CRD summary
The authors’ conclusion, that tetanus vaccination is associated with a reduced risk of multiple sclerosis, appears to be supported by the evidence presented. However, poor reporting of the review methods, and the lack of a quality assessment in a review that is reliant upon observational data, make it difficult to confirm the reliability of the authors’ conclusion.

Authors’ objectives
To examine the association between tetanus vaccination and the risk of multiple sclerosis (MS).

Searching
MEDLINE (from 1966), LILACS, EMBASE and the Science Citation Index were searched to September 2005 using the reported search terms. In addition, reference lists of identified studies and published articles on the epidemiology of MS were screened.

Study selection
Study designs of evaluations included in the review
Case-control and cohort studies were eligible for inclusion. All of the included studies were case-control studies; some were nested case-control studies.

Specific interventions included in the review
Studies that attempted to ascertain vaccinations for the period before the diagnosis of MS were eligible for inclusion. Most of the included studies ascertained vaccination status by self-report; others used computerised records. Exposure period of vaccination, where reported, ranged from lifetime exposure to less than 3 years before the diagnosis of MS; however, most studies did not specify the exposure period. The studies were conducted in six countries.

Participants included in the review
Studies of patients with a physician-confirmed diagnosis of MS were eligible for inclusion. Comparator groups were hospital patients, the general population, patients with other neurological diseases, blood donors, friends and relatives.

Outcomes assessed in the review
Studies had to report a measure of association between tetanus vaccination and the incidence of MS, along with its 95% confidence interval (CI), or sufficient data to calculate these data, to be eligible for inclusion.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity. Information on vaccination assessment, use of adjustment variables and exposure period were reported.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For each study, data were extracted to calculate a log odds ratio (OR) with 95% CI. Authors of reports with missing data were contacted for additional information.

Methods of synthesis
How were the studies combined?
The studies were combined to calculate a pooled log OR with 95% CI, weighted by the inverse of their variance. Random-effects and fixed-effect models gave similar results, thus only the results for the fixed-effect model were
presented. The possibility of publication bias was explored using a funnel plot and using sensitivity analyses (where the pooled OR was calculated assuming an equal number of unidentified studies which all had an OR of 1).

How were differences between studies investigated?
Heterogeneity was examined using the parametric bootstrap technique (1,000 replications), and the I-squared statistic was also calculated. Subgroup analyses were performed on studies that adjusted for age and gender, studies nested in a well-defined cohort, studies that attempted to verify vaccination before the first symptom of MS (compared with diagnosis of MS), and studies that reported an association with recent (5 years or less) tetanus vaccination.

Results of the review
Nine case-control studies (963 cases and 3,126 controls) were included.

Six of the 9 included studies did not specify which variables were adjusted for in the analyses. Seven studies used self-reporting vaccination assessment and six did not define the period of exposure.

The pooled analysis showed that tetanus vaccination was associated with a statistically significantly reduced likelihood of MS (OR 0.67, 95% CI: 0.55, 0.81). No significant statistical heterogeneity was found (p=0.41; I-squared 2.5%).

The subgroup analysis showed that the results were similar for studies that adjusted for age and gender (3 studies), studies nested in a well-defined cohort (2 studies), studies that attempted to verify vaccination before the first symptom of MS (3 studies), and studies that reported an association with recent (5 years or less) tetanus vaccination (2 studies).

The funnel plot showed no evidence of sizeable publication bias, but was based on a small number of studies. The sensitivity analysis showed a similar result.

Authors’ conclusions
Tetanus vaccination is associated with a one-third reduced risk of MS compared with no vaccination.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched but no specific attempts to minimise language or publication bias were reported. However, the potential for publication bias was assessed and no evidence of it was found. The absence of a systematic validity assessment means it is difficult to ascertain the reliability of the evidence presented. This is of particular importance in this review since the evidence is based on case-control studies which are particularly at risk of confounding and biases. The methods used to select studies and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer error and bias. Statistical heterogeneity was assessed, studies appear to have been appropriately combined in a meta-analysis, and subgroup analyses were used to examine the influence of several factors. Overall, the authors’ conclusions appear to be supported by the evidence presented. However, lack of reporting of review methods and, more importantly, the lack of a quality assessment make it difficult to confirm the reliability of the authors’ conclusion.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated the need for further epidemiological research to evaluate the effect of timing and number of doses of tetanus vaccination on the risk of MS.

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