Journal of INTERNAL MEDICINE

Click here to view the article Letter to the Editor by C. Chao
doi: 10.1111/j.1365-2796.2012.02551.x

# No autoimmune safety signal after vaccination with quadrivalent HPV vaccine Gardasil?

**Dear sir,**

Recently, the *Journal of Internal Medicine* published a study by Chao *et al.* [1] on autoimmune conditions following the routine use of Gardasil, which failed to identify any significant autoimmune safety concerns. This study was conducted in collaboration between two managed care organizations, Kaiser Permanente Southern California (KPSC) and Kaiser Permanente Northern California (KPNC), as a post-licensure commitment to the FDA, the European Medicines Agency (EMA) and other regulatory authorities to help evaluate the autoimmune safety of the vaccine. In particular, Chao *et al.* [1] noted that 'well-designed postlicensure safety studies for newly approved vaccines facilitate *proper* evaluation of their autoimmune safety' [emphasis added]. We certainly do agree with the authors that such studies are needed for determining whether or not new vaccines have adequate safety profiles. The study population for the autoimmune surveillance by the Kaiser's research team thus included 189 629 women of diverse ethnical and socio-economic background, 99% of whom were in the recommended age range for HPV vaccination (9–26 years) [1]. Nonetheless, two potential biases might have influenced the outcome of the safety analysis conducted by the authors. First, the study included all women who received at least one dose of Gardasil, thus making this particular population sample less sensitive for the detection of serious adverse reactions (ADRs), as such events may be expected to occur less frequently if fewer doses of the vaccine are administered. As the authors did not report how many women actually completed the recommended three-dose HPV vaccination regimen, it is impossible to know what proportion of the study population was actually at high risk from vaccine-related serious ADRs. Secondly, the Safety Review Committee (SRC) that reviewed all safety data included a general paediatrician/clinical epidemiologist, a perinatologist/teratologist, a vaccinologist, a paediatric rheumatologist and a pharmacoepidemiologist [1]. In view of the fact that the autoimmune conditions of interest to be examined by this expert Committee included (i) rheumatologic/autoimmune disorders, (ii) autoimmune endocrine conditions and (iii) autoimmune neurological/ophthalmic disorders [1]; the question must be asked about why the Kaiser's research team failed to recruit an expert panel with similar expertise if, in fact, the study aimed to facilitate *proper* evaluation of autoimmune safety for Gardasil? It is thus surprising to note the absence of an immunologist/autoimmunologist, neurologist and ophthalmologist from the SRC especially because such experts were in fact present at a later stage, in the analysis of case reports selected by the SRC [1]. As demonstrated repeatedly in the scientific literature, inadequately designed research cannot be used to reliably evaluate the safety of any drug [2,3].

We have previously pointed out to existing HPV vaccine-related safety concerns as well as uncertainties about the efficacy of HPV vaccination against actual cervical cancer incidence [3, 4]. Whilst results from clinical trials show that Gardasil can reduce the incidence of a subset of abnormal CIN 2/3+ cytologies (i.e. those related to HPV-16/18) in women with no pre-existing HPV infections [5], the vaccine is unlikely to reduce the overall frequency of cervical cancers (at least not beyond what Pap screening has already accomplished) [6, 7], yet this is the primary aim for which the vaccine was developed [8]. Furthermore, current data show that antibodies against HPV-18 after Gardasil fall rapidly, with 35% of women having no measurable antibody titres by 5 years postinjection [6]. This outcome suggests that rather than preventing future cases of cervical cancer, Gardasil, at best, may only be effective in postponing them.

In addition, unlike screening and the loop electrosurgical excision procedure (LEEP), Gardasil offers no therapeutic benefits as it cannot cause regression of pre-existing HPV-16/18 infections or associated lesions. On the contrary, Gardasil may exacerbate cervical cancer disease in women with pre-existing HPV-6/11/16/18 infections [5]. It thus appears that the current widespread optimism regarding the putative long-term benefits of HPV vaccination has only been made possible by invalid and premature extrapolations from such often inadequate surrogate markers [3, 9, 10]. As recently noted by Gerhardus and Razum [9], the, 'unwarranted confidence in the new [HPV]

 

vaccines led to the impression that there was no need to actually evaluate their effectiveness'.

On the other hand, abundant evidence now exists that HPV vaccines can cause serious adverse events, including death and long-term disabling autoimmune conditions [3, 6]. Moreover, because currently there are no active surveillance programs for monitoring vaccine safety outcomes anywhere in the world, the true rate of serious ADRs following Gardasil remains unknown. In context, whilst 12-year-old preadolescents are at zero risk of dying from cervical cancer, they are faced with a risk of death and a permanently disabling lifelong autoimmune or neurodegenerative condition from a vaccine that thus far has not prevented a single case of cervical cancer, let alone cervical cancer death. For vaccines with uncertain benefits designed to prevent a disease that is already preventable by Pap screening and LEEP, both of which carry no such risks, the potential for harm to those vaccinated should be negligible [3, 4].

### Conflict of interest statement

LT and CAS conducted a histological analysis of autopsy brain samples from a Gardasil-suspected death case.

### Funding

This work was supported by the Katlyn Fox, Lotus and the Dwoskin Family Foundations.

**L. Tomljenovic[1] & C. A. Shaw[1,2,3]**

*From the [1]Neural Dynamics Research Group, Department of Ophthalmology and Visual Sciences, [2]Program in Experimental Medicine; and [3]Graduate Program in Neuroscience, University of British Columbia, Vancouver, BC, Canada*

### References

1 Chao C, Klein NP, Velicer CM *et al.* Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. *J Intern Med* 2011; **271:** 193–203.
2 Demicheli V, Jefferson T, Rivetti A, Price D. Vaccines for measles, mumps and rubella in children. *Cochrane Database Syst Rev* 2005; **4:** CD004407.
3 Tomljenovic L, Shaw CA. Human papillomavirus (HPV) vaccine policy and evidence-based medicine: are they at odds? *Ann Med* 2011. doi: 10.3109/07853890.2011.645353
4 Tomljenovic L, Shaw CA. Mandatory HPV vaccination. *JAMA* 2012; **307:** 254; author reply -5.
5 Food and Drug Administration Vaccines and Related Biological Products Advisory Committee (VRBPAC) background document: Gardasil™ HPV Quadrivalent Vaccine. May 18, 2006 VRBPAC Meeting. Available at: http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222B3.pdf [Accessed on 20 March 2012].
6 Harper DM, Williams KB. Prophylactic HPV vaccines: current knowledge of impact on gynecologic premalignancies. *Discov Med* 2010; **10:** 7–17.
7 Harper DM, Vierthaler SL. Next generation cancer protection: the bivalent HPV vaccine for females. *ISRN Obstet Gynecol* 2011. doi: 10.5402/2011/457204.
8 Frazer I. God's gift to women: the human papillomavirus vaccine. *Immunity* 2006; **25:** 179–84.
9 Gerhardus A, Razum O. A long story made too short: surrogate variables and the communication of HPV vaccine trial results. *J Epidemiol Community Health* 2010; **64:** 377–8.
10 Spinosa JP, Riva C, Biollaz J. Letter to the editor response to the article of Luisa Lina Villa HPV prophylactic vaccination: the first years and what to expect from now. *Cancer Lett* 2011; **304:** 70.

*Correspondence:* Lucija Tomljenovic, Neural Dynamics Research Group, Department of Ophthalmology and Visual Sciences, University of British Columbia, 828 W. 10th Ave, Vancouver, BC V5Z 1L8, Canada.
(fax: +1-604-875-4376; e-mail: lucijat77@gmail.com)

 