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LETTER TO THE EDITOR

Comment on "Safety of Human Papillomavirus Vaccines: An Updated Review"

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Dear Editor

We read with interest the article *Safety of Human Papillomavirus Vaccines: An Updated Review* by Phillips et al. [1] published recently in *Drug Safety*. We would like to take this opportunity to challenge the apparent devotion of the authors to an increasingly outdated hierarchy of evidence, particularly in the face of a shifting paradigm within the field of vaccinology.

Within vaccinology, there is a growing appreciation of a variability in immunological responses, with subsequent implications on both the benefit and the harm individuals may experience from vaccines. Research has identified the presence of inter-individual variation in vaccine responses based upon differences in innate immunity, microbiomes, and immunogenetics [2]. Several publications have already identified a number of individual-level factors associated with an increased risk of adverse events following immunization (AEFI), such as sex, age, past infection status, and genetics. There is evidence of both an increased production of immune responses (cellular and humoral) and the development of more frequent and more severe adverse reactions in females than in males [3, 4]. Older individuals have been found to produce different immune signatures to influenza vaccination, which result in decreased vaccine effectiveness [5, 6]. An increased risk of severe dengue fever after vaccination with the first marketed dengue vaccine, Dengvaxia®, has been ascribed to the absence of previous exposure to the dengue virus [7]. Examples of genetic variant-based risks are multiple: narcolepsy after Pandemrix® vaccination [8]; febrile convulsions after the measles, mumps, and rubella vaccine [9]; cutaneous reactions after smallpox vaccine [10]; and osteitis after Bacille Calmette-Guerin (BCG) vaccine [11].

While the magnitude of many of these risks is large enough to be estimated by observational studies, others may be rare enough to escape epidemiological detection. For example, despite multiple observational studies concluding no elevated risk of Guillain–Barré Syndrome (GBS) with tetanus toxoid-containing vaccines [12–14], there exists a famous case report of a 42-year-old man who developed a self-limited episode of GBS after each of three vaccinations with tetanus toxoid over a 13-year period [15]. With progress in vaccinology over the last 40 years, it is likely that cases such as these may now be understood and that explanations such as "unusual susceptibility to Guillain–Barré Syndrome" [14] may be further elaborated.

The current construction of hierarchy of evidence lies at the core of evidence-based medicine, the limitations of which are increasingly recognized [16]. The randomized controlled trials upon which licensure is based and the observational epidemiological studies by which post-marketing signals are investigated provide only population-based estimations of risk. No epidemiological study can answer the question "Did this vaccine cause this event in this patient?" A recent review in the journal *Vaccine* describes a new era of "predictive vaccinology" [17]. In

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this new paradigm, the traditional concept in vaccination policy that "one size and dose fits all" is abandoned as we acquire the ability to make predictions for each individual: predictions regarding the likelihood of producing a protective response (benefit) and the likelihood of a significant AEFI (harm) [17].

Within this new landscape, vaccine pharmacovigilance will play an important role in identifying the "outliers," informing us on the heterogeneity of immune responses. Case reports and case series can no longer be discarded simply as "anecdotes" or "coincidence," and their contribution to the evidence base should not be "trumped" by the findings of an epidemiological study. Using them to further elucidate why certain individuals experience AEFI would represent an important step in the development of vaccine safety science and could serve to preserve and ultimately improve public confidence in the safety of vaccines [18].

Epidemiology can provide evidence of statistical association, but it can never alone determine causality in the individual. A new focus on understanding variations in individual response, as a complement to population studies, is essential to our progress in vaccinology in the 21st century.

Compliance with Ethical Standards

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