Comment on the Hawke, Lea and Berryman Paper
'Answering human papillomavirus concerns; a matter of science and time'
By Judy Wilyman MSc (Population Health)

1. HPV vaccines have not been tested for efficacy in preventing cervical cancer. HPV vaccines have been tested for efficacy by investigating the effect of the vaccine in preventing pre-cancerous lesions (CIN 2 and 3) in young women 15-26 years old. The authors of this paper state 'this is a good predictor of cervical cancer risk' yet they have not provided evidence that pre-cancerous lesions in this age-group are a good predictor of the risk of cervical cancer later in life.

   It is known that the majority of pre-cancerous lesions in this age-group clear naturally and never progress to cancer later in life so this end-point is inadequate for predicting the efficacy of this vaccine in preventing cervical cancer.
2. The authors also inform the reader that 'HPV infection rates' are a good predictor of cervical cancer'. Yet the majority of women with high-grade HPV infections in developed countries are not at risk of cervical cancer because an HPV infection on its own does not cause cervical cancer. Co-factors are required for an HPV infection to progress to cervical cancer and these co-factors are not prevalent in developed countries such as Australia, UK, and the US. In other words, an HPV infection on its own is not an independent cause of disease.
3. The data in Table 1 of the Hawkes et al paper is incorrectly labelled as data from 'Phase III Trials'. This table contains data from phase 1, 2 and 3 trials. The only data collected from phase III trials for Gardasil (quadrivalent) vaccine was the Future II study conducted from 2003 -2007. This study was the first trial of the efficacy of Gardasil vaccine in preventing pre-cancerous lesions in 15 -26 year old women.

This fact needs to be clarified by the authors because this 4 year study was the only trial for the efficacy of this vaccine in the prevention of cervical cancer. As it is known that the majority of pre-cancerous lesions in this age-group (15-26 years) will never lead to cervical cancer then this end-point cannot be considered a good predictor of the efficacy of the vaccine in preventing cervical cancer.

4. In addition, this 3 to 4 year clinical trial of Gardasil vaccine did not use an inert placebo to demonstrate the safety of the vaccine. An accurate comparison of adverse events cannot be made with the unvaccinated group because the placebo used in the manufacturer funded clinical trials was aluminium adjuvant - aluminium hydroxyphosphate sulphate - the same adjuvant used in the HPV vaccine (Future II 2007). This is a chemical known to be linked to serious adverse events including hypersensitivity and autoimmune diseases (Shoenfeld and Agmon-Levin 2011).
5. The authors incorrectly suggest that there is conclusive evidence of cross-protection against the other 13+ HPV types that are not covered in the vaccine but are associated with cancer development. Scientists do not agree that HPV vaccines will protect against other high-grade HPV strains that are not included in the vaccine.
6. The authors mislead the public by claiming '*CIN 2/3 are pathological signs of an HPV infection*'. This is misleading because these lesions (CIN 2/3) associated with an HPV infection do not produce disease symptoms and may never progress to disease. A high-grade HPV infection does not produce disease on its own – co-factors are required. This point is not clarified in the paper. HPV is not an independent cause of disease - either cervical cancer or warts.
7. Hawkes et al state "HPV vaccination reduces CIN lesion incidence" (p.7).

   This needs to be qualified because the ability of the vaccine to reduce lesions depends upon an individual receiving all 3 doses of the vaccine and being naive for HPV

16/18. The correct statement is “HPV vaccine may reduce CIN lesions if specific criteria are met”. If these criteria are not met then efficacy is variable and unknown in different populations.

In addition, reducing CIN in the majority of women in developed countries where the risk factors for pathogenesis are not common is not reducing the burden of disease (either warts or cancer) because HPV infection (and CIN 2/3) in most women does not progress to disease. This needs to be clarified by Hawkes et al.

8. Hawkes et al incorrectly stated that “Overall HPV can be associated with 99.7% of cervical cancers and can be considered as a necessary cause of cancer”.

   This figure comes from a small study of 1,000 tumours (Bosch et al 1995) which were re-analysed using different assay techniques by Walboomers et al in 1999. The figure cannot be extrapolated to ‘all cancers worldwide’.

   In addition, HPV infection is considered a necessary cause of ‘most’ cervical cancer but not all cervical cancer. Some scientists claim 5-10% of cc does not contain HPV infection (Haverkos 2005).

9. Hawkes et al state that ‘*the safety of the ingredients has been well established’.*

   The authors have selected a single reference to make this claim. In addition, they have ignored all the adverse events and deaths that have been documented as linked to this vaccine by VAERS. Slade et al (2009) indicate that these cases cannot be properly reviewed because the vaccine manufacturers did not collect enough medical information to allow a medical review of the reported cases and therefore the VAERS database cannot establish causal links with the vaccine.

   In addition, the authors agree that a passive post-vaccination surveillance system is inadequate for determining causal events and their frequency in the population. This contradicts the statement that ‘the safety of the ingredients is well established.’

Science is about utilising all the science to come to a consensus and this paper is selective. Hawkes et al have not discussed the evidence produced by Tomljenovic et al, Harper, Haug, Slade et al and others.

10. Hawkes et al have made the following claim *'there was no increase in relative risk (RR) of experiencing an autoimmune event compared with a control group that containing nonadjuvanted, or aluminium-/aluminium hydroxide-adjuvanted vaccines (RR 0.98, confidence intervals 0.8, 1.21).*' [sic] (p.7)

    This comment does not make sense. It also is not clear whether the vaccinated group was compared to a 'non-adjuvanated' group or an 'adjuvanated' group – it states both and gives no clear discussion or evidence. Table 2 indicates that Cervarix was compared to the Hepatitis A vaccine and the AS04 adjuvant and not an inactive placebo. There is no evidence that systemic adverse events were compared to an unvaccinated group (with a true placebo). The discussion is not clear and it mixes data for Gardasil with data for Cervarix. These vaccine trials were different and separate and the criteria used in each trial needs to be clearly presented in order to claim 'the safety of this vaccine is well established'.

11. Hawke et al state '*However when systemic adverse events were examined there was no difference between vaccine and placebo'* (p.7).

    The authors do not explain that this result was ***not*** obtained by comparing a vaccinated group with a true inert placebo group. This is a misleading statement about the safety of the vaccine and it is not transparent science. This result was obtained for Gardasil using the aluminium adjuvant as the placebo in the non-vaccinated group. This adjuvant has been linked to causing autoimmune diseases and is not a suitable placebo. It is important to clearly describe the placebo that was used for each vaccine and to clarify the reactions that occurred.

12. The paper describes the inadequacies of the passive monitoring system with an example of the significant disparity between the number of adverse events (AE's) reported in the US compared to Australia (p.8) yet the authors conclude:

    '*The benefits of HPV vaccines far outweigh the risk and the mechanisms are in place to continue monitoring possible adverse events into the future*.'

    The paper provides no evidence to claim that 'the benefits of HPV vaccines far outweigh the risks' or that adequate mechanisms are in place for the monitoring of adverse events into the future.

13. The paper makes conclusions that are not supported with evidence in this paper:

    For example:

    'This review describes studies that have demonstrated the safety of vaccines and answered the very specific concerns raised particularly in regards to nervous system reactions, interactions with other vaccines and HPV vaccine influencing the course of existing lesions.'

    My Reply: These conclusions have not been sustained (or discussed) with evidence in this paper.