PE1574/H

Dear Ms Robinson,

Please find attached my submission re human papillomavirus vaccine (HPV) administered to adolescents. I support a round table discussion at Edinburgh between scientists and medical professionals and politicians to discuss the safety of HPV vaccines.

The attached submission followed three young teens from my own practice in NSW diagnosed with premature ovarian insufficiency following receipt of this vaccination.

Incidentally, I had the pleasure of attending Scottish Parliament as an observer a few years ago and was deeply impressed by the courtesy and respect which attended the discussions.

Yours faithfully

Dr. Deirdre Little

Regarding the Inclusion of Quadrivlent Human Papillomavirus Vaccine in the Adolescent Vaccination Programme.

Introduction

Review of safety research of the quadrivalent human papillomavirus vaccine (HPV4) known as Gardasil ® published in peer-reviewed medical journals has noted the absence of ovarian safety research of this vaccine. This follows two case series of premature menopause (now known as Premature Ovarian Insufficiency) developing in multiple young adolescents after receiving a course of Gardasil ® vaccinations. This is particularly disturbing since the background incidence of idiopathic (unknown origin) adolescent premature menopause is so rare at this very young age there are no figures available for its incidence in this teenage bracket. There are no age- specific background rates for comparison.

The Product Information concerning Gardasil® has been shown to misrepresent the safety trial placebo used to establish comparative safety of this vaccine in the targeted recipient age group. The placebo is misrepresented as ‘saline’ in the product Information suggesting inadequate review of safety research data. This matter was brought to the attention of the Therapeutic Goods Administration (TGA) who have confirmed the misrepresentation (Aug 31st 2015). Incorrect product information misinforms immunization providers and vaccine recipients and compromises informed consent.

The introduction of this vaccine against human papillomavirus (HPV) targeting peri-pubertal girls represents a new development in infectious disease prevention. New population vaccines must meet rigorous standards of safety study size, design, principles of scientific method and reliable ‘Product Information’ relevant to the target group to maintain vaccine confidence.

Review of safety research

Published case series of idiopathic, adolescent, premature ovarian failure[1] [2] [3] following quadrivalent human papillomavirus vaccination prompted review of vaccine ovarian safety research, which accompanies publication of the Australian case series. This information is summarized below and is presented in the accompanying peer- reviewed medical journal articles by this author and is to be read in conjunction with my published articles hereto attached:

- 'Human papillomavirus vaccine and the ovary: the need for research.' 18th Congress of Controversies in Obstetrics, Gynaecology and Infertility Vienna October 2013;

- 'Premature ovarian failure three years after menarche in a 16-year-old girl three years after human papilloma virus vaccination' BMJ Case Reports 2012. doi:10.1136/bcr-2012-006879;

- Brighton Collaboration Vaccine Safety Quarterly 2 2014;

- 'Adolescent premature ovarian insufficiency following human papillomavirus vaccination: a case series seen in general practice' Journal of Investigative Medicine High Impact Case Reports October-December 1-12 2014. There has been no formal refutation.

Preclinical trials: A review of toxicology research of the ovary finds a histology report of the male rat testis after vaccination, but not of the female ovary. No ovary histology report is available from phase one rodent studies[4]. Rat corpora lutea were numbered but with no accompanying cellular histology report of the vaccinated rat ovary. Studied rats received only two of the three HPV4 vaccination doses prior to testing their ability to conceive,[5] [6] although 'Guidance for Industry' research guidelines state: 'where possible we recommend that you administer the maximum human dose (eg, 1 human dose = 1 rabbit dose) regardless of body weight'[7]. Five-week old tested rats conceived only one litter before euthanasia. This precluded assessment of future litter frequencies, spacing and size and of duration of female rat reproductive life span after vaccination.

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[1] Little DT, Ward HR. Premature ovarian failure three years after menarche in a 16-year-old-girl following human papillomavirus vaccination. *BMJ Case Rep. 2012* doi 10.1136/bcr-2012-006879*.*

[2] Colofrancesco S, Perricone C, Tomljenovic L et al. Human papilloma virus vaccine and primary ovarian failure: another facet of the autoimmune/inflammatory syndrome induced by adjuvants. *Am J Reprod Immunol. 2013;70:309-316.*

[3] Little DT, Ward HR. Adolescent premature ovarian insufficiency following human papillomavirus vaccination: a case series seen in general practice. *Jour Invest Med High Impact Case Reports.* Oct-Dec 2014:1-12.

[4] FOI Request 001-1112 in relation to Gardasil testing and complied with in the public interest Sept. 2011. Application not displayed on TGA FOI website listing due to 'commercially sensitive nature'.

[5] Wise LD, Wolf JJ, Kaplansky CV et al. Lack of effects on fertility and developmental toxicity of a quadrivalent HPV vaccine in Sprague Dawley rats. *Birth defects Res B Dev Reprod Toxicol*. 2008;83:561-572.

[6] Intramuscular developmental toxicity and immunogenicity study in rats with post-weaning evaluation. Extract Study no. TT#03-703-0 (CTD Module4, volumes 1-3). Table A-6.

[7] US Department of Health and Human Services. *Guidance for industry: Considerations for Developmental toxicity studies for prevention and therapeutic vaccines for Infectious Disease Indications*. Rockville, MD: Center for Biologics Evaluation and Research.

Clinical trials: Phase II and III studies identified at licensing as safety studies by the Vaccine and Related Biological Products Advisory Committee (VRBPAC) to the Food and Drug Administration and referred to in the Gardasil® Product Information, were study protocols V501 007[8], 016[9], 018[10] and 013[11] and 015[12] respectively. There were only small numbers of safety trial participants in the vaccine target age group of young adolescents (under 16 years of age). Only protocols 016 and 018 studied safety in the young female target group. Mean ages were 12.6 and 11.9 years. It is not clear what proportion had commenced menstruation.

In **protocol 016**, only 240 fully vaccinated girls remained in the study at 12 months. The study had no placebo control and over 52% of the screened healthy girls who commenced the study had been lost to follow-up one year after first immunization. Loss of the majority of participants to safety observation compromised this study's effectiveness as a younger adolescent safety study. One remaining girl had developed vaginal haemorrhages after the 2nd and 3rd immunizations which met criteria for a Serious Adverse Event, but were subsequently thought to be due to a pre-existing condition not excluded at general health screening. The majority of boys, 60%, were also lost to safety follow-up. One 15-year-old boy in the study died unexpectedly, with no cause identified at post mortem. His death was therefore deemed not related to the vaccination.

Protocol 018 fully vaccinated 587 girls, with 52.3% in the usually pre-menarche years of 9 to 12. Health interviews with safety trial participants a year after completing vaccinations might not have been able to determine menstrual abnormalities while cycles were still commencing ovulatory patterns. A vaccine report card was issued to safety trial participants to record vaccine adverse events occurring within 2 weeks of each vaccination. This safety study design, common to all HPV4 safety studies, had very little ability to detect altered or diminishing menstrual cycles.

Protocols 007, 013 and 015 studied older young women over 16 years. These studies required participants to use reliable contraception for the first 7 months of each safety trial. Hormonal contraception will mask menstrual abnormalities. Use of hormonal contraception rose to 68% to 83%[13] during the two sub-studies of protocol 013.

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[8] Villa LL, Costa RL, Petta CA. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16 and 18) L1 virus-like particle vaccine in young women: a randomized double-blind placebo-controlled multicentre phase II efficiency trial. *Lancet Oncol*. 2005;6:271-278.

[9] Block S, Nolan T, Sattler C et al. Comparison of the immunogenicity and reactivity of a quadrivalent human papillomavirus types 6, 11, 16 and 18 L1 virus-like particle vaccine in male and female adolescents and young adult women. *Pediatrics*. 2006;118:2135-2145.

[10] Reisinger KS, Block SL, Lazcano-Ponce E et al. Safety and persistent immunogenicity of quadrivalent human papillomavirus Types 6, 11, 16 and 18 L1 virus-like particle vaccine in preadolescents and adolescents*. Pediatr Inf Dis J*. 2007;26:201-209.

[11] Garland SM, Hernandez-Avila M, Wheeler CM et al. Quadrivalent vaccine against human papillomavirus to prevent ano-genital diseases. *N Engl J Med* 2007;356:1928-1943.

[12] Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007;356:1915-1927.

[13] Miller NB*. Clinical Review of Biologics License Application for human papillomavirus 6, 11, 16 and 18 L1 Virus Like Particle Vaccine (S. cerevisiae)* (STN 125126 Gardasil). Rockville, MD: Center for Biologics Evaluation and Research Food and Drug Administration; 2006. p 143.

Hormonal contraception rose to 75% to 82%[14] within 15 days of any vaccination in 007, and more than two thirds of young women recorded concomitant hormonal contraception usage within 2 weeks of any vaccination in protocol 015[15]. A limited number of safety trial participants would have been able to observe natural menstrual cycles during the safety study.

A major review of the HPV4 vaccine safety profile reports: "new medical conditions were not considered adverse events if they occurred after month 7 or were not considered by the investigator to be vaccine related"[16]. If new menstrual problems arose after month 7 when they were able to cease contraception, these would not have been 'considered adverse events' by the recording investigator. When the Centre for Biologics Evaluation and Research requested an analysis of auto-immune conditions across the entire safety database, the sponsor replied "there were subjects with additional new medical conditions that were not reported in the Clinical Study Reports for 011 and 012 [within protocol 013]. These included two subjects with amenorrhoea"[17]. Safety study design for these protocols again chose a 'vaccine report card' to record Non-Serious Adverse Events (NSAE's) for two weeks after each vaccination. This 'fortnight restriction' design limited the ability of these protocols to detect diminishing menstrual cycles. Longer term follow-up beyond the vaccine interval was limited to Serious Adverse Events. Menstrual dysfunction, oligo- and amenorrhoea will not signal as Serious Adverse Events, since SAE's are defined as life threatening, resulting in death, permanent disability, congenital abnormality, hospitalization, prolongation of hospitalization, or necessitating medical or surgical intervention to prevent one of these outcomes.[18]

Clinical safety study placebos. Vaccine constituents formed the placebo in all placebo controlled safety trials of Gardasil. Although use of a 'saline placebo' was claimed by Merck Sharp and Dohme, a saline placebo was not used in safety trials. The placebo in the only controlled safety trial for under 16-year olds (protocol 018) is misrepresented by Merck Sharp and Dohme as saline in Product Information to all providers and consumers, and in licensing application review. Upon this author's request to the TGA that Product Information be corrected, the TGA **replied[19] they have requested Merck Sharpe and Dohme correct their product information** as a result of my communication. By definition a placebo should lack the substance being tested. The young adolescent safety study placebo contained the vaccine constituents 50 µcg polyoxyethylene sorbitan mono-oleate (also known as Tween 80 or Polysorbate 80), 35 µcg borax, 0.78mg L-histidine together with 9.56 mg sodium chloride. Polysorbate 80 in

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[14] Ibid 13 Miller NB. p216.
[15] Ibid 13 Miller NB. p244.
[16] Block S, Brown D, Chatterjee A et al. Clinical trial and post licensure safety profile of a prophylactic human papillomavirus (types 6, 11, 16 and 18) L1 virus-like particle vaccine. *Pediatr Infect Dis J*. 22010;29:95-101.
[17] Miller NB*. Clinical Review of Biologics License Application for human papillomavirus 6, 11, 16 and 18 L1 Virus Like Particle Vaccine (S. cerevisiae)* (STN 125126 Gardasil). Rockville, MD: Center for Biologics Evaluation and Research Food and Drug Administration; 2006. p198.
[18] US Food and Drug Administration. CFR-Code of Federal Regulations Title 21. Sec. 314.80 Postmarketing reporting of adverse drug experiences. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.80.
[19] TGA letter J. Skerritt Dep. Sec. TGA to Dr D. Little 31st August 2015.

this vaccine and in the safety comparator placebo has particular significance. It has known, delayed rat ovary toxicity[20] evident 5 months after injection into very young rats. This ovarian toxicity is demonstrated to occur at all injected dosages tested, over a ten-fold range, with no dose-response curve evident to establish ovary-safe dosages. Oral doses were not ovary toxic to rats until polysorbate 80 comprised 20% of the rat's diet[21]. Its inclusion in both vaccine and placebo is of concern. A potential ovary toxin in both vaccine and control arms of the study would have blurred the already limited ability to observe risk differences of new abnormal menstrual patterns.

The placebo which formed the control for older women's phase III studies contained the vaccine constituent amorphous aluminium hydroxyphosphate sulfate. Its role in the development if an 'autoimmune inflammatory syndrome induced by adjuvants' has been suggested by some immunologists to be implicated in premature ovarian failure. The existence of this syndrome is disputed. However, a possible auto-immune implication reinforces the research principle that safety trial placebos should not contain the substance being tested.

Post licensing studies include two large safety cohort studies and sentinel cohort follow-up. The first cohort study claimed to evaluate vaccine safety 'during the course of routine clinical care'[22]. It followed 189,629 vaccinees of whom 44,000 had been fully vaccinated, studying their emergency department visits and hospitalizations. Emergency departments and hospital admissions are not the consultation context for diminishing menstrual cycles. Analysis of these emergency/hospital presentations reviewed the risk of 16 auto-immune conditions excluding ovarian failure. This study had no capacity to evaluate ongoing ovarian health and safety. The recent largest cohort study[23] of 997,585 girls measured hospital diagnosed autoimmune, neurological and thromboembolic events. Menstrual aberration/decline were not included. Again, deteriorating menstrual function consultations are not the province of hospitalizations or hospital presentations. This massive study's design had no capacity to evaluate ongoing reproductive function or ongoing egg-bearing capacity.

The sentinel follow-up[24] [25] of 577 girls from protocol 018 assessed safety by monitoring for Serious Adverse Events and pregnancy outcomes. The Nordic extension of the long term follow-up of protocol 015[26] will connect with national hospital registers and has the capacity to search health registries for 'safety events of interest'. Ovarian dysfunction is

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[20] Gajdova M, Jakubovsky J, Valky J. Delayed effects of neonatal exposure to Tween 80 on female reproductive organs in rats. *Food Chem Toxicol*. 1993;31:183-190.
[21] Oser BL, Oser M. Nutritional studies on rats of diets containing high levels of partial ester emulsifiers.II. Reproduction and Lactation. *J Nutr* 1956;31:183-190.
[22] Klein NP, Hansen J, Chao C et al. Safety of human papillomavirus vaccination routinely administered to females. *Arch Pediatr Adolesc Med*. 2012;166:1140-1148.
[23] Arnheim-Dahlstrom L, Pasternak B, Svanstrom H et al. Autoimmune, neurological and venous thromboembolic events after immunization of adolescent girls with quadrivalent human papillomavirus vaccine inn Denmark and Sweden: cohort study. *BMJ.* 2013;347:f509.
[24] Bonanni P, Cohet C, Kjaer SK et al. A summary of post licensure surveillance initiatives for Gardasil/Silgard. *Vaccine*. 2010;28:4719-4730.
[25] Iverson O. Longterm extension study of Gardasil in adolescents; results through month 96. http://www.dagensme-disin.no/Global/Dagens_medicin_norge/Bilder/PDF%20og%20word-dokumenter/018%20extension%201versen%20revised%2017May2013.pdf.
[26] Ibid. 22 Bonanni et al.

not stated in its research focus. The Vaccine Safety Datalink has reviewed associations between Gardasil ® and specific outcomes not including ovarian dysfunction. Rapid cycle analysis of vaccine safety data requires comparison with an unvaccinated cohort or statistics on the background incidence, which, for idiopathic premature ovarian insufficiency in young teens is not known. The Clinical Immunization Safety Assessment Network reviews SAE's and have reported on deaths, venous thromboembolic, neurological and allergic events.

None of these studies have reviewed ovarian function after a course of Gardasil vaccinations, and most have no capacity to do so.

Reliance on adverse event notifications

Relying on the number of vaccine doses distributed in Australia (7 million) as a substitute for ovarian safety research is flawed. In addition to necessary vaccine destruction (due to shelf life limitations, damaged packaging and cold chain storage issues), the vaccination course of 3 injections suggests a maximum 2.3 million vaccinated adolescents. Furthermore, voluntary passive reporting of potential vaccine adverse events is far less than 100%[27]. Usage of the oral contraceptive pill in Australian adolescents for contraception, 'cycle control' and acne management and use of long-acting reversible hormonal contraception (which is increasing) will mask the onset of ovarian dysfunction. Only those vaccinated adolescents not using hormonal contraception would be able to observe or report on declining menstrual function. The number of girls in the population who may currently have delayed onset menopause – like the girls in this G.P's series – is not knowable.

In addition, the delay to diagnosis of premature ovarian failure has been shown to be several years[28]. The menopausal high school girls in the published Australian series from one practitioner had each (100%) consulted other GPs and each had been commenced on the oral contraceptive pill to 'restore periods' without diagnosis. None had been notified to the TGA. Such hormonal 'therapy', further masking and delaying case diagnosis, increases concern at reliance on TGA notifications for demonstration of ovarian safety rather than research in a vaccine to be mandated for all Australian young adolescents.

Ovarian failure adverse event reporting efficiency will be further compromised by instruction to all Australian immunization providers - health workers, GPs, public hospitals immunization clinics and immunization nurses –
that there is 'no biologically plausible' link between HPV vaccination and infertility[29].

Conclusion

The under-representation of the vaccine target age group in HPV4 safety studies; incomplete and short term follow-up; safety study participant hormone usage; fortnight

[27] Varrichio F, Iskander J, Destafano F. Understanding vaccine safety information from the vaccine adverse event reporting system. *Pediatr Inf Dis J.* 2004;23:287-294.
[28] Alzubaidi NH, Chapin HL, Vanderhoof VH. Meeting the needs of young women with secondary amenorrhea and spontaneous premature ovarian failure. *Obstet Gynecol*, 2002;99(5 pt 1):720-725
[29] *Myths and Realities: A Guide for Providers*. TGA Australian Government Department of Health and Ageing; 2013.

reporting restrictions of adverse events; definitional limitations of SAE's; absent reporting of menarche and menstrual patterns in HPV4 safety trials; the decision not to report new medical conditions arising after month 7 from first vaccination; the inclusion of an injected substance with established ovarian toxicity (polysorbate 80) in the young adolescent placebo control and its misrepresentation as 'saline'; omission of a true placebo; and inconsistent ovary toxicity studies have seriously weakened ovary safety research.

Ovarian function surveillance is absent from post-marketing cohort safety studies, and precluded by their design. Reproductive health following this vaccine has not been assessed.

The context of two published, peer-reviewed case series of devastating premature menopause in young teens and a subsequent research report of new onset menstrual dysfunction[30] in 48% of unwell young women following Gardasil vaccination suggest further ovarian research is needed to test the hypothesis of an association between the HPV vaccine and premature ovarian demise.

Vaccination for young adolescents with a product supplying misinformation to providers and consumers and with significant research omissions could impact public vaccine confidence and constitute a broader and potentially more devastating safety issue. It is not known whether there may be a group of girls for whom this vaccine is contraindicated.

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[30] Brinth, L., A. Theibel, and K. Pors, Suspected side effects to the quadrivalent human papilloma vaccine. *Danish Medical Journal*, 2015. **62**(4): p. 1-5.