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Ongoing inadequacy of quadrivalent HPV vaccine safety studies

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The quality of quadrivalent human papillomavirus vaccine (QHPV) safety studies has been a source of conflict within the Cochrane Collaboration. The establishment of its safety for the young girl target age group has been a source of unease in other sectors including those with an interest in ovarian safety. Academic rigour and integrity in medical journal publications is guarded by editorial and peer-reviewed processes. The observation, however, that medical journals are at risk of becoming arms of the pharmaceutical industry[1] highlights an increased scientific need for alert and active critique of industry-funded trials. Where biased publications are identified around one product there is perhaps a greater cause for concern.

A problem identified by the Cochrane conflict is that internal validity and generalisability of published drug trials need more probing than afforded by current systematic analyses. Cochrane[2] confirms the limitations of using vaccine components as controls, since these components may be important to safety analysis. The importance of correctly identifying all placebo components is also just this. The Cochrane QHPV review and its critique,[3] however, did not identify the misrepresentation of safety trials' control constituents in published Future I and Future II trials. Both trials represent their controls as 'aluminum hydroxyphosphate sulfate'. However Future I,[4] Future II[5] and Villa *et al*'s[6] published trials passing both Cochrane's inclusion standards and QHPV licensing failed to identify the additional presence of polysorbate 80 within their controls.[7] Does this matter? Don't pharmaceutical trials need to correctly state the composition of controls? Ought such research procedure pass unnoticed by a Cochrane efficacy and safety review? Injected polysorbate 80 is known to cause similar ovarian damage[8] to injected diethylstilboestrol in baby rats at 4 mg dosages. The threshold dose for ovarian effects is not known, which may or may not be relevant to published case series of premature ovarian insufficiency (POI) in QHPV recipients.[9 10] This vaccination culminates a possible 0.8 mg polysorbate 80 administered in the completed Australian childhood schedule.

The QHPV target age group of peripubertal girls is missing from phase III safety trials. This also passes without comment by Cochrane. Does this matter? Food and Drug Administration licensing analysis[11 12] of safety trials reports most adverse events occur in girls naïve to the four vaccine HPV types prior to vaccination. Girls seronegative and PCR negative to types 6, 11, 16 and 18 at baseline record the highest incidence of systemic adverse events, the highest proportion of 'moderate to severe' systemic adverse events and the highest incidence of headache compared with women who evidenced prior exposure to vaccine HPV types at baseline. The disparity between clinical adverse events in naïve girls and exposed girls increased with each successive dose in the Detailed Safety Cohort[13] of Future II. Less marked disparity was present within aluminium+polysorbate 80+LHistidine control groups.

The Cochrane HPV vaccine review methodology excluded licensing[14] studies of the current QHPV vaccine's target age group. QHPV V501-018[15] and V501-016[16] phase II studies were the only trials enrolling the vaccine target group. While Cochrane exclusion raises questions about licensing standards, it also missed the documented unexplained death (possible ventricular arrhythmia) of a 15-year-old boy 27 days after second dose in trial 016. Since Cochrane could not exclude an increased risk of HPV vaccine mortality, all documented vaccine trial deaths should bear particular statistical and clinical scrutiny.

In the journal *Pediatrics*, official journal of the Academy of Pediatrics, Naleway et al recently published a Vaccine Safety Datalink study from one site (Kaiser Permanente Northwest), correlating ovarian failure with vaccinations including HPV vaccines. [17] Titled 'Primary Ovarian Insufficiency and Adolescent Vaccination', it claims to 'describe POI incidence and estimate POI risk after HPV vaccination' despite significant omissions and errors. Responding to published case series of POI following QHPV vaccination authors omit to cite the second case series of POI they describe.[10] All cases in this series were prescribed hormonal treatment for 'cycle control' of uninvestigated oligomenorrhoea and amenorrhoea. The proportion in the Naleway study using primary health treatments masking symptoms and tests of POI is not known. The seriousness of POI requires diligent case capture. Naleway *et al* do not state the number of undiagnosed enrollees receiving menstrual disorder treatment, nor hormonal contraception, nor the number of vaccine doses received, nor determine which HPV vaccine was administered, even though no series' cases concerned the bivalent vaccine (licensed for 7 years during the study period). The number vaccinated late into data capture, with insufficient reporting/investigation time, is also not stated, though it takes 5 years to diagnose under 75% of POI.[18] Those enrolled for 1 month would have increased the denominator but not contributed to investigation data. The authors falsely claim vaccine exposure in the described Australian series was not verified. The omitted citation provided verifying

documentation from the Health Department Register. Affected girls were not from 'selected sites' as wrongly claimed but presented to one site and one practitioner. These are significant misrepresentations. Had reviewers/editor required authors adhere to usual academic referencing, misrepresentations would have been clear. Although 92% of women with premature ovarian failure describe an altered menstrual cycle as their initial symptom,[18] the authors did not include the International Classification of Diseases-Ninth Revision codes of amenorrhoea, dysfunctional uterine bleeding and oligomenorrhoea and omit to describe the 13% of 'presumed idiopathic POI' cases they excluded. Inadequate medical records were classed 'not POI' and 1.7% 'POI diagnosis code' records were missing. Vaccine dosage numbers are premised irrelevant and are omitted. Failure to record hormonal usage including long-acting reversible contraception lasting several years disables ovarian function observation, reduces the pool of observable enrollees to an unknown number and reduces the power of this study. All presumptive cases were abstracted by the three authors with a declared conflict of interest. There was no acknowledged gynaecologist input.

Conclusions permitted by the study's reviewers are not adequately supported by its data, power or premise. Evidence-based medicine is not served. Since only 39% of women developing amenorrhoea consult a doctor,[19] ovarian safety research would be better served by menses recording in vaccinated and unvaccinated cohorts for at least 5 years from completed vaccination or anti-Mullerian hormone measurement before and at appropriate interval after vaccination. Rat ovary histology or ongoing fecundity would investigate the issue better than industry-devised studies.

Correction notice This article has been updated since its first publication to correct the appearance of the author names and initials.

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