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Cochrane re-arranged: Support for policies to vaccinate elderly people against influenza

Walter E.P. Beyer[a], Janet McElhaney[b], Derek J. Smith[c,d,a], Arnold S. Monto[e], Jonathan S. Nguyen-Van-Tam[f], Albert D.M.E. Osterhaus[a,*]

[a] Erasmus MC, Department of Viroscience, PB 2040, 3000 CA Rotterdam, The Netherlands
[b] University of Connecticut Health Center, Department of Immunology, 263 Farmington Avenue, Farmington, CT 06030-1915, USA
[c] University of Cambridge, Department of Zoology, Downing Street, Cambridge CB2 3EJ, UK
[d] World Health Organization Collaborating Center for Modeling, Evolution, and Control of Emerging Infectious Diseases, Cambridge CB2 3EJ, UK
[e] University of Michigan, School of Public Health, 1415 Washington Heights, Ann Arbor, MI 48109-2029, USA
[f] University of Nottingham, Health Protection and Influenza Research Group, Division of Epidemiology and Public Health, Clinical Sciences Building, Hucknall Road, Nottingham NG5 1PB, UK

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ABSTRACT

The 2010 Cochrane review on efficacy, effectiveness and safety of influenza vaccination in the elderly by Jefferson et al. covering dozens of clinical studies over a period of four decades, confirmed vaccine safety, but found no convincing evidence for vaccine effectiveness (VE) against disease thus challenging the ongoing efforts to vaccinate the elderly.

However, the Cochrane review analyzed and presented the data in a way that may itself have hampered the desired separation of real vaccine benefits from inevitable 'background noise'. The data are arranged in more than one hundred stand-alone meta-analyses, according to various vaccine types, study designs, populations, and outcome case definitions, and then further subdivided according to virus circulation and antigenic match. In this way, general vaccine effects could not be separated from an abundance of environmental and operational, non vaccine-related variation. Furthermore, expected impacts of changing virus circulation and antigenic drift on VE could not be demonstrated.

We re-arranged the very same data according to a biological and conceptual framework based on the basic sequence of events throughout the 'patient journey' (exposure, infection, clinical outcome, observation) and using broad outcome definitions and simple frequency distributions of VE values. This approach produced meaningful predictions for VE against influenza-related fatal and non-fatal complications (average ~30% with large dispersion), typical influenza-like illness (~40%), disease with confirmed virus infection (~50%), and biological vaccine efficacy against infection (~60%), under conditions of virus circulation. We could also demonstrate a VE average around zero in the absence of virus circulation, and decreasing VE values with decreasing virus circulation and increasing antigenic drift.

We regard these findings as substantial evidence for the ability of influenza vaccine to reduce the risk of influenza infection and influenza-related disease and death in the elderly.

1. The Cochrane review is challenging policies to vaccinate the elderly against influenza

If infected with seasonal influenza (virus type A or B), elderly people encounter a substantially elevated risk of developing non-fatal and fatal complications than adult persons of younger age [1]. Does influenza vaccination protect the elderly from influenza-related disease and death, and to what degree? A heated debate has recently arisen about this question. In particular, the comprehensive Cochrane review of 75 selected publications on influenza vaccine effectiveness (VE) and safety in the elderly [2] has been cited as a reason not to vaccinate the elderly, or at the very least to be highly sceptical about the possible public health benefits. Policies to vaccinate the elderly, as established in many countries [3], have been challenged and sometimes undermined.

Indeed, the Cochrane review concludes that the data from the selected original publications "*are so biased as to be virtually uninterpretable*". Principal concerns relate to the scarcity of randomized

* Corresponding author. Tel.: +31 10 7044066; fax: +31 10 7044760.
E-mail addresses: eva.editorialassistant.vaccine@gmail.com, a.osterhaus@erasmusmc.nl (A.D.M.E. Osterhaus).

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controlled trials (RCTs), the large number of observational studies of "*very low quality*" (with concomitant risk of selection bias), and inconsistent findings. The authors conclude that policies for vaccinating the elderly are either non evidence-based or, at best, based on poor quality evidence, and therefore vaccination of the elderly is not encouraged; a placebo-controlled trial run over several seasons should instead decide the question.

We hesitate to accept that the research efforts already made over several decades, with hundreds of studies performed and millions of persons participating, "*consistently fails to give satisfactory answers*" and has led to nothing more than inconclusive results. We note that the Cochrane authors had arranged the included data in more than one hundred stand-alone strata, according to various vaccine types, study designs, populations, outcome case definitions, virus circulation and degree of antigenic matching. When analysing the data in this way, general vaccine effects might not be visible given an abundance of non vaccine-related variation. In this case, it is potentially not the original studies that fail to give satisfactory answers, but the method in which they have been meta-analyzed.

Encouraged by the invitation of the Cochrane authors to produce "*any alternative interpretation*" of the evidence, we wondered how the *very same data* would behave when stratified according to a small number of soundly-based and disease-informed scenarios rather than in a blind meta-analysis textbook approach that has more than 100 scenarios. To be able to directly test the choice of stratification, we accepted *verbatim* the choices for inclusion and exclusion of publications made by the Cochrane authors, and used the exact same data. We approached our analysis from the basic sequence of events in the patient journey (exposure, infection, outcome/disease, and observation) to construct a simple biological and conceptual framework (Supporting Material 1). Accepted knowledge of the infection process [4], the rationale of vaccination [5], and a consideration of vaccine quality [6,7] were all taken into account. With only few, but broad, outcome definitions, we could express the results by simple frequency distributions of VE values, and corroborate them by the inverse variance-weighted method [8], which produces meta-analyzed VE means and associated confidence intervals.

Here, we show that our approach leads to meaningful predictions for VE against influenza-related fatal and non-fatal complications (average ~30% with large dispersion), typical influenza-like illness (ILI) without virus confirmation (~40%), disease with laboratory confirmation of virus infection (~50%), and biological vaccine efficacy against infection (at least 50%, more likely ≥60%), under conditions of known virus circulation. Minor and major antigenic drift has only a small average impact. We regard these findings as substantial evidence for the ability of influenza vaccine to reduce the risk of influenza infection and consequently influenza-related disease and death in the elderly. In our view, existing policies to vaccinate the elderly are vindicated and should be further implemented worldwide.

2. The original publications comprise 40 years of clinical research and are inevitably heterogeneous – this can be positively exploited

In their latest update published in 2010 [2], the Cochrane authors excluded 255 of 330 retrieved candidate publications (77%), and presented detailed information about the 75 included publications. Safety issues regarding influenza vaccines were not raised, and accordingly these are not examined in our paper. We focussed on vaccine effectiveness (VE), *i.e.*, the vaccine's ability to prevent an observed clinical outcome. Eventually, 248 VE values from one hundred trial-seasons were available from the Cochrane tables. Studies were performed in community-dwellers and nursing home residents, and took place across four continents from 1965 to 2005. This period covers the A-H3N2 pandemic (1968) and the re-emergence of the A-H1N1 subtype (1977). Few trials were RCTs, while the vast majority of trials were observational (case–control trials and cohort trials).

Inevitably, these data are heterogeneous by accidental, not vaccine-related variation, *i.e.*, the varying influence of individual, social, viral, seasonal, spatial, temporal and operational factors. Meta-analyses with an abundance of outcome definitions and formal strata may not be the optimal method to analyze these kinds of data. To unravel the real biological vaccine efficacy, *i.e.*, the vaccine's ability to prevent infection, the number of outcome definitions was substantially reduced from 14 to only three: laboratory-confirmed disease of any kind, influenza-like illness (ILI), and non-fatal and fatal complications (*i.e.*, serious morbidity and death from influenza-related causes). The outcome 'all-cause death' was handled separately because of extremely low specificity (see below).

Fig. 1 shows how the VE values from large numbers of heterogeneous trials would be distributed, with similar impacts of positive and negative accidental factors assumed (details are given in Supportive Material 1). When virus circulates during a trial and the vaccine is efficacious (Fig. 1A), the VE distributions rank hierarchically from lowest average outcome specificity (complications, blue) to that with highest specificity (laboratory-confirmed disease, green); all together they point to biological vaccine efficacy (black), the principal preventive effect of vaccination, which is not assessed directly. In the case of vaccine failure (vaccine efficacy varying around zero, Fig. 1B), the VE distributions would all peak at zero. In this visual way, we could discriminate between two basic scenarios despite, or thanks to, large heterogeneity between the original studies.

3. Within a biological framework, Cochrane's data reveal the efficacy of vaccinating the elderly

All we had to do was to group Cochrane's VE values according to virus circulation and alternative outcome, and to inspect, whether the resulting distributions would fit with the scenarios in Fig. 1. Our data processing is described in Supportive Material 2. We first excluded a number of VE values, mostly to avoid data redundancy. Our final database consisted of 165 VE values from 95 trials, involving 2,504,162 elderly persons, and described in 64 publications. We identified 40 VE values from trials likely performed in absence of virus circulation. Another 13 VE values against 'all-cause death' were treated separately. Finally, we could examine the vaccine performance under virus circulation, from the remaining 112 VE values (Fig. 2).

The distributions clearly do not resemble Fig. 1B, the scenario of vaccine failure and zero biological vaccine efficacy. Instead, the resemblance with the patterns of Fig. 1A is striking. The VE values against complications peak between 30 and 50%, with a meta-analyzed mean of 28% (95% CI 26–30%). VE values against ILI have a broad maximum between 30 and 70%; their meta-analyzed mean is plausibly larger (39%; 35–43%) than the effect against complications. VE values against laboratory-confirmed disease show a narrow distribution, which peaks between 50 and 70% (49%; 33–62%). Visual examination of the three distributions and comparison with those in Fig. 1 let us predict the biological vaccine efficacy in this dataset as being at least 50%, but likely 60% or larger.

In our approach, the data produce plausible VE patterns with respect to degree of virus circulation (decreasing VE values with decreasing virus circulation, see Supportive Material 2). Moreover, we found two interesting time trends, not noticed by the

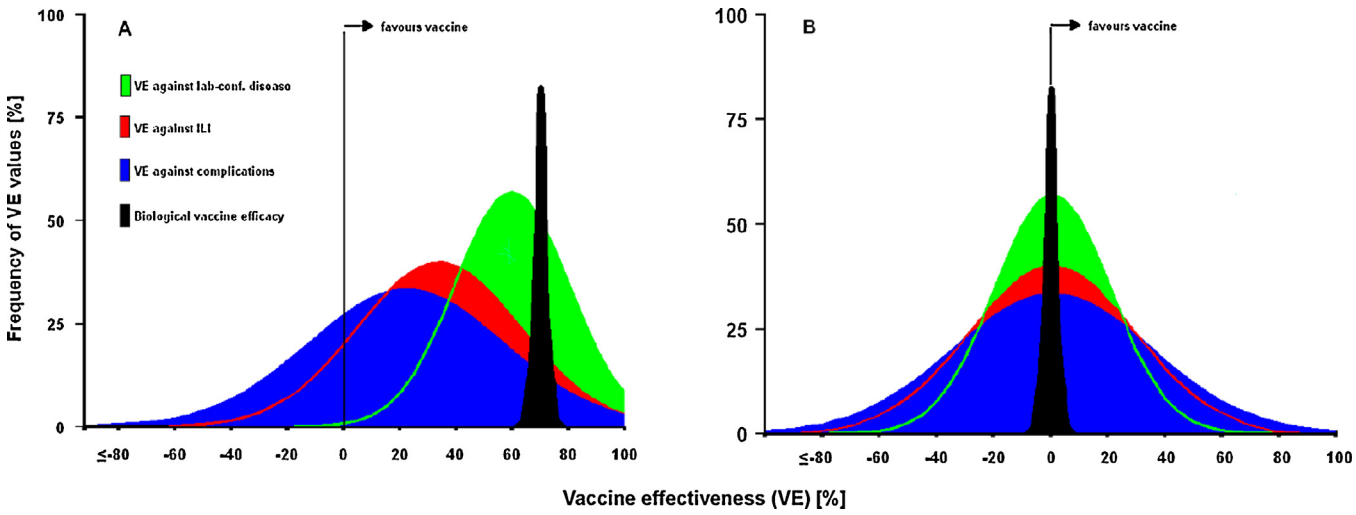

Fig. 1. Expected frequency distributions of vaccine effectiveness values during seasons with virus circulation. Scenario A: Efficacious vaccine. Scenario B: Vaccine failure (vaccine has zero efficacy).

Cochrane authors: The average vaccine coverage substantially rose from 43% in 1971 to 64% in 2004, and the average VE substantially fell from 52% to 26% in the same period. We discuss whether these time trends maybe causally related. Annually increasing vaccine coverage may successively hamper virus transmission and reduce exposure risk. This beneficial mass treatment effect would have a paradoxically negative impact on the VE measure, which decreases with decreasing exposure risk, falsely suggesting a decline in vaccine benefits.

The VE patterns with respect to antigenic drift are also plausible: VE values decrease with increasing antigenic distance between vaccine components and circulating strains. It is worth noting that even under conditions of substantial antigenic drift, vaccine still provided considerable protection, a finding not presented in the Cochrane review.

The outcome 'all-cause death' was analyzed separately. Given a low outcome specificity of up to 10%, VE values against this outcome would be expected to peak between zero and 5%. The distribution of the 13 all-cause death values, however, showed a surprising maximum between 50 and 70%, and a meta-analyzed mean of 48% (95% CI 47–50%) suggesting an overriding 'healthy user' bias. According to Simonsen et al. [9], the combination of both low outcome specificity and bias "*has produced a high degree of mismeasurement, leading to greatly inflated estimates*". Simonsen advises against using this outcome for the assessment of VE. We agree, certainly for the studies involved here. Interestingly, Fireman et al. [10] applied a new ingenious manner of bias control to all-cause mortality data from a large elderly population during nine influenza seasons. They found a plausible VE estimate of 4.6% (95% CI 0.7–8.3%) during influenza season, while the average excess mortality was estimated at 7.8%.

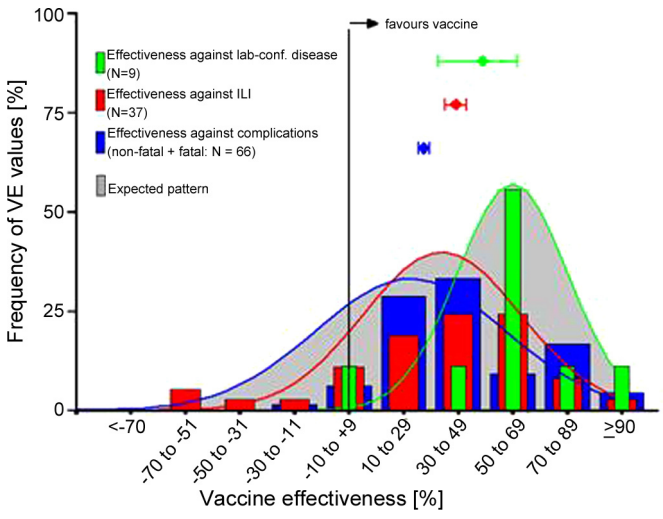

Fig. 2. Frequency distributions of vaccine effectiveness values from the original studies, during seasons with virus circulation.

4. Why did the Cochrane review not reach similar conclusions?

The Cochrane authors arranged the 248 identified VE values into 15 main comparisons with more than 100 different strata. Furthermore, there is an abundance of fourteen outcome definitions. We would call this arrangement an over-stratification, which has impeded the identification of vaccine effects. Their analysis was further weakened by disturbing misclassification. We could demonstrate, for example, that Cochrane's sub-division for the dichotomy 'outbreak/epidemic' *versus* 'no outbreak/no epidemic' was not successful: Some trials performed under virus circulation as described in the original publications, were nevertheless classified as 'no outbreak/no epidemic', and *vice versa* (Supporting Material 3).

In conclusion, the Cochrane review usefully collects data from a large number of studies on the effects of influenza vaccination in the elderly, but Cochrane's data analysis is not guided by biological criteria and has consequently regarded the data as being inconclusive and uninterpretable. In contrast, our re-arrangement of the same data into more clinically meaningful scenarios has demonstrated the beneficial effects of vaccination. We suggest that vaccination of the elderly is efficacious in reducing infection, disease, and death, caused by influenza virus infection; is worthwhile as a public health intervention; and that there is a sound scientific basis for the recommendations made by the World Health Organization, and multiple international and national bodies.

Certainly, the Cochrane authors have a point when criticizing short-cut messages to the public as "flu shot prevents death". Such misleading messages are based on biased 'all-cause death' studies and should be avoided. A more correct notion would be: "Influenza vaccination reduces the likelihood of suffering from disease and death caused by influenza virus infection."

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Conflict of interest

WEPB has held consultancies with pharmaceutical companies. JEM has received honoraria, consultancies, reimbursement for travel to meetings and research grants from the pharmaceutical industry. DJS reports no conflicts of interest. ASM has received consulting fees from pharmaceutical companies. JSNVT has received funding to attend influenza related meetings, lecture and consultancy fees and research funding from several influenza antiviral drug and vaccine manufacturers. Research funding from GlaxoSmithKline, Astra-Zeneca and F Hoffmann-La Roche is on-going; all forms of personal remuneration ceased in September 2010. He is a former employee of SmithKline Beecham plc. (now GlaxoSmithKline), Roche Products Ltd. (UK) and Aventis-Pasteur MSD (now Sanofi-Pasteur MSD), all prior to 2005, with no remaining pecuniary interests by way of share holdings, share options and accrued pension rights. A.D.M.E. Osterhaus is no longer CSO but a consultant to Viroclinics Biosciences BV, a contract research organization that collaborates with pharmaceutical companies and also CEO of Artemis BV, a organization which deals with infectious and non-infectious causes of wildlife disease.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.09.063.

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