Appendix 5

Comment on the Hawke, Lea and Berryman Paper

Answering human papillomavirus concerns; a matter of science and time

In June 2013 the journal *Infectious Agents and Cancer* published two papers that made opposing conclusions about the safety and efficacy of HPV vaccines. These papers were titled 'Answering human papillomavirus concerns; a matter of science and time' (Hawkes, Lea and Berryman 2013) and 'HPV vaccines have not been demonstrated to be cost-effective in countries with comprehensive Pap screening and surgery' (Wilyman 2013). Whilst the first paper claimed HPV vaccines have been demonstrated to be safe and effective in preventing cervical cancer the second paper claimed that HPV vaccines have not been demonstrated to be safe and effective in preventing cervical cancer. It is necessary to investigate the type of evidence being used in both papers to see how the different conclusions have been drawn.

Below is a critique of the evidence provided by Hawkes et al to illustrate how claims about the safety and efficacy of HPV vaccines can be made on a lack of scientific evidence.

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 the only factor needed for the development of cervical cancer.

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. 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.
5. The authors claim '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. An HPV infection does not produce disease on its own – co-factors are required. This point is not clarified in the paper.
6. 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.

7. 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 cervical cancer does not contain HPV infection (Haverkos 2005; Schiffman 2002).
8. Hawkes et al state that ‘the safety of the ingredients has been well established’ yet they have not provided definitive evidence to support this claim. The authors have provided only a single reference for this claim and 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 review of the reported cases and therefore the VAERS database cannot establish causal links with the vaccine.
   In addition, Slade et al agree that a passive post-vaccination surveillance system is inadequate for determining causal events and their frequency in the population. Hawkes et al have also not discussed the evidence produced by Tomljenovic et al, Harper, Haug, Slade et al and others that questions the safety of this vaccine.
9. 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)
   The authors do not clearly state whether the vaccinated group was compared to a ‘non-adjuvanated’ group or an ‘adjuvanated’ group – it refers to 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 provided that systemic adverse events were compared to an unvaccinated group with a true inert placebo. The discussion is not clear and it mixes data for Gardasil with data for Cervarix.

10. 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 a true inert placebo was not used in the clinical trials to obtain this data. This data was obtained for Gardasil using the aluminium adjuvant that was present in the vaccine. This adjuvant has been linked to causing autoimmune diseases and it is not a suitable inert placebo for establishing the safety of the vaccine. It is important to clearly describe the placebo that was used for each vaccine and to clarify the reactions that occurred in a transparent manner.
11. 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 claim that ‘the benefits of HPV vaccines far outweigh the risks’ is unsubstantiated and adequate mechanisms for monitoring adverse events into the future are not in place.
12. The conclusions drawn by Hawkes et al (2013) and quoted below have not been sustained or discussed with evidence in this paper:
    ‘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.’ [sic].

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