

ORIGINAL RESEARCH

Efficacy of influenza vaccination in HIV-positive patients: a systematic review and meta-analysis

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Background

International treatment guidelines recommend that HIV-positive patients be vaccinated for influenza annually. Evidence supporting this recommendation is limited. We assessed the efficacy of influenza vaccines in preventing influenza in HIV-positive patients through a systematic review and meta-analysis.

Methods

We searched 10 electronic databases independently, in duplicate (from inception to June 2007). We extracted data on study design, population characteristics and outcomes related to influenza symptoms and antibody titres. We pooled data using a random effects model and conducted sensitivity analyses to evaluate heterogeneity.

Results

We included four studies. Three studies were evaluable for meta-analysis and yielded a pooled relative risk reduction (RRR) of 66% [95% confidence interval (CI) 36–82%; $I^2 = 73\%$]. One case–control study yielded an odds ratio of 1.98 (95% CI 0.75–5.20). When we assessed heterogeneity according to study design, we found that the study of the highest quality, a randomized clinical trial (RCT), yielded the most conservative estimate (RRR 41%; 95% CI 2–64%).

Interpretation

Evidence supporting influenza vaccination of HIV-positive individuals is limited, poorly quantified and characterized by substantial methodological shortcomings. A reasonable estimate of influenza vaccination effectiveness in HIV-positive patients cannot be derived from these data. There is an urgent need for randomized trials to guide policy and clinical practice.

Keywords: HIV, influenza vaccination, meta-analysis

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Introduction

Influenza has been responsible for considerable morbidity in HIV-infected individuals, including those treated with highly active antiretroviral therapy (HAART) [1,2].

Domestic and international guidelines recommend that HIV-infected individuals receive once-yearly vaccination [3–5]. However, conflicting information exists with regard to the effectiveness of influenza vaccines in HIV-positive individuals. A previous systematic review and meta-analysis of four studies attempted to assess the efficacy and clinically effectiveness of influenza vaccines in HIV-positive individuals [6]. However, methodological limitations of the study warrant re-evaluation of this issue. We re-conducted a systematic search and pooled data according to established meta-analysis techniques [7].

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Methods

Eligibility criteria

We included any randomized clinical trial (RCT), cohort, or case–control study evaluating the efficacy of influenza vaccine in HIV-positive individuals. We included studies of any duration. Studies had to compare influenza vaccine with no vaccine in assessing the clinical endpoint of

influenza symptomology. We excluded studies assessing only antibody titres, but abstracted information on this as a secondary outcome.

Search strategy

In consultation with a medical librarian, we established a search strategy (available from the corresponding author on request). We searched independently, in duplicate, the following 10 databases (from inception to June 2007): MEDLINE, EMBASE (Excerpta Medica), Cochrane Central Register of Controlled Trials (CENTRAL), Allied and Complementary Medicine Database (AMED), Cumulative Index to Nursing and Allied Health Literature (CINAHL), TOXNET, Development and Reproductive Toxicology, Hazardous Substances Databank, Psych-info and Web of Science. We also searched databases that included the full text of journals (OVID, ScienceDirect and Ingenta, including articles in full text from approximately 1700 journals since 1993). In addition, we searched the bibliographies of published systematic reviews [8] and protocols. We also contacted the authors of studies for clarifications, where required. Searches were not limited by language, sex or age.

Study selection

Two investigators (AA and EM) working independently, in duplicate, scanned all abstracts and obtained the full-text reports of records that indicated or suggested that the study met inclusion criteria for the outcomes of interest. After obtaining full reports of the candidate trials, the same reviewers independently assessed eligibility from full-text papers. We judged study quality according to the established hierarchy of evidence, with randomized trials judged as superior, followed by observational studies and case–control studies.

Data collection

The same two reviewers conducted data extraction independently using a standardized pre-piloted form. Reviewers collected information about the study design, vaccine strain, dosage schedule, population studied (age, sex and underlying conditions), treatment effects on specified outcomes, antibody responses and HAART regimens. We entered the data into an electronic database such that duplicate entries existed for each study; when the two entries did not match, we resolved differences by consensus.

Data analysis

In order to assess inter-rater reliability in terms of inclusion of articles, we calculated the π statistic, which provides a measure of inter-observer agreement independent of chance [9]. For prospective studies, we calculated the relative risk (RR) and appropriate 95% confidence interval (CI) of outcomes according to the number of events reported in the original studies or substudies. For the case–control study, we calculated the odds ratio and 95% CI. In the event of zero outcome events in one arm of a trial, we used the Haldane method and added 0.5 to each arm [10].

We pooled prospective studies for an analysis of all prospective studies combined using the DerSimonian–Laird random effects model [8], which recognizes and anchors studies as a sample of all potential studies, and incorporates an additional between-study component to the estimate of variability [11]. We calculated the I^2 statistic for each analysis as a measure of the proportion of the overall variation that is attributable to between-study heterogeneity [12]. Because of the small number of studies pooled, we evaluated heterogeneity according to *a priori* defined criteria, assuming that randomized trials would yield a more conservative effect estimate than nonrandomized studies.

As a secondary analysis, we re-conducted the analysis performed by Atashili *et al.* [6], pooling studies using the risk difference (RD). We did not pool case–control studies with prospective studies, given their very different approaches and objectives. Forest plots are displayed for each analysis, showing individual study proportions with Clopper–Pearson 95% CIs, and the overall DerSimonian–Laird pooled estimate. Analyses were conducted using STATSDIRECT (version 2.6.2; Stats Direct Ltd, Manchester, UK).

Results

We screened 62 abstracts for inclusion in our meta-analysis, and excluded 55 of these on the basis that either their content was irrelevant or their reporting was not amenable to quantitative analysis. We retrieved seven full-text articles for potential inclusion. Three of these were eliminated as they did not adequately address the outcomes of interest. We excluded a randomized trial on the basis that outcomes were described solely in terms of serological, HIV virological and CD4 immunological responses [13]. A further study was eliminated because the outcome described influenza antibody titres, as opposed to confirmed influenza incidence [14]. A case–control study was excluded because it provided incomplete information about incident influenza cases, which were mentioned as secondary outcomes [1].

The study characteristics and results for the four studies included in our review are described in Table 1. We did not include the case–control study in the pool as the impact of

Table 1 Study characteristics and results

Author, year [reference]	*n*	Setting	Mean patient age (years)	Study design	Active	Control	Vaccine strain	Baseline measurement	Outcome measurement	Primary outcome: influenza incidence (active)	Primary outcome: influenza incidence (control)
Yamanaka *et al.*, 2005 [17]	328	Japan	40.8	Cohort	Vaccinated $n = 262$	Unvaccinated $n = 66$	A/New Caledonia 20/99 (H1N1) A/Panama 2007/99 (H3N2) B/Shanton 7/87	CD4 cell counts Plasma HIV-1 RNA Influenza antibody titres HAART use	Influenza symptoms: $\geq 38^{\circ}C$, and two of the five following clinical symptoms: cough, rhinitis, myalgia, sore throat and headache, and 4-fold increase in antibody titre	Vaccinated 16/262	Unvaccinated 14/66
Ranieri *et al.*, 2005 [18]	145	Italy	20–26	Cohort	Co-vaccinated for pneumonia and influenza $n = 90$	Vaccinated for pneumonia $n = 55$	Inflexa V, Berna	CD4 cell counts Plasma HIV-1 RNA HAART use History of pneumonia and influenza vaccines	Influenza virus	Vaccinated for pneumonia 12/90	Vaccinated for pneumonia and influenza 34/55
Fine *et al.*, 2001 [15]	71	USA	38	Case–control	Vaccinated $n = 42$	Unvaccinated $n = 29$	A/Nanchang 933/95 (H3N2) A/Texas 36/91 (HINI) B/Harbin 07/94 York 83/97 (H3N2)	CD4 cell counts Plasma HIV-1 RNA Influenza antibody titres HAART use Vaccination status, job type, work schedule, smoking habits	Influenza symptoms: $\geq 37.8^{\circ}C$ and presence of cough/sore throat, and 4-fold increase in antibody titre or laboratory isolation of influenza virus	Vaccinated 19/42	Unvaccinated 18/29
Tasker *et al.*, 1999 [16]	102	USA	33	Randomized	Vaccinated $n = 47$	Placebo $n = 55$	A/Johannesburg 33/94 (H3N2) A/Texas 36/91 (H1N1) B/Harbin 07/94	CD4 cell counts Plasma HIV-1 RNA Influenza antibody titres HAART use	Influenza antibody titres Change in HAART regimen Viral culture Influenza symptoms: rhinitis, pharyngitis, cough	Vaccinated 23/47	Placebo 16/55

HAART, highly active antiretroviral therapy.

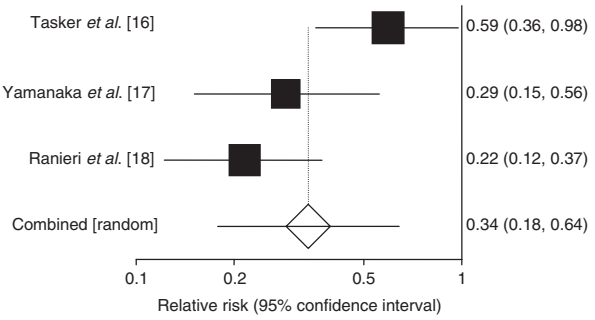

Fig. 1 Relative risk meta-analysis plot (random effects).

influenza vaccine on HIV-positive individuals was not determined prospectively [15]. There was near-perfect inter-reviewer agreement on three studies for pooling, enrolling a total of 575 HIV-positive patients ($\pi \geq 0.9$). Studies were conducted in a variety of developed countries, including the USA [16], Japan [17] and Italy [18]. One study was a RCT ($n = 102$) and two were controlled cohorts (total $n = 473$). Patients were evaluated for an average of 21 weeks (range 4–52 weeks). Different vaccine strains were utilized in each study.

We pooled the prospective studies. Figure 1 displays the pooled forest plot for all the prospective studies. The pooled RR was 0.34 (95% CI 0.18–0.64; $P < 0.0001$; $I^2 = 73\%$; heterogeneity $P = 0.02$). As we anticipated heterogeneity, we evaluated whether cohort studies yielded larger effect sizes than the RCT and found that the study design contributed to overall heterogeneity ($P = 0.0013$). The single case–control study yielded an odds ratio of 1.98 (95% CI 0.75–5.20). When we re-conducted the analysis performed by Atashili *et al.* [6], we found a pooled RD of -0.27 (95% CI -0.49 to -0.06; $P < 0.0001$; $I^2 = 86\%$; heterogeneity $P = 0.001$).

Discussion

Our pooled analysis indicates that the use of influenza vaccination is associated with a relative risk reduction (RRR) of 66% for the development of symptomatic disease in HIV-infected individuals. However, there is reason to question this figure as the single RCT, which is considered the optimal study design in terms of producing precise estimates of risk, yielded a far more conservative RRR estimate of 41% (95% CI 2–55%). Based on these considerations we feel that there is a clear and pressing need for definitive RCTs to evaluate the effectiveness of influenza vaccination in HIV-infected individuals.

We re-analysed the study by Atashili *et al.* [6] and found that their analysis had two important limitations: (1) case–control studies were pooled with prospective studies; and (2) numerical values were incorrectly entered into the meta-analysis, leading to skewed outcomes. While we do not wish to unreasonably criticize the authors of this otherwise well written paper, we believe that our meta-analysis provides a closer approximation to the real estimate of the effect and, rather than providing a clinically useful effect estimate, we believe that we demonstrate that further RCTs are needed.

Given the small number of studies included, we were unable to perform more detailed sensitivity analyses, such as assessments of the effects of specific vaccine strains or the effect of vaccines on patients currently receiving HAART. A comparative analysis of secondary outcomes was also not possible because of the variability in the impact measurement techniques. Several of these studies were conducted in the early era of HAART therapy. The populations assessed may not therefore be fully comparable to currently treated HIV-infected patients in terms of HAART efficacy and baseline immune status.

A better understanding of the role of influenza vaccination in developing countries is also warranted. The studies included in this meta-analysis were conducted only in developed countries. Given the now recognized burden of influenza in tropical regions [19], future research should be directed at understanding vaccine efficacy in settings where risk of co-infection is greatest.

Conclusion

Evidence supporting influenza vaccination within the HIV-positive population is limited, poorly quantified and characterized by substantial methodological shortcomings. Our analysis highlights the urgent need for further RCTs assessing the clinical effectiveness of influenza vaccine on HIV-positive individuals.

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