Reviewer's report

Title: Evaluating human papillomavirus vaccination programs in Canada: should provincial healthcare pay for voluntary adult vaccination?

Version: 1 Date: 27 November 2007

Reviewer: Ralph Insinga

Reviewer's report:

General

This study describes a mathematical model of HPV infection in the Canadian population and projected reductions in the incidence of infections over time following the introduction of HPV vaccines. While this is a timely topic given the recent approval of HPV vaccines in a number of countries, the manuscript needs to be more transparent with respect to data sources and values used as assumptions, and also more realistic in modeling sexual activity within the population and prevalent HPV infections at the time of vaccination as described within the major comments below. Otherwise, I am concerned that the simplifying assumptions made by the model significantly over-estimate the degree to which HPV infections can be eradicated within the population and that the results lack face validity.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Abstract – In the abstract, and throughout the paper, it should be made clear that the results concerning eradication apply to vaccination against a specific HPV type. There are more than 100 HPV types, the vast majority of which fall outside the coverage of current vaccines and many of which I suspect will never be covered by a vaccine due to their benign nature. Thus, it is not really practical to speak of eradication of all human papillomavirus infections at this time.

Pg. 3 – First paragraph – The statement regarding HPV vaccines not being likely to be efficacious in men should be deleted as clinical trials in men are on-going and the results will be known relatively soon. Also, how do imperfect “take” and incomplete “efficacy” differ?

Pg. 3 – To make the model results more informative, some of the parameters should better reflect population data. First, please specify the age at which females enter the model as children. If the age is between 9 and 13 years then it would seem unlikely that the time until progression to sexual activity (adults) would be 10 years given that the median age of sexual debut in Canada is likely to be in the range of 16 to 18 years of age (and thus time in the sexually active pool will be longer than 4 years on average). Also, can heterogeneity in time to sexual debut be modeled as occurs in practice? I would expect adjustments to
these values to have important consequences for the conclusions regarding
ability to eradicate infection and disease. Finally, vaccination will be less effective
if there is sexually mixing across different age groups (e.g., older infected males
outside of the vaccine age range infecting younger females who have not been
vaccinated who in turn infect other males). It is unclear from the Methods section
if, and how, this was modeled and clarification is needed.

Pg. 5 – Last paragraph – In the second limitation does this also mean that each
man can only have one sexual partnership in his lifetime with someone in his
own or an immediately adjacent age group? If so, this would greatly
under-estimate the degree of sexual activity in the population.

Pg. 6 – Second paragraph – The conclusion regarding adult vaccination being
more efficient than childhood vaccination, all else equal, does not seem to be
correct. Adults will be more likely to be previously infected with one or more HPV
types targeted by a vaccine than a child, and with equivalent coverage rates and
lifetime duration of vaccine efficacy, childhood vaccination would more efficiently
contribute towards infection eradication. Also, if a binary choice and a continuous
rate are to be compared equivalently, they should be equalized over their
duration so that cumulative coverage rates are truly equal among children and
adults.

Pg. 6 – Second paragraph – The findings of this model should be placed in the
context of prior work involving dynamic transmission models of HPV infection and
population impact by others (e.g., Barnabas, Elbasha, Hughes, Kim). Are there
major differences in findings with respect to these prior studies? Can the reasons
be explained?

Pg. 6 – Last paragraph - It does not seem appropriate to assume that all
individuals are vaccinated before infection among the adult women, given that
HPV is prevalent among this age group. Some modeling of vaccination of
individuals with prior HPV infection is needed.

Pgs 6-10 – There are major gaps in the Methods section in terms of the
presentation of model assumptions. Data assumptions and sources for important
parameters such as the total age range encompassed by the model (and what
age categories were used), mean number of sexual partnerships by age,
assortativeness of sexual partnerships, probability of transmission, duration of
HPV infection, presence/duration of natural immunity following HPV infection and
the specific HPV type or types modeled should be included. Also the age-specific
prevalence of HPV infection in the absence of vaccination that is outputted by the
model should be reported, and described in comparison to available population
data.

Figure 3A – This should probably be separated into two figures as it is very
confusing to read as a single figure (e.g. vertical axis which goes from 0 to 2).

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of
a term, which the author can be trusted to correct)

Abstract – Background - Please indicate the exact ages ranges for vaccination (i.e., substitute exact age range for "school-aged" as well as for "adult women"). Also note that $400 vaccine cost is in Canadian dollars.

Abstract – Conclusions – Please indicate an age range for recommendation of voluntary adult vaccination, or at least where in the life cycle (young adult women, mid-adult women, elderly women).

Pg. 2 – First paragraph – "Infections" should be changed to "disease" and vaginal and vulvar cancers as well as cancers of the head and neck could also be mentioned here. HPV is typically characterized by "types" rather than "strains". Reference 3 appears to be miscited. "Incidence" in middle of paragraph should really be "risk of transmission given contact with an infected partner". In the last sentence, the Pap smear does not detect HPV, but only provides an indication that HPV disease may be present. HPV tests can actually detect HPV but are not yet widely in use worldwide.

Pg. 2 – Second paragraph – Progression to malignancy – as noted in the Lowy article "usually takes at least 10 years". This is not an exact number as cited in the text. The Merck and GSK vaccines have now been licensed in various countries.

Pg. 2 – Third paragraph – Please specify that vaccine efficacy figures quoted are for HPV types targeted by the vaccines.

Pg. 5 – Second paragraph - Most young women are sexually active. Those who are not may well become sexually active in the future. The logistical need to determine whether a young woman is sexually active would not seem to apply to current efforts to vaccinate young adult women as described here.

Pg. 5 – Third paragraph – It would be helpful to elaborate a bit more on the reasons why vaccine efficacy or immunogenicity in practice would be expected to differ from that observed in clinical trials. Has evidence of that been seen with other recently developed vaccines? Why would a vaccine generate a better immune response or better prevent HPV infection when administered in a woman in the clinical trials than in the general population?

Pg. 7 – In general, throughout the text, it should be clearly specified whether one is referring to merely vaccinated or "successfully vaccinated" individuals. For instance, the function 'f' seems to apply to successful vaccination rather than just vaccination as currently presented. It would make for easier reading to have a table that lists and defines all symbols in one place.

Pg. 7 – Second paragraph – The term "leaving rate" refers to mortality, correct? If so, that should be stated so as to avoid confusion with leaving due to progression to adulthood.

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Discretionary Revisions (which the author can choose to ignore)

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**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:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I am employed by Merck and Co., Inc. which has developed and received licensure for a quadrivalent HPV vaccine. Through my employment I may receive corporate stock options.