Commentary

Exposure to low-dose mercury (from thimerosal) & premature puberty - A new avenue for research with the vaccine safety datalink

The paper by Geier et al\(^1\) addresses the plausible association of premature puberty after a typical pattern of exposure to ethylmercury in thimerosal-containing vaccines (TCVs) taken by young children in the USA before TCVs were discontinued. Both precocious puberty and low-level mercury are *per se* high-profile topics of public health interest. Given that TCVs are still currently given to pregnant women, infants and young children around the world, the paper raises a unique opportunity for discussing the role of mercury-based preservatives.

The study took advantage of the vaccine-safety datalink (VSD) system of the USA. Black \textit{et al}\(^2\) summarized the advantage of the VSD over the former Vaccine Adverse Event Reporting System (VAERS) in use until 1991 in the USA. Until then, potential vaccine safety issues could only be evaluated by the passive data collected through the VAERS. The current VSD system links outcome and vaccine exposure information, demographic and other covariate information, from the automated clinical databases within several Health Maintenance Organizations (HMOs). As pointed out by Black \textit{et al}\(^2\) this data bank can be utilized to screen for possible associations of events after vaccination and also, as in the case of Geier \textit{et al}\(^1\), to evaluate hypotheses. Geier \textit{et al}\(^1\) analyzed the data from 1990 to 1996 (n = 278,624) and explored a possible link of premature puberty to TCV received at young ages by comparing this outcome to outcomes not related to mercury exposure (controls). It is worth mentioning the disproportionate percentage of males (7\%) in the sample. If encountered in future studies, this information confirms gender differences in thimerosal toxicity\(^3\). Constitutional differences in gender determine hormonal balance and represent a biologic variable\(^4\) to be considered in reproductive and neurologic outcomes.

Premature sexual development is a topic of current interest because of social and attendant health-associated issues, especially for girls. Unwanted teenage pregnancy and sexually transmitted diseases are among the important social and biological issues affecting poor countries and disadvantaged segments of rich countries. Reports from different parts of the world indicate that precocious gynaecological-age is significantly associated with early sexual initiation\(^5\) and with teenage pregnancy\(^6,7\). Additionally, as reviewed by Karaolis-Danckert \textit{et al}\(^8\), an accelerated age of puberty onset may influence the life-time risk for breast and testicular cancer, insulin resistance, and adiposity. It is becoming clear that environmental factors are strongly associated with precocious puberty\(^9\). Studies indicate that increasing rates of precocious puberty are among the endocrine-system related effects of endocrine-disruptor chemicals found in the environment\(^10\).

Generally described as endocrine disruptors, there are a broad range of these substances capable of affecting the endocrine system. Some of these can act specifically on the reproductive system having estrogenic, anti-estrogenic, androgenic, and anti-androgenic activity. Besides that, these chemicals can also interfere with the hypothalamo-pituitary unit, and also disrupt estrous cyclicity. The endocrine-disrupting activity of these pollutants on developmental toxicology depends on timing and dosage. However, since these occur as mixtures, it is not yet possible to know if their end-point effects are additive or antagonistic. Therefore, this type of exposure is difficult to study because of the variety of possible outcomes\(^10\). A wide range of endocrine disruptors listed by Abaci \textit{et al}\(^18\) include biocides (herbicides, fungicides, insecticides, nematocides), and industrial compounds made up of organic substances and metals (that includes mercury).
Mercury exposure is widespread and can affect billions of people around the world\(^\text{12}\). Depending on the population, non-occupational mercury exposure can happen in different chemical forms and is determined by different factors. Food such as fish and shellfish contains mainly methyl-mercury\(^\text{12}\), which can also be found in rice grown in China\(^\text{15}\). It has been recently reported that a substantial part of dietary exposure to mercury for American consumers can be derived from high-fructose corn-syrup as a residual contaminant of plants that use mercury cells\(^\text{14}\). Metallic or elemental Hg is commonly used in dental fillings and it is the most common form of exposure to inorganic mercury\(^\text{12}\). Despite its known toxicology, Hg compounds (inorganic and organic) are still used in medicinal products all over the world: eastern traditional medicine\(^{15}\), whitening and skin care products mainly in African countries\(^\text{16}\) and as a preservative in immunogens in the form of thimerosal\(^\text{12}\).

The use of thimerosal in vaccines dates back to the 1930s. Since then it has been used as an antiseptic and antifungal agent in multi-dose vaccine vials\(^\text{12}\). However, in recent years, there have been concerns over postnatal exposure to low levels of ethylmercury (degraded from thimerosal). The amount of ethylmercury exposure during infancy depends on the immunization schedule of the country and how it is practiced in vaccination clinics (single or in combination).

Until recently, low-dose exposure to preservatives and adjuvants (in vaccines) was not an issue, because specific effects are not likely to result in an acute post-vaccine adverse event. However, advances in molecular toxicology and epigenetic research have called for a change in thinking concerning low-dose exposure to toxic metals. Animal studies on the specific effects of low-dose thimerosal (at concentrations found in vaccines) have shown negative effects on nervous tissues and system capable of affecting animal behaviour\(^\text{17}\). However, due to sensitivity and vulnerability issues related studying toxic substances in infancy, untoward effects cannot be ruled out\(^\text{18}\). Mercury exposure can result in a wide range of reproductive effects, such as spontaneous abortion, stillbirths, congenital malformations, infertility, disturbances in the menstrual cycle, abnormalities in sperm production, inhibition of ovulation, and behavioural effects in offspring\(^\text{16}\). The mechanisms of action have been discussed by others\(^\text{19}\) and are thought to occur through (a) accumulation in the endocrine system; (b) specific cytotoxicity in endocrine tissues; (c) changes in hormone concentrations; (d) interactions with sex hormones; and (e) up- or down-regulation of enzymes within the steroidogenesis pathway.

Despite what is known about Hg exposure and the reproductive system, studies of the relationship between human sexual development and low-mercury exposure are nevertheless rare and the study by Geier et al\(^\text{11}\) is in line with previous findings. The onset of menarche among American-Mohawk girls exposed to a mixture of six environmental pollutants that included mercury was studied by Denham et al\(^{20}\). The ability of the studied pollutants to affect age of menarche was statistically significant for lead (delay) but marginally significant for mercury (accelerate). Premature puberty is a process in time that can be influenced by various environmental variables. Therefore, it should be clear that this study\(^1\) is not an unequivocal epidemiological finding, but within the conceivable rationale and limitations of the VSD, it raises interesting questions about the impact of ethylmercury on children’s health and development. In the early system, only acute and, relatively rarely, adverse effects most likely related to the immunogen components of the vaccine were notified. Possible subclinical effects related to low doses of preservatives and adjuvants can only emerge in systems like the VSD. Therefore, in spite of the acknowledged limitations, the work of Geier et al\(^\text{11}\) constitutes a supplementary source of information that should be used to expand our understanding of infant exposure to ethylmercury compatible with supporting immunization.

There are obvious differences between large trials conducted to specifically observe treatment effects on sexual maturation in paediatric population. However, such studies, which might include detailed prospective measures, are realistically unwarranted due to obvious difficulties and ethical considerations. Therefore, retrospective studies can reveal probabilistic associations of low doses of preservatives and adjuvants and chosen outcomes. Indeed, allergenicity, one of the recognized clinical effects of thimerosal, has been seen to decrease in Danish children in response to its removal from vaccines\(^\text{21}\). As a result of an increased number of vaccines used in infancy and the attendant additive burden of preservatives (thimerosal) and adjuvants (Al) plus a wider coverage of immunized populations, susceptible subgroups of children may emerge with a detectable frequency of unforeseen outcomes.
Immunization is necessary to keep individuals healthy and rid populations of the risk of infectious diseases, and modern technology can produce vaccines without thimerosal. Because mercury is detrimental to young children, rather than challenging the pragmatic vaccinology or conventional toxicology, there is urgency in translating laboratory toxicology to clinical significance. Such feedback to the medical community is critical for the clinical engagement and public health decisions necessary for successful immunization campaigns.

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References