

Questions to EMA

There is a growing number of adolescents becoming seriously ill after HPV vaccinations. Consequently many parents, general physicians, medical specialists (including cardiologists, gynecologists, immunologists, neurologists, rheumatologists, pathologists, etc.) and scientists (biochemists, neuroscientists, etc.) around the globe strongly disagree with your conclusions that the benefits outweigh the risks of HPV vaccines (Cervarix/Gardasil) currently offered to young girls to prevent cervical cancer.

It is a commonly accepted rule that the risks of any preventive interventions offered to healthy people should be close to zero. An emerging amount of peer-reviewed literature suggests this is not the case with Gardasil and Cervarix, both of which contain aluminum as an adjuvant.

On the other hand, it is well known that health authorities have more raw data for risk/benefit evaluation than what can be found from the published literature. Consequently, the continuously expanding group of laity and academic professionals wish to ask you the following questions divided into major and other concerns:

Major points of concern

I. Pharmaceutical Questions

- a. HPV vaccine (Gardasil) has been shown to contain DNA impurities that have been related to fatal adverse events (SAEs, Refs.: e.g. Lee SH, 2012a *Advances Biosc Biotech*, 3: 1214-24; Lee SH, 2012b *J Inorg Chem*, 112: 85-92, Lee SH 2013, *Advances Biol Chem*, 3:76-85). What is the impact of these pertinent findings on the benefit/risk ratio? Shouldn't the marketing authorization be reconsidered (see recent [open letter of complaint to the Director-General of the WHO, Dr Margaret Chan](#))

II. Preclinical questions

- a. What is the LD50 of aluminum? How does it compare to the amount of aluminum in HPV vaccines?
- b. Has aluminum been shown to be safe in animal models when applied parenterally (i.e. sc, im, ip or iv) at doses equivalent to human exposure? If not, what toxic reactions have been found?
- c. Based on the literature, aluminum is involved with 'autoimmune/autoinflammatory syndrome induced by adjuvants' (ASIA) syndrome (refs. e.g. Shoenfeld Y & Aron-Maor A, 2000, *J Autoimmun* 14: 1-10; Shoenfeld Y & Agmon-Levin N, 2011, *J Autoimmun*, 36: 4-8). This syndrome has been described in several animal models (Refs. in textbook '*Vaccines & Autoimmunity*' 2015, edited by Shoenfeld, Y, Agmon-Levin N & Tomljenovic L, pp. 35-41). Has the possibility of aluminium induced ASIA syndrome been acknowledged before

approval of marketing authorization for Cervarix or Gardasil, or at some point afterwards?
Do these findings have any implications for human safety? If yes, what?

III. Clinical Questions

- **Safety: POTS, CRPS and co-existing symptoms**

- a. Why have health officials evaluated only a few distinct symptoms (POTS, CRPS) in spite of the fact that in most cases there are usually a number of other co-existing symptoms?

It was not surprising to learn from EMA's report that the criteria of POTS/CRPS were not met in all cases. In clinical realm, there is a vast number of those who have become seriously ill after being vaccinated regardless of whether the diagnostic criteria for POTS/CRPS are fulfilled or not. A wide variety of SAEs reported to the health officials has been published in peer-reviewed journals (refs. e.g. Chang J et al., 2011, *J Neurol Neurosurg Psychiatry*, 82(11): 1296-304; Chao C et al., 2011, *J Intern Med*, 271: 193-203; Colafrancesco S et al., 2013, *Am J Reprod Immunol*, 70: 309-16; Das A et al., 2008, *Med J Aust*, 189: 178; Di Mario FJ et al., 2010, *J Child Neurol.*, 25: 321-7).

Therefore, shouldn't different SAEs (experienced by previously healthy adolescents) be assessed as a group of post-vaccination symptoms (instead of focusing only on a single symptom at a time) when estimating the overall benefit/risk ratio?

- b. Since the diagnostic criteria for CRPS was not established until 2010 (refs. 1,2 in EMA report for POTS, CRPS), how was a background rate for this condition determined?
- c. Presumably the data for the referred background rate at EMA report was collected in the Netherlands by de Mos and colleagues (ref, 5 in EMA report); can this be considered to give a reliable estimate of the background rate for any other country?

Do health authorities have some relevant statistics available from other member states or other countries (e.g. US, Japan) for comparison? In other words, shouldn't the possible variation in the incidences of CRPS in various regions / countries be known in general population before any definite conclusions can be drawn of the CRPS risks related to HPV-vaccines?

- **Safety: reproductive toxicity**

- a. Could there be a real causality between HPV vaccination and premature ovarian failure as suggested in series of published case reports (e.g.. Colafrancesco S et al., 2013, *Am J Reprod Immunol*, 70: 309-16; Little DT & Ward HR, 2014, *J Investig Med High Impact Case Report*, 28(2):1-12, <http://www.ncbi.nlm.nih.gov/pubmed/26425627>, <http://hic.sagepub.com/content/2/4/2324709614556129.full>, <http://www.acped.org/the-college-speaks/position-statements/health-issues/new-concerns-about-the-human-papillomavirus-vaccine>)?

Are there any preclinical (unpublished) studies, where enduring ovarian capacity and duration of function have been researched in vaccinated female rats or other animals?

- b. In the case of possible causality between HPV vaccination and premature ovarian failure, one would expect to see an increase in congenital abnormalities and miscarriage rate. Prematurely ageing ovaries would have an increased chance of producing eggs with defects such as trisomies i.e. chromosome abnormalities. Increased chromosomal abnormalities would also be expected to be associated with an increased miscarriage rate. Has such trend been observed in any preclinical/clinical studies or during post-marketing surveillance? Is there any clinical data available for public review (see also QVa)?

- ***Safety: causality and reliability of safety data***

- a. There are several cases where the symptoms have increased after each booster (see e.g. [Cervarix: Will my life ever be normal again?](#), [My daughter's life altering changes after Gardasil](#), [Gardasil Injuries: No more excuses, we need answers](#)). Shouldn't such cases with a clear dose-response between symptoms and number of vaccinations be considered as a direct proof of true causality? Shouldn't additional boosters be contraindicated whenever the vaccinated has experienced unexpected adverse reactions as advised in the medical literature (<http://www.ncbi.nlm.nih.gov/pubmed/20541691>)?
- b. Has the safety of HPV vaccines been studied in any of the conducted trials in a reliable way – i.e. by using an inert saline as a placebo and by carrying an active (not just passive) safety follow-up?

As far as we know the placebo vaccines (that have been used in most of the clinical trials) have contained aluminium and other excipients, which may induce harmful effects without the vaccine's active (antigen) components (see also Q11c above). Thus, comparisons between such active and placebo groups cannot be expected to prove anything about the safety of HPV-vaccines. Thus, the quality of safety data is not convincing. The poor reliability of safety data is further emphasized by the notion that the safety data of clinical trials is based on a passive follow-up, which is commonly believed to reveal only 1-10% of all adverse reactions. For further details related to biased study designs see e.g. the following published papers: Busch FX & deSanjose S, 2003, *J Natl Cancer Inst Monogr*, 31: 296-304; Tomljenovic L & Shaw CA, 2012a, *J Intern Med*, 272: 514-15; Tomljenovic L & Shaw CA, 2012b, *J Law Med Ethics*, 40: 673-81; Tomljenovic L & Shaw CA, 2012c, *Am J Public Health*, 102: e13-14, Tomljenovic L & Shaw CA, 2013, *Ann Med*, 45: 182-93.

Based on personal correspondence between Dr Deidre Little and Dr John Skerritt from Australian Government Department of Health (31 August 2015, R15/554600) the vaccine constituents have formed a placebo in all safety trials of Gardasil. Afterwards, upon this clinician's request, the national regulatory authority requested the sponsor to correct their product information stating erroneously that saline had been used in one controlled safety trial for under 16-year olds (protocol 018) as explained in the original letter:



- 3 SEP 2015

Australian Government
Department of Health
Therapeutic Goods Administration

Dr Deirdre Little
58 Wheatley Street
Bellingen NSW 2454

Our Reference: R15/554600

Dear Dr Little

Subject: Gardasil Product Information Safety Trial Data

Thank you for your correspondence of 20 June 2015 regarding the representation of Gardasil's safety trial information in its Product Information (PI).

Following a review of the PI, I have been advised that your observation about the composition of the placebo in study 018 is valid and that the current information is a misrepresentation of the situation. That is, that the current reference to the placebo being 'saline' misrepresents the actual placebo used in protocol 018.

As a result of this review, the sponsor, Merck Sharpe and Dohme Australia Pty Ltd, have been requested to amend the relevant headings in Table 11 and Table 12 of the PI from "Saline Placebo" to "Placebo^{***}" and under each table include an additional footnote^{***} stating the composition of the (non-aluminium containing) placebo. Merck have been asked to undertake this amendment when they next revise the Product Information.

Thank you for bringing this matter to my attention.

Yours sincerely

Dr John Skerritt
Deputy Secretary
Therapeutic Goods Administration
Department of Health

27 August 2015

- c. Is it possible that rather similar, multiple symptoms experienced by HPV vaccinated girls around the world are coincidental?

- Efficacy

- d. So far there has been only indirect evidence of the efficacy. Are there perhaps already by now some direct data demonstrating that either Cervarix or Gardasil can prevent cervical cancer and/or deaths from cervical cancer? If yes, what?

IV. Questions on overall benefit/risk ratio of HPV vaccines

- a. Based on the accumulating scientific proof (obtainable from the published literature) the benefit/risk ratio of HPV vaccines (Cervarix/Gardasil) appears negative. Does EMA have some extra data suggesting otherwise? If yes, what?
- b. What is the critical threshold rate of SAE's for HPV vaccines that would result in withdrawal of marketing authorization?

V. Regulatory questions

- a. Are all safety and clinical studies conducted for HPV vaccines available for public review or are some of those still considered confidential (as were in 2014)? Is EMA still facing a legal procedure over the release of certain documents?
(http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/04/news_detail_001779.jsp&mid=WC0b01ac058004d5c1)

To our knowledge some academic individuals have had difficulties in receiving the data that they have asked the EMA to provide for their review in relation to the suspected reproductive toxicity of HPV-vaccines (see 'Safety/reproductive toxicity' questions above).

Other points of concern

I. Preclinical questions

- a. Are the potential long-term health consequences of injected foreign DNA known?
- b. The weight limit for DNA contamination is 10 nanograms for a single vaccine and children are commonly exposed to several vaccines and to their varying amounts of impurities. Has the safety limit for accumulative exposure of humans to different types of foreign DNA been estimated or has it been just considered an irrelevant concern?

- c. Are there any long-term carcinogenicity studies for HPV vaccines and/or their ingredients?

II. Clinical questions

- a. As far as we know health professionals have not been warned to look for the risk of leukaemia among vaccinated adolescents as suggested in the assessment report referred to below (*). What actions (if any) have been undertaken to determine whether or not HPV vaccines could cause or trigger this condition in certain pre-disposed individuals?

(*) Reference: Info 26 March 2015 EMA/CHMP/76591/2015

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003852/WC500189113.pdf

Page 117: *"Five cases (4 with 9vHPV vaccine and 1 with qHPV vaccine) of acute leukaemia have been reported, three of which occurred in subjects younger than 20 years of age at diagnosis. While the observed number of cases of leukaemia exceeded the expected number of cases, this observation is based on a few cases in relation to a very low background risk for leukaemia in this age group. Such a comparison will inevitably be sensitive to random occurrences of single cases and it is not considered sufficient to implicate a causal relation at this stage. There is no sufficient evidence to support a biological plausibility for a causal relation. While it is considered that the finding is most likely a random occurrence, further reassurance can be gained from the ongoing study program, which will add substantially to the total exposed person-time. Occurrence of any further cases of leukaemia, with a main focus on the ongoing/planned studies, should be reported as a part of close monitoring of leukaemia in PSURs."*

Conclusions on page 118: *"There was one case of pulmonary vasculitis and few cases of leukaemia, which upon assessment do not constitute sufficient evidence to raise a specific safety concern at the moment."*

- b. Has a possible genetic predisposition (resulting in an increased sensitivity to aluminium toxicity (<http://www.ncbi.nlm.nih.gov/pubmed/24238833>) been acknowledged when assessing the benefit/risk profile of HPV-vaccines all of which contain aluminium? If yes, how?
- c. What do health officials consider as the acceptable percentage of SAEs for HPV vaccines?

Given that there has been so far only indirect proof of the benefits (i.e. the capability of HPV-vaccines to prevent cervical cancer) the percentages of SAEs observed in clinical trials do appear alarming:

- Serious adverse events representing 2.3% (Gardasil 9) of the population and 2.5% (Gardasil)

- 4.5% of the participants in a trial for Gardasil 9 in India reported new medical conditions potentially indicative of systemic autoimmune disorders.

III Regulatory questions

- a. Is testing for adventitious agents in HPV vaccines obligatory, or based on nonbinding recommendations?
- b. Did the rapporteurs have all raw data available for the assessment of marketing authorization application? Was it considered sufficient and reliable?

Based on the published literature (outlined above) and the other unpublished information available for international independent clinicians and scientists, the reliability of study results should be seriously questioned.

- c. Did the clinical assessors of the EMA report (on CRPS & POTS) consult specialists in autonomic disorders? If they did, had those specialists declared any conflict of interests?