Reviewer’s report

Title: Robustness of the healthcare utilization results from the Rotavirus Efficacy and Safety Trial (REST) evaluating the human-bovine (WC3) reassortant pentavalent rotavirus vaccine (RV5)

Version: 1 Date: 13 January 2010

Reviewer: Mark Jit

Reviewer’s report:

Overall this is a highly useful paper. Although the original analysis of REST study results has already been published in the NEJM, that paper only provided PP results. For predictions of vaccine impact in real world situations (eg economic evaluations), more inclusive results such as the MITT results provided here are more applicable. The statistical analysis used to produce these results appears to be sound. However, there are a number of areas in presentation that could be considered to make the results more useful.

Major compulsory revisions

1. The main point of the paper is to compare vaccine-related rate reductions in healthcare encounters between the original, less externally valid figures reported in the NEJM paper (PP, G1-G4 serotypes only) and those in this re-analysis (MITT, all serotypes). However, the paper as it is written does not make it very easy to do a direct comparison. It would be helpful to readers to provide the original figures for comparison when the new ones are reported. For example, on page 11 to provide the rate reduction against G1-G4, on page 12 to provide the PP rate reduction and so forth. Some (though not all) of this information can be obtained from the tables, but it would be helpful if direct comparisons were made in the text.

2. I don’t think the authors can claim that “the estimates of rate reductions in healthcare utilization were consistent regardless of differences in study population, timing of healthcare encounters, intensity of surveillance, serotypes and geographical region”. What the paper shows is that there is (as expected) a small but not negligible reduction in the protective effect of vaccination when moving from a PP to MITT population, or from G1-G4 serotypes to all serotypes. I think a milder claim eg. “the estimates of rate reduction in healthcare utilization remained very high” is more justifiable.

3. The differences between the PP rate reduction in the NEJM paper and the MITT rate reduction in this paper could be due to a number of reasons, the most obvious being: (i) inclusion of more of the vaccinated infants excluded from the PP analysis who are less likely to benefit from vaccination and (ii) inclusion of the time period during which infants only received one or two doses of vaccine, as well as the time period immediately following vaccination when vaccine-induced
antibody titres have not reached protective levels. It would be useful if there could be some attempt to separate out the two effects as far as possible. For example, the authors could conduct a separate MITT including as many participants as possible but only counting events occurring two weeks after the final vaccine dose. (There would obviously be some differences between the included cohort in MITT and the new MITT2, but at least there would be some basis for comparison which is better than guessing.)

4. Also, the authors describe well the participants excluded from the MITT analysis, but do not describe the participants included in the MITT analysis but excluded from the PP – presumably some of these exclusions contribute towards the higher PP rate reduction.

Discretionary revisions

1. The original NEJM paper also provided the PP clinical efficacy of the vaccine against rotavirus gastroenteritis of any severity. Would it be possible to now provide MITT figures for the same endpoint?

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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

Declaration of competing interests:

I declare that I have no competing interests.