

Response to Dr. Silvia de Sanjose's comment on Tomljenovic et al's

Letter to the Editor, titled

“HPV vaccines and cancer prevention, science versus activism”

Dr. Silvia de Sanjose has answered the questions asked by Tomljenovic et al with information that needs to be debated. I will address each of the 8 answers provided by de Sanjose to determine whether there is a consensus on the science that has been presented by this researcher:

- 1. HPV vaccines have not been demonstrated to prevent any cervical cancers so why are they being promoted as cervical cancer vaccines?**

Silvia de Sanjose: *It is still early to claim that existing HPV vaccines have prevented a single cervical cancer [sic].*

Discussion:

Silvia de Sanjose agrees that HPV vaccines have not been demonstrated to prevent any cervical cancer. Therefore the vaccine has been incorrectly marketed as a ‘cervical cancer’ vaccine and not an ‘HPV vaccine’

- 2. If the majority of HPV infections and a great proportion of pre-cancerous lesions clear spontaneously and without medical treatment and are thus not a reliable indication of cancer later in life, then how can these end-points be used as a reliable indicator of the number of cervical cancer cases that will be prevented by HPV vaccines?**

Silvia de Sanjose:

In the same way that we do not allow women to get invasive cervical cancer when undergoing screening, similarly we expect that women with cervical cancer will arise from those infected that cannot resolve spontaneously the infection. The same argument could go for any other vaccine [sic].

Discussion:

Silvia de Sanjose has not answered the question. Pre-cancerous lesions have been used as the surrogate end-point for determining the efficacy of the vaccine against cervical cancer and if most of these lesions do not lead to cancer then they are not a reliable indicator of efficacy of the vaccine. This end-point should not be used in cost-effectiveness mathematical models for determining the benefits of HPV vaccines (to prevent cervical cancer) because it can only speculate about ‘how much’ cervical cancer can be prevented. This figure is not objective – it will depend upon the perspective of the researcher and the chosen mathematical model.

In addition, the argument that de Sanjose uses to promote Pap screening to all women is flawed when it is applied to the use of an invasive medical procedure such as vaccination. Participating in Pap screening programs is virtually risk free so it is ethical to suggest that all women be screened as a preventative measure for cervical cancer. However participation in vaccination programs carries a risk of significant adverse events for some people. At present this risk is undetermined due to flawed clinical trial data and a 'passive' post-vaccination surveillance system that cannot determine the frequency and types of causal events.

3. How can the clinical trials make an accurate estimate of the risk associated with HPV-vaccines if they are methodologically biased to produce type-2 errors (false negatives [2, 4, 13])?

Silvia de Sanjose:

The risk associated to secondary effects of the vaccines is not exclusively evaluated on the data generated from trials phase III trials. Additional monitoring is routinely done to complement the information [sic]

Discussion: A *passive* post-vaccination monitoring system is not adequate for ensuring the safety of the population and cannot be said to 'complement the information' from phase III clinical trials that were also flawed because they used the placebo in the unvaccinated group.

4. Can a passive monitoring system such as that used by most vaccine surveillance systems world-wide allow the medical regulatory agencies to make accurate estimates on the real frequency of HPV-vaccine related adverse reactions?

Silvia de Sanjose: *Surveillance systems should be able to allow identification of short and long term effect for any intervention done in the general population. If the system is wrong then it needs to be improved but why should this be different for a specific vaccine with a very good record of safety from the trials.? [sic].*

Discussion:

This researcher has observed that a good surveillance system needs to pick up long and short term adverse-effects and 'if the system is wrong then it needs to be improved.' It is agreed that a passive system cannot pick up long and short term causal events and this is the system that is used by all government regulators worldwide. Therefore the system *does* need to be changed and improved.

Contrary to this researcher's statement, HPV vaccine does not have a good safety record from the trials because an inert placebo was not used in the unvaccinated group in the trials. The safety record of the vaccine can only be established if the trials compared vaccinated participants with a 'truly' unvaccinated group. This means adjuvant cannot be use in this group and this was not the case in the phase III clinical trials for quadrivalent HPV vaccine.

5. Can an accurate estimate of the real frequency of HPV-vaccine related adverse reactions be made if appropriate follow-up and thorough investigation of

suspected vaccine related ADRs is not conducted but instead, these cases are a-priori dismissed as being unrelated to the vaccine?

Silvia de Sanjose:

To my knowledge, ADR have been fully monitored in many countries with established surveillance systems. See as a good example the reports of the Vaccine Adverse Event Reporting System (VAERS) which publishes regularly the information for the US [sic].

Discussion:

This researcher has ignored the scientific evidence to make this claim of safety. Firstly passive surveillance systems cannot determine causal events and this was stated in the Letter to the Editor. In addition, the evidence from Slade et al has been ignored to suggest that the US VAERS is presenting accurate information about the adverse events from HPV vaccine. It is stated on the US VAERS website that the information provided by this passive monitoring system cannot be used to establish causal relationships and therefore the events that occur after vaccination may be a 'coincidence'.

This is not evidence-based science. De Sanjose also ignores the evidence from Slade et al that shows the majority of adverse events reported to VAERS by the vaccine manufacturers cannot be followed up because of a lack of 'identifying information' to allow medical review of the cases.

- 6. Why are women not informed of the fact that in some circumstances (i.e., prior exposure to vaccine-targeted and non-targeted HPV types), HPV vaccination may accelerate the progression of cervical abnormalities [4, 26-28]?**

Silvia de Sanjose:

The most recent data support the fact that women that have a cervical abnormality and that are vaccinated do not have any acceleration of their abnormalities and that on the contrary seem to be getting a better prognosis.

Discussion:

When *all* the evidence is included in the assessment the science on the progression of HPV related abnormalities due to vaccination is undetermined. Therefore the conclusion should be that 'we do not know yet whether exposure to HPV types in the vaccine accelerate the progression of cervical abnormalities.'

- 7. How can women make a fully informed decision about whether or not to consent to vaccination if crucial information regarding HPV vaccine efficacy and safety is not being disclosed to them?**

Silvia de Sanjose:

I believe that any program introducing the HPV vaccine massively has promoted the channels by which women can get information on the safety and efficacy of this vaccine. See for example many Government based web sites informing the public [sic].

Discussion:

Here are many of the facts about this vaccine that women have not been informed about:

The vaccine was promoted to women as a cervical cancer vaccine without specifically informing women that this vaccine has not been demonstrated to prevent cervical cancer. Women have also not been informed that the phase III trials did not use an inert placebo and therefore the safety profile has not been tested against unvaccinated (and unadjuvanted) women.

In addition, women were not informed that HPV infections – high-grade or low-grade – are harmless in the majority of cases. So whilst HPV is a common infection (80% of women will have an HPV infection in their lifetime) the majority of women (particularly in developed countries) are not at risk of cervical cancer. Hence the majority of women using the HPV vaccine will be exposed to the risk of the drug but will not be at risk from cervical cancer.

In addition, women have not been informed that co-factors are necessary for an HPV infection to progress to cervical cancer. These co-factors are not prevalent in developed countries and this fact has not been provided to the parents of young adolescent girls (and now boys) who are receiving this vaccine.

8. Should the medical health regulators and authorities rely solely on data provided by the vaccine manufacturers to make vaccine-policy decisions recommendations [12, 29]?

Silvia de Sanjose:

Vaccine manufactures run the necessary trials and should provide their data as requested by the official agencies in such a way that can be evaluated and contracted. Many countries provide recommendation on a sum of different aspects of evidence not only on the manufacture trials but also on independent research studies on the natural history of the disease, mathematical models and more. Care indeed must be taken that all this information is adequately traceable [sic].

Discussion:

This researcher observes that ‘vaccine manufacturers *should* provide their data’ for independent assessment by official agencies which is not the same as stating that they *do provide* their data for independent assessment. There is no evidence of balanced information being presented to government agencies on the HPV vaccine by vaccine manufacturers and the evidence provided here and in my article ‘*HPV vaccination programs have not been*

demonstrated to be cost-effective in countries with comprehensive Pap screening and surgery' demonstrates that there is no consensus amongst scientists about the benefits and risks of this vaccine.

The suggestion by de Sanjose that 'there has been a reduction in HPV related disease such as genital warts', even if the data is valid, does not provide evidence for the safety and efficacy of this vaccine against cervical cancer. And the suggestion that '*probably HPV DNA detection tools could remove some of the caveats of cervical cytology*' is speculation about an infection that is harmless in the majority of women unless co-factors are present.

In other words, the majority of women detected with HPV infections are not at risk of cervical cancer, particularly in developed countries because the co-factors necessary for cancer to develop are not prevalent in these countries.

This vaccine is founded on the assumption that HPV is an independent cause of cervical cancer and this assumption is incorrect. A fact that is clearly demonstrated by the geographic distribution of cervical cancer: 80% of cervical cancer occurs in the developing countries and most developed countries have a very low incidence of this disease. This vaccine has not been developed on evidence-based science and public health is at risk if 'co-incidence' is being used to explain the adverse events that are occurring after HPV vaccination in many individuals.

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