect of the influenza vaccine in the table in the Cochrane review of influenza vaccine in the elderly5.

Statistical methods are commonly used to control for both positive and negative confounding. By doing so a protective effect obscured by negative confounding is then possible to see. Residual confounding is however often a problem because measured factors are not able to capture all the differences between vaccine recipients and non recipients. Residual negative confounding will act to underestimate an effect. Less well recognised though, is the scope to over-estimate the true benefit of an intervention if there is residual confounding by the "healthy vaccine" effect. Luckily the presence of residual confounding can be assessed by seeing if there is any effect of the vaccine in seasons where no influenza is circulating. This method was first used for influenza vaccine by Ohmit and Monto looking at hospital admissions in the elderly. A 31% protective effect against hospitalisation for pneumonia and influenza was noted that was not seen in the corresponding peri-influenza winter season6. More recently we conducted a large UK cohort study using the General Practice research Database over several years that included over 2 million person- years of follow-up. Overall vaccine effectiveness was 21% (95% CI 17-26%) for respiratory disease hospitalisations and 12% for respiratory deaths (95% CI 8-16%) in over 64 year olds, with no protective effect seen in the corresponding non-influenza winter season. In contrast a protective effect against all-cause mortality was seen in the non-influenza season suggesting a "healthy vaccinee" effect for that outcome. This protection against respiratory disease deaths, after adjustment for confounding, is missing from the full Cochrane review7 and incorrectly noted as not significant in the summary paper5. An analysis with similar logic found that though unvaccinated elderly persons showed mortality peaks following peaks of influenza circulating in the community, those vaccinated were substantially protected from these mortality peaks. 8 It would have been preferable that the systematic review of observational studies in the elderly that Thomas Jefferson refers to had conducted a more rigorous assessment of the methods studies used to deal with confounding. As experts in systematic reviews have pointed out, the presence of heterogeneity in the results of studies, especially observational studies,

should be carefully examined rather than dismissed9 .

The final constraint of observational studies also applies to trials without laboratory confirmation of the aetiological agent - misclassification error in measuring outcome. Such error can be easily shown to under-estimate any effect of an exposure 10. Given outcomes that are inevitably non-specific it is thus not surprising that estimated effects of vaccine are often low. A related issue is Jefferson's inappropriately dismissive interpretation of the modest effect of the influenza vaccine. A just over 20% protective effect on a non-specific outcome such as an admission for acute respiratory disease must reflect a much larger effect in more specific outcomes.

Finally the article suggests that influenza vaccination requires resources which could be used for other interventions. Seasonal influenza can be mild. It is certainly so in some years but not in others. The seasonal epidemic in 1989/90 is but one example with about 18,000 excess deaths in the UK after taking into account a slight deficit of deaths after the epidemic11 ; with an average of over 12,000 deaths per year when crudely compared with death rates in similar weeks in other years when influenza is not circulating12. These are rough estimates as laboratory tests to confirm seasonal influenza as the cause of death are not usually done. Because the severity of seasonal influenza as a result of antigenic drift cannot be easily predicted, yearly influenza vaccination is required. Cost-effectiveness studies of influenza vaccine have been conducted with sensitivity analyses of the results to varying the attack rate or assuming no deaths occurred1. In those at high risk for complications of influenza, including over 64 year olds, the cost per quality adjusted years of life saved of vaccination is under a few thousand pounds, well below the accepted threshold for funding in the heath sector in the UK including smoking cessation activities or breast cancer screening13.

In short, inactivated trivalent influenza vaccines are highly effective against laboratory confirmed influenza, with more evidence in younger adults but also clear evidence in elderly people. In addition observational studies have shown that the influenza vaccine currently in use prevents not only hospitalisations but also death in over 64 year olds. It is not clear why the BMJ should publish such a flawed article, contrary to the judgement of virtually all other scientists who have looked at the question, particularly at a time of year when optimising influenza vaccine coverage can save lives.

Reference List

(1) Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modelling for the prevention and treatment of influenza A and B. Health Technol Assess 2003; 7(35):iii- xiii, 1.

(2) Govaert TME, Thijs CTMCN, Masurel N, Sprenger N, Dinant GJ. The efficacy of influenza vaccination in elderly individuals: a randomised double-blind placebo-controlled trial. JAMA 1994; 272:1661-1665.

(3) Christensen B, Lundbergh P. Comparison between cohorts vaccinated and unvaccinated against influenza and pneumococcal infection. Epidemiol Infect 2002; 129:515-524.

(4) Mangtani P, Breeze E, Kovats S, Ng ES, Roberts JA, Fletcher A. Inequalities in influenza vaccine uptake among people aged over 74 years in Britain. Prev Med 2005; 41(2):545-553.

(5) Jefferson T, Rivetti D, Rivetti A, Rudin M, Di PC, Demicheli V. Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. Lancet 2005; 366(9492):1165-1174.

(6) Ohmit SE, Monto AS. Influenza vaccine effectiveness in preventing hospitalization among the elderly during influenza type A and type B seasons. Int J Epidemiol 1995; 24:1240-1248.

(7) Rivetti D, Jefferson T, Thomas R, Rudin M, Rivetti A, Di PC et al. Vaccines

for preventing influenza in the elderly. Cochrane Database Syst Rev 2006; 3:CD004876.

(8) Armstrong B, Mangtani P, Fletcher AE, et al. Influenza vaccination protects against excess deaths occurring during periods of high circulation of influenza. BMJ 2004; 329:660-661.

(9) Egger M, Smith GD, Altman D. Systematic reviews in health care: meta-analysis in context. 2nd Ed ed. London: BMJ; 2001.

(10) Mertens TE. Estimating the effects of misclassification. Lancet 1993; 342:418-421.

(11) Ashley J, Smith T, Dunnell K. Deaths in Great Britain associated with the influenza epidemic of 1989/90. Population Trends 1991; 65:16-20.

(12) Fleming DM. The contribution of influenza to combined acute respiratory infections, hospital admissions and deaths in winter. Communicable Disease and Public Health 2000; 3:32-38.

(13) Mason J, Drummond M, Torrance G. Some guidelines on the use of cost effectiveness league tables. BMJ 1993; 306:570-572.