Reviewer's report

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

Version: 2 Date: 18 September 2012

Reviewer: Johannes A Bogaards

Reviewer's report:

IA Korostil et al. Is HPV-16 seropositivity a correlate of immunity? Insights from compartmental models

The authors have performed an interesting modelling study with regard to the protective value of HPV-16 seropositivity, which is evaluated in a variety of transmission models, all with different assumptions as to how seropositivity is related to natural immunity. Using Bayesian model comparison criteria, the authors claim that a model of type SIS (which does not equate seropositivity with immunity) provides the best description of "real data".

Major Compulsory Revisions

The paper is clearly written and the mathematics appears to be well understood. The possibility of inferring natural immunity from cross-sectional age-specific prevalence data of HPV infection (DNA prevalence) and seropositivity is an interesting notion that deserves more investigation. The simplicity of the models under investigation in this paper is attractive as well as a drawback. For instance: all models perform poorly in predicting HPV DNA prevalence among women, and it seems that the selection of SIS-type models is mainly driven by their ability to at least provide predictions within the 95% confidence intervals of the data. My guess is that predictions would be substantially improved if viral persistence is included in the models, which could give a completely different ordering of models from "best" to "worst" according Fig 5. As far as HPV-16 goes: the proportion of DNA-positive women with a persisting infection rapidly increases as a function of age, which lessens the requirement for reinfection as a means to reproduce a certain level of HPV infection in the population.

Another major concern is the construction of priors and the lack of information given about posteriors. It seems that the authors have used highly informative priors, even if there is no substantial (or clear-cut) empirical evidence (a case in point: duration of natural immunity; Tsc, Tsr and Tcl are also not clear from Table 3). In the few instances that information is given about posteriors, it seems that they do not diverge strongly from the priors. This suggests that MCMC does not contribute much to DIC and raises the possibility that model selection is performed on a rather static (and far from optimal) set of models. More information on model fitting procedures is definitely needed to judge the validity of model estimates, and of model selection.
The authors should contrast their findings and interpretations with those of others. Although it is claimed that "these [i.e. serological] data have generally not been considered in the development and calibration of transmission models", some of the cited references already calibrated models to HPV-16 seroprevalence (e.g. Barnabas, PLoS Med 2006) with explicit assumptions about the relationship between seropositivity and immunity. Others (e.g. Bogaards, Am J Epidemiol 2010) have also estimated rates of natural immunity from prevalence data over the range from SIR, SIRS, to SIS models; and concluded that SIRS provided the description of data. It is of interest to know if (and if so; why?) the authors arrive at different conclusions as compared to previous modellers.

Finally, the take-home message (that SIS-type models provide superior fit of "real data" and that HPV-16 seropositivity is not a correlate of natural immunity) might be slightly misleading. Regarding the former: the authors do not investigate SIS models, because the risk of reinfection is always reduced after resolution of infection. In effect, the authors model partial immunity on a population level, which translates into a certain probability to become immune upon viral clearance on the individual level. In this sense, I cannot imagine that a SIRS model with initially fast decay of natural immunity could not describe the data as well as a "SIS-type" (=partial SIR) model does. Regarding the latter: the authors might as well conclude that HPV-16 seropositivity is a correlate of immunity (albeit a poor one) since there is a correlation between seropositivity and being protected from reinfection in their models. The point is that this correlation is far from perfect, as seropositive individuals may still be at risk for reinfection. The authors must soften their conclusions and the epidemiological literature on this topic could also be discussed to greater extent.

In conclusion, I think that the authors hint at an interesting interpretation of seropositivity in HPV infection dynamics but must make a more convincing case that their conclusions are valid and robust to alternative assumptions.

Minor Essential Revisions

Table 2 = Table 1 and Table 3 = Table 2. Fig 5 is not at all informative; this information should be in a Table (Table 3).

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.