Response to the fourth Brighton Collaboration Journal Club reviews on BMJ case presentation by Little DT and Ward HRG.
Deirdre Little

Thank you for the invitation to respond to the interesting discussion and comments of the Brighton journal club. The interactive conversation was constructive, raising various points for consideration.

In response, I would like to address the role of case reporting regarding possible adverse events, the capacity of existing Human Papillomavirus vaccine research to comment on ovarian safety, the role of the placebo, and factors which may discourage case notification. A population vaccine delivered to young, healthy persons requires a greater level of scientific confidence in its long term safety than therapeutic medications prescribed for illness. This touches on the matter of providing for informed consent and the quality of information we have.

It is widely accepted that notifications of possible vaccine adverse events may generate hypotheses but cannot test them. Doctors report cases even if causal relationships are uncertain. It is not incumbent on the physician to prove the link before notification of an adverse event. From temporal sequences, early warning signals may prompt further epidemiological and clinical research. This is not usually the role of primary caregivers. Prior to research, all we have is suspicion. Since I have recently notified the Therapeutic Goods Administration of a second case of teenage hypergonadotrophic amenorrhea post HPV vaccination (anti-Mullerian hormone 1.5 pmol/L Beckman Coulter Gen II ELISA assay), suspicion is not unreasonable. There are other unknowns here. What is the background rate of idiopathic premature ovarian insufficiency at age 13? At age 14? Rates vary with age so we need finer gradations of age categories than comparing with ‘under thirties’ or ‘under twenties’ incidence.

Just as a causal link depends on research, reassurance of ovarian safety requires some evidence base. The design of clinical safety studies are usually informed by pre-clinical findings. It is perhaps unfortunate that toxicology studies only provide histology of the male rodent reproductive system after HPV vaccine and not of the female rodent reproductive tract or ovaries. It would have been helpful to have toxicology studies to consult, or long term fecundity studies of vaccinated female rodents. Assessment of ongoing women’s fertility was similarly absent from phase II and III clinical studies.

The Phase II and Phase III studies identified as safety studies at the time of vaccine licensing are study protocols 007, 016, 018, and 013 and 015 respectively. Only 016

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2 ADR report number 333136, Jan. 2014.
3 Extract Study no TT#03-703-0(CTD) Module 4, volumes 1-3, summary for non-clinical study report ‘Intramuscular developmental toxicity and immunogenicity study in rats with postweaning evaluation’.
and 018 focused on the young female target group, with mean ages of 12.6 and 11.9 years. It is not clear what proportion were post menarche. In 016 only 240 girls were left in the study at 12 months (47.4% completed 12 month follow-up). One participant experienced vaginal haemorrhages meeting Serious Adverse Event criteria after 2nd and 3rd vaccinations which were initially deemed vaccine-related. Protocol 018 fully vaccinated 587 girls with 52.3% of enrolled girls aged 9 to 12 and an unclear number post menarche. Health interviews with the participants 18 months after the first vaccination may not have been able to determine menstrual abnormalities at an age when cycles are commencing or establishing ovulatory patterns.

Phase III studies report 58 to 60% of vaccine recipients using hormonal contraception with concomitant use in up to 83% of participants in one trial protocol. Phase III participants were required to use effective contraception for at least 7 months. A major review of the HPV vaccine safety profile reports: ‘new medical conditions were not considered adverse events if they occurred post month 7, or were not determined by the investigator to be vaccine related’. When the Center for Biologics Evaluation and Research requested an analysis of autoimmune conditions over the entire safety database the sponsor noted ‘that there were subjects with additional new medical conditions that were not reported in the CSRs for 011 and 012 [within protocol 013]. These included two subjects with amenorrhea’. Participant use of Vaccine Report Cards to record adverse events occurring within two weeks of each vaccination has limited ability to detect diminishing menstrual cycles.

6 Block SL, Nolan,T, Sattler C et al Comparison of the Immunogenicity and Reactogenicity of a Prophylactic Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) L1 Virus-like Particle Vaccine in Male and Female Adolescents and Young Adult Women *Pediatrics* vol 118, No.5, Nov. 2006.
10 Serious Adverse Events Defined by Code of Federal Regulations USA 21CF600.80 Postmarketing reporting of adverse experiences. (Hospitalization, life-threatening illness, disability, death, illness requiring surgical/medical correction).
11 Block SL, Nolan T, Sattler C et al. p 2141.
13 Miller Nancy B, Medical Officer, Vaccines Clinical Trial Branch, Center for Biologics Evaluation and Research, Food and Drug Administration: Clinical Review of Biologics License Application for Human Papillomavirus 6, 11, 16, 18 L1 Virus Like Particle Vaccine (*S. cerevisiae*) (STN 125126 Gardasil).
15 Miller Nancy B, FDA p 198.
The use of aluminum placebo in older girls’ safety trials has been commented on. It is noted that the placebo control in the only young teen HPV4 study was the vaccine carrier, containing surfactant polyoxyethylene-sorbitan-20-mononucleate (polysorbate 80/Tween 80) 50μg, sodium borate, L-histidine and sodium chloride (normal saline). When injected into newborn rats, polysorbate 80 caused similar ovarian damage to injected diethylstilboestrol, affecting ovaries at all doses tested over a tenfold range. No toxicological endpoint was identified. This chemical is used in medicines and foods, but did not effect rat reproduction when comprising up to 5% of their oral intake. These findings are at odds with statements that biologic plausibility for HPV4 ovarian toxicity is lacking. The Australian Government Department of Health and Ageing states ‘there is no biologically plausible way in which HPV vaccine could cause infertility’, citing its use in some foods. I’m not sure of the basis for accepting this null hypothesis. Toxicity and autoimmune mechanisms are two plausible biological explanations. Such assertions could discourage related vaccine adverse event notifications, and possibly jeopardize future safety signaling. The use of this placebo in the young teen safety trial could have confounded the already limited potential for observation of menstrual abnormality risk differences between vaccine and control recipients. More care could have been used identifying the placebo. It is referred to as ‘normal saline’, ‘non-alum’ ‘saline placebo’. The reviewer’s comment conflicts with the researchers’ reference to the ‘carrier solution’ stating: ‘protocol 018 provides saline placebo-controlled safety data for subjects 9 to 15 years’.

Post licensing review of 44,400 females after three HPV vaccinations, measuring emergency department visits and hospitalizations, had limited capacity to detect ovary dysfunction. Nor would ovarian decline signal as a Serious Adverse Event in the 018 long term sentinel study. Review of the Vaccine Adverse Event Reporting System database in August 2013 revealed 104 cases of new amenorrhoea after HPV4 vaccination, of whom one subject had an FSH recorded, which was ‘elevated at 72’ (no units given). None recorded an anti-Mullerian hormone level. This also suggests that teenage amenorrhoea may be under-investigated in primary care. Current surveillance for

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20 Myths and Realities, a guide for providers 5th Ed. May 2013 pp 48-49.
21 Block Brown Chatterjee et al p 96,98,99.
22 Reisinger KS, Block SL, Lazcano-Ponce E et al p 204,207.
23 Miller, Nancy B FDA p316.
24 Miller, Nancy B FDA p330.
27 https://vaers.hhs.gov/data/index
Serious Adverse Events will not pick up diminishing menstrual periods by definition. Rapid Cycle surveillance requires knowledge of background prevalence or a control group. Vaccine Safety Datalink has reviewed diagnostic categories but not including ovarian dysfunction\textsuperscript{28,29}.

Weak investigation of teenage amenorrhoea, the invisibility of cases using hormonal contraception and Government disparagement of notifications as ‘not plausible’ thereby reducing ‘reporting efficiency’\textsuperscript{30}, may render any association between HPV4 vaccine and diminished ovarian reserve slow to surface. Carefully structured research is needed.

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\textsuperscript{29} Baggs J, Gee J \textit{et al} ‘The Vaccine safety datalink a model for monitoring immunization safety’

\textsuperscript{30} Varrichio F, Iskander J, Destefano F \textit{et al} p289.