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## Letter to the Editor

**The fallacy of small sample size - Comment on: Geier D.A., Kern J.K., Homme K.G., Geier M.R., 2018. The risk of neurodevelopmental disorders following thimerosal-containing Hib vaccine in comparison to thimerosal-free Hib vaccine administered from 1995 to 1999 in the United States. Int. J. Hyg. Environ. Health. 221: 677–683**



## ARTICLE INFO

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Current evidence suggests that neurodevelopmental disorders have multiple causes - genetic, social and environmental. Suspected environmental risk factors comprise a rather large number of conditions and toxicants (summarized by Lyall et al., 2017). For organic mercury, one of the most infamous neuro-toxicants, the body of clinical studies has detected no risk attributable to low-level uptake of mercury during the first years of life (Karagas et al., 2012).

To unearth a potential hazard from vaccines containing organic mercury has been the aim of the authors of a recent paper published in the Journal. For their case-control study, Geier et al. searched the Vaccine Adverse Event Reporting System (VAERS) database to examine an association of vaccines with mercury-containing thimerosal as a preservative and neurodevelopmental disorders (Geier et al., 2018). Because the VAERS database builds on a passive reporting system available to the public, the VAERS managers caution against variable quality and completeness of the reports stating that they often lack details and may contain erroneous information. The obvious strength of the database however is in the large number of reports amenable to research.

In their study the authors retrieved events associated with H. influenzae vaccines of which they chose two brands, one including thimerosal as preservative (HibTITER) and one without thimerosal (PedvaxHIB). The data published in the article suggest that the incidence of neurodevelopmental disorders was higher among the total number of events reported with HibTITER than with PedvaxHIB. I wish to point out that delimiting the analysis to two select vaccine brands was instrumental in arriving at the suggested conclusion which introduces an unjustified bias into the discussion of environmental risk factors. The bias creates concern because it adds to skewing public attitude in disfavor of childhood vaccination.

In order to test the association of thimerosal-containing vaccines with neurodevelopmental disorders I replicated the database search (update as of August 2018) exactly employing the authors' criteria but expanded the number of reports by including other vaccines for use in infants (up to two years). The vaccines were those recommended by the US immunization guidelines issued for the studied period, from 1995 through 1999 (Centers for Disease Control and Prevention, 1995;

Centers for Disease Control and Prevention, 1999, Table 1). The individual vaccine brands were listed by the American Academy of Pediatrics (American Academy of Pediatrics. Committee on Infectious Diseases and Committee on Environmental Health, 1999) and are represented in the VAERS database.

With more than 15000 reports associated with each thimerosal-containing and thimerosal-free vaccines respectively, the sample of reports was considerably larger than the one analyzed by the authors (2654 vs. 832). Table 2 shows that the search results failed to identify a significant association of neurodevelopmental disorders (autism, psychomotor disorders, neurodevelopmental delay in general) with thimerosal-containing childhood vaccines. It reproduced a statistically significant difference only in one category (developmental delay).

Overall, the relative rates of neurodevelopment reports were very close for thimerosal-containing and thimerosal-free vaccines. This highlights the power of the database (large samples allow estimates to regress to the true mean). The relative difference between thimerosal-containing and thimerosal-free vaccines was around 0.1% of the total number of reports in all four categories including < developmental delay > . For the latter category, the numbers were proportionally different albeit very small (20 versus 7), which is suggestive of a reporting bias. In fact, twelve reports referred to two out of eight thimerosal-containing vaccine brands only (Engerix-B and Recombivax HB). Such bias cannot be ruled out for individual reports to the VAERS database.

Thus the most likely reason for the discrepancy between the authors' results and the pertinent evidence from the literature is that the authors evaluated a small sample by limiting the search to two H. influenzae vaccines only. Increasing the sample size refutes the purported difference between thimerosal-containing and thimerosal-free vaccines and corroborates the notion that studying a small population with a low event rate may lead to false inferences. Rather, the correct conclusion from examining the VAERS database is that the use of thimerosal-containing childhood vaccines is unrelated to the incidence of neurodevelopmental disorders.

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**Table 1**  
Vaccines for childhood immunization from 1995 through 1999 in the United States.

Type of Vaccine	Vaccine with Thimerosal	Events n	Vaccine with No Mercury	Events n
DTaP (diphtheria-tetanus-acellular pertussis)	Tripedia	2384	Infanrix	678
	Acel-Imune	1327		
	Certiva	19		
DTwP-Hib (diphtheria-tetanus-whole cell pertussis-H. influenzae type b)	Tetramune	4211		
Hib (H. influenzae type b)	HibTITER	2619	ActHIB	2427
	ProHIBit	488		
Hepatitis B virus	Recombivax HB	2842		
	Engerix-B	1924		
IPV (inactivated polio vaccine)			IPOL	49
MMR (measles-mumps-rubeola)			MMR-II	5040
Varicella			Varivax	5956
Rotavirus			Rotashield	606
n, total		15573		15814

n ... all events (irrespective of their medical nature) reported to VAERS per vaccine brand.

**Table 2**  
Number of reports (percent values relate to overall number of reports) of a neurodevelopmental disorder (categories according to Geier et al., 2018).

Reported Syndrome	Vaccine with Thimerosal	Vaccine with No Mercury	p-Value <sup>a</sup>
Autism	229 (1.51%)	245 (1.61%)	0.512
Developmental Delay	20 (0.13%)	4 (0.03%)	0.002
Psychomotor Disorder	235 (1.55%)	218 (1.43%)	0.426
Neurodevelopmental Disorders in General	358 (2.36%)	336 (2.20%)	0.393

<sup>a</sup> The difference in proportions was assessed by Chi-square statistics.

### Conflicts of interest

The author has no competing interests to declare. The author

declares no financial or personal relationships with other people or organizations that could have inappropriately influenced his work.

### Submission declaration

The work described has not been published previously, is not under consideration for publication elsewhere and its publication is approved by Medizinische Universität Wien where the work was carried out. Medizinische Universität Wien has no involvement with the study design; the collection, analysis and interpretation of data; the writing of the report; and the decision to submit the article for publication. The author declares no external funding source involved in the work.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijheh.2018.10.003>.

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