

Aluminum Adjuvants in Childhood Vaccines and Asthma Risk: What do We See?

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THERE IS A statement attributed to Ralph Waldo Emerson, the early 19th century American transcendentalist philosopher: “*People only see what they are prepared to see,*” a watchword for our current age if ever there was one. In this issue of *Academic Pediatrics*, Daley and co-authors¹ present a set of observations that interrogates the relationship between aluminum exposure in childhood vaccines and the subsequent development of reactive airways disease. What are they showing us, and are we prepared to see it?

The study addresses an important question of vaccine safety: is the receipt of higher cumulative doses of aluminum adjuvant contained in routine vaccines during the first two years of life associated with subsequent development of persistent asthma. To explore this association, the authors conducted a retrospective observational study by assembling a cohort of 326,991 children born between January 1, 2008 and December 31, 2014 who received care at 7 sites that participated in the Vaccine Safety Data-link network and whose clinical outcomes were ascertained between 24 and 59 months of age. The sample was divided into children with and without eczema recognizing the increased predisposition of the former group to the development of persistent asthma. The median accumulated vaccine-associated aluminum dose was 4.18 mg for both groups of children.

Among children with eczema, the authors found that for each mg of vaccine-associated aluminum exposure, the adjusted hazard ratio of developing persistent asthma by 59 months of age was 1.26 (CI 1.07–1.49). For children without eczema, it was 1.19 (CI 1.14–1.25) per mg. This is no small thing. Since the median child in the sample received somewhere between 4 and 4.5 mg of aluminum, a hazard ratio of 1.26 per mg received would translate for the median child into an increased risk of 2.5 to 2.8 meaning those children would be *more than two and one half times* more likely to develop persistent asthma compared with those who had not had this exposure. On a national scale this suggests that children are experiencing

persistent asthma rates more than twice what might otherwise be the case.

The prudent investigator does not wade lightly into the turbulent waters of potential adverse vaccination effects. It is, therefore, reassuring to see the lengths to which Daley and colleagues went to verify their results. Exposures and outcomes were carefully defined and prudently measured using a known database with a large number of observations where inclusion and exclusion criteria could be verified appropriately and where the length of follow-up was adequate to ascertain the outcome of interest. In their discussion, the authors were careful to qualify each of these elements acknowledging potential pitfalls for each one. Cognizant of the risks associated with a retrospective observational study design, the authors were determined to stress test the robustness of their findings. They judiciously adjusted the analysis for a series of potentially confounding covariates including the use of a fixed effects specification to account for the influence of the venue where care was received. They ran different permutations of the analysis by excluding extreme exposure levels for aluminum and by confining the analysis to only fully immunized children. They also conducted a negative control exercise looking to see if aluminum exposure was associated with an outcome (injuries) that should not plausibly be linked to the exposure. All these efforts speak to the rigor with which the authors approached this fraught topic.

Given all of this and the magnitude of their findings, how should we interpret these data? The answer is: carefully. While the analytic caution of the authors is to be applauded, it cannot entirely mitigate the challenges posed by the study design, particularly issues of selection bias. The findings do give some reason for concern in this regard. Are the small numbers of children with little to no aluminum exposure somehow systematically different from the modal child in ways that we do not directly observe but that might be correlated with the likelihood of developing persistent asthma?

The vast majority of children in this study received 4 to 4.5 mg of aluminum during the course of their childhood immunizations. When the authors restricted their analysis to only children who had been fully immunized, the effect of aluminum exposure on the eczema sub-sample is no longer significant and is barely so among the non-eczema cohort. It is possible that by restricting the analysis only to the fully vaccinated, variation in the magnitude of aluminum exposure has been largely eliminated making it impossible to see its effect. On the other hand, systematic unobserved differences between fully immunized children and those with fewer immunizations (and therefore less aluminum exposure) should not be discounted as a potential source of bias. The same is true when the analysis is restricted to only those on whom breastfeeding data are available. Among those children, aluminum exposure is not associated with persistent asthma development in either the eczema or non-eczema cohort. Breastfeeding may itself be protective or may be a proxy for unobservable characteristics of these families such that variation in those factors, rather than aluminum exposure, is what is responsible for the association that the authors have uncovered.

Then there's the issue of dose response. The authors could not demonstrate such an effect among the eczema cohort. If, as the authors contemplate, the biological mechanism underlying a potential association of aluminum with persistent asthma relates to such exposures inducing an immune profile, "biased toward Th2 and away from T helper 1 cell (Th1) immune responses," one might expect a more exaggerated dose response in atopic

children than in non-atopic children. That's not what these data indicate.

Finally, as the authors rightly point out, other environmental aluminum exposures, particularly dietary sources such as breast milk, formula, and food, were not accounted for in the present analysis although the extent to which children absorb aluminum from these sources is questionable.

All of which returns us to Emerson's admonition. Are the results that Daley and colleagues have presented determinative with respect to an association between the exposure to vaccine-related aluminum and the subsequent development of persistent asthma? By no means. Nor do the authors suggest otherwise. But are they, despite important caveats, intriguing? Here the answer must be yes. The pediatric community is daily witness to the power of vaccines to mitigate, even to eradicate, severe suffering and death. And we remain, in midst of other woes, surrounded by misinformation, politicization, and occasional delusional thinking regarding this verifiably beneficial tool. Yet despite whatever unwarranted claims and speculations persist about vaccinations, as scientists, as stewards of public health, we must be "prepared to see" possible complications from their use. Daley and colleagues offer a useful contribution to our ability to see this. . . if we are prepared to do so.

REFERENCES

1. Daley MF, Reifler LM, Glanz JM, et al. Association between aluminum exposure from vaccines before age 24 months to persistent asthma at age 24 to 59 months. *Acad Pediatr*. 2023;23. (PAGES TBD).