Reviewer's report

**Title:** Proton Pump Inhibitors and the risk of pneumonia: a comparison of cohort and self-controlled case series designs

**Version:** 3 **Date:** 10 January 2013

**Reviewer:** Jessica Myers

**Reviewer's report:**

Major Compulsory Revisions

Now that the methods have been described more fully, I have some concerns about the design. Specifically, the assessment of several confounders is done on an annual basis, and is time-varying throughout the follow-up period. Therefore, these confounders (including number of comorbidities, number of prescription, etc.) may be (and several likely are) mediators on the pathway from exposure to outcome. For example, initiation of a PPI for some patients will cause an increase in the use of health services and subsequently an increase in hospitalization for pneumonia. There is a large literature on the detrimental effects of adjusting for a mediator. It is for this reason that most new-user cohort designs measure covariates only prior to exposure and do not consider time-varying confounding.

p.8 - Removing the period of unexposed time immediately prior to exposure seems like a good idea in the SCCS. However, the same concern exists for the cohort design, since that time contributes to the unexposed time in that analysis.

**Level of interest:** An article whose findings are important to those with closely related research interests

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

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests