Reviewer's report

Title: Is HPV-16 seropositivity a correlate of immunity? Insights from compartmental models

Version: 2 Date: 29 August 2012

Reviewer: Zoe R Edelstein

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In this paper, the authors' used modeling techniques and national data from Australia to attempt to answer the extent to which seropositivity confers immunity against re-infection with the same HPV type (in this case, HPV type 16). The limited number of studies that measure HPV seroconversion is a testament to the difficulty of carrying out individual level studies that measure both HPV serology and infection status (by presence of HPV DNA) over time. Thus, the authors’ approach using population level transmission models and Bayesian techniques with evidence-based “priors” could help fill a gap in knowledge, using an innovative and grounded approach.

I have listed suggested revisions below.

Major Compulsory Revisions

1. The authors use 8 disease transmission models in total. Clearly a lot of thought went into the construction of these models and the authors describe their components in the Background and Methods section, as well as in Table 1, Figures 1-3 and Appendix. However, I still had some trouble following these explanations and how the models differed from one another. Some suggested revisions and clarifications are listed below. Though some are minor, taken together they appear to be a major revision:

a. The definition of “+” as seropositive should be added to the methods section text

b. I found Table 1 to be the most effective guide for understanding the differences between models once the number of model types went from three (SIS, SIR and SIRS) to eight. I suggest referencing Table 1 earlier in the text and describing the differences between models with reference to it.

c. . . . However, with regard to Table 1, “immunity” against infection, as it appears to be defined (more this below) does not seem to apply to SIRS3 and SIRS4, unless I misunderstanding the loops R+ to S+ to I+.

d. For the list of parameters in Table 2,

i. My understanding is that betas come be represented as lambda in the technical appendix and in Figures 1-3. This needs to be clearer either by footnote or other edit, as do other differences in definition between the list of coefficients and
Table 2 (e.g. risk reduction versus degree of protection; probability of transmission versus force of infection)

ii. Are the durations in years?

2. It should be stated if the DIC value is based on calibration to the serology data, the DNA detection data or both, as well as either or both genders. It appears there is only data for DNA prevalence for women aged 15-39 (based on the results and the cited article). This should be clarified in the methods and if used in the DIC value please state how the data limitations for DNA prevalence limit the DIC estimation.

3. The authors compartmentalize age and gender. There are some limitations to their models regarding age (regarding serology parameters), but these are acknowledged. For gender they state that they assume the natural history of infection to be the same in men and women, though rates of transitions may differ. This may be a strong assumption especially when comparing SIS to SIRS models, based on the little that is known about HPV natural history regarding serology and also simulated serology results in Figure 4. Unless I am mistaken, the authors have the ability to use their data to test this assumption (e.g. a best fit by DIC for each gender).

It is possible that this is what is being referred to in the sentence on page 14 that begins “Unfortunately…” (Either way, the results from which this statement is derived should probably be made more clear.)

4. I am not entirely sure that the results support the conclusion that seropositivity and immunity are completely “decoupled,” especially for women. In the model with the best fist (SIS2), the degree of protection inferred is between 0.7 and 0.9 for women, suggesting a high probability of immunity. This high degree of protection is explained in the discussion, but not the abstract or conclusions. It appears that the authors define immunity as it exists in the SIR model: 100% (at a population level) and as lifetime immunity. Without some tempering statements regarding the lack of relationship between seropositivity and immunity (for example mentioning the degree of protection or using a term such as “lifetime immunity”), their conclusions could be misinterpreted.

5. The authors should discuss the possibility of re-activation of infection as opposed to re-infection. They should also discuss any limitation of using prevalence of infection (by DNA) versus a measure of incidence, as well as only measuring DNA prevalence at the cervix.

Minor Essential Revisions

1. On page 4, the sentence that starts “However, in view…” is quite confusing. Please either restructure the sentence or split it up.

2. On page 8, the sentence that begins “Differences…” is also confusing. Consider cutting the text from “in” to “models”
Discretionary Revisions

1. In the abstract, the authors should consider mentioning that they included both men and women, as many readers will want to know this.

2. The text on the 60+ category seems non-essential unless the authors want to discuss Burchell et al’s review (Vaccine, 2006) that showed HPV DNA prevalence goes up in the older women w/o adjustment for age (but not with adjustment).

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests