

Vaccines and autism in primate model

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The fear that vaccines cause autism has been a tale of changing hypotheses: first, involving the measles–mumps–rubella (MMR) vaccine followed by thimerosal, an ethylmercury-containing preservative in vaccines, and, most recently, the number and timing of vaccines. The primate study by Gadad et al. (1) addresses all three concerns.

MMR

In 1998, Andrew Wakefield and colleagues published a case series of eight patients who developed autism within 1 mo of receiving MMR vaccine. The paper, which was published in the *Lancet*, has since been retracted; technically, it no longer exists. The impact of the media firestorm that followed, however, cannot be retracted. The authors argued that measles vaccine virus—because it was combined with both mumps and rubella vaccine viruses—weakened the immune system. This allowed measles virus to reproduce at the intestinal mucosal surface and damage the lining of the intestine, which then allowed for the ingress of unidentified encephalopathic proteins that entered the bloodstream, crossed an undamaged blood–brain barrier, and caused autism. No evidence was provided to support any aspect of this hypothesis. The study also did not include a control group of children who had not received MMR. Despite the authors' failure to provide either epidemiological or biological evidence for a connection, the notion that MMR caused autism was born and tens of thousands of parents in Europe and the United States withheld MMR vaccine for their children. Outbreaks and deaths from measles followed [see Offit (2) for review].

The public health and academic communities responded. Thirteen ecological, case control, retrospective cohort, and prospective cohort studies were performed between 1999 and 2006, all of which failed to show a causal relationship between receipt of MMR vaccine and development of autism [see Gerber and Offit (3) for review]. Perhaps the most compelling study to date—which mined a database of more than 95,000 children—examined the risk of autism in

children whose older siblings had been diagnosed with the disorder. MMR vaccine was not associated with autism in this at-risk group (4).

Thimerosal

One year after the *Lancet* paper claimed an association between MMR and autism, the US Public Health Service, concerned that a growing number of vaccines given to young children contained thimerosal, asked vaccine makers to move toward eliminating its use. The precipitous and frightening manner in which this issue was handled implied that vaccines might be causing neurological

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disorders, including autism. As was the case with MMR—given that the signs and symptoms of autism are distinct from those of mercury poisoning—the thimerosal hypothesis lacked a sound biological basis (5). Despite the weakness of the hypothesis, the academic community responded. Between 2003 and 2007, seven ecological, retrospective cohort, and prospective cohort studies all found a lack of association between thimerosal and autism [see Gerber and Offit (3) for review].

Too Many Vaccines

By the mid-2000s, the hypothesis shifted again. Now parents were worried that too many vaccines were causing autism. Given that more immunological components were contained in the one vaccine given a hundred

years ago (smallpox) than the combination of all 14 vaccines given to infants and young children in the United States today, this, too, did not make biological sense (6). Still, in response to this concern, two retrospective studies failed to show an association between the number and timing of vaccines and autism (7, 8).

Enter Gadad et al. (1), who took advantage of recent studies that revealed changes in the brains of children with autism; specifically, differences in the size of neuronal cells in the limbic system; the numbers of Purkinje cells in the cerebellum; as well as other abnormalities in the brainstem, amygdala, hippocampus, and neocortex [see Gadad et al. (1) for review]. Using a rhesus macaque model that has been used previously to study the effects of neurotoxins like lead and tetrachlorodibenzodioxin, the authors subjected the animals to a series of vaccine schedules: (i) the 1990 pediatric vaccine schedule, which included both MMR and the full complement of thimerosal-containing vaccines; (ii) thimerosal-containing vaccines only; (iii) MMR vaccine only; and (iv) the 2008 pediatric vaccine schedule, which included all of the vaccines currently given to young children today. Consistent with the epidemiological studies done to date, Gadad et al. found no behavioral or neuropathological differences among the groups of rhesus macaques receiving various vaccine schedules and those receiving a saline control.

One could reasonably wonder whether it is necessary to continue to spend more money chasing this fruitless, dead-end hypothesis.

However, the constant drumbeat of negative studies has made a difference. Unlike 10 y ago, the media no longer covers the vaccine–autism controversy by telling both sides of the story when only one side is supported by the science; for the most part, they have chosen perspective over false balance. Legislators are also stepping up; both California and Vermont recently eliminated their philosophical exemptions to vaccination.

More importantly, parental concerns about the safety of vaccines might be waning. In August 2015, Medscape completed an online

Author contributions: P.A.O. wrote the paper.

The author declares no conflict of interest.

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interview of 1,577 pediatricians, family physicians, nurse practitioners, and physician assistants (9). The results were generally reassuring; 42% believed that parents were more accepting of vaccines; 38% believed that parents were particularly more accepting of measles-containing vaccine; 18% believed that fewer patients were now asking for delayed or alternate vaccine schedules; and 32% had not noticed any change. Worrisome, however, was that, among those parents who were still choosing to delay, withhold, separate, or space out vaccines, 61% gave fear of autism as a reason. It appears that, at least for some parents, no amount of biological, epidemiological, or animal model data will shake a belief held with the strength of a religious conviction.

So what will change these parents' minds? In a sense, the situation is reminiscent of polio in the early 1900s. Like parents of

children with autism today, parents did not know what caused polio or who would be stricken next. So they postulated a variety of causes. Parents of children with polio blamed rats, cats, fleas, chickens, shark vapors, doctors' beards, organ grinders' monkeys, and poisonous gases from Europe. Then Karl Landsteiner discovered that poliovirus caused polio and all of those crazy ideas, and the crazy therapies that followed,

melted away. The same is likely to be true for autism today. Until the cause or causes of autism are clear, the notion that vaccines might be the cause will persist.

The vaccine-autism controversy teaches us that, although it is easy to scare people, it is much harder to unscare them. Even with papers as clear and definitive as that by Gadad et al. (1), it is hard to unring the bell.

1 Gadad B, et al. (2015) Administration of thimerosal-containing vaccines to infant rhesus macaques does not result in autism-like behavior or neuropathology. *Proc Natl Acad Sci USA* 112:12498–12503.

2 Offit PA. (2008) *Autism's False Prophets: Bad Science, Risky Medicine, and the Search for a Cure* (Columbia Univ Press, New York).

3 Gerber JS, Offit PA (2009) Vaccines and autism: A tale of shifting hypotheses. *Clin Infect Dis* 48(4):456–461.

4 Jain A, et al. (2015) Autism occurrence by MMR vaccine status among US children with older siblings with and without autism. *JAMA* 313(15):1534–1540.

5 Nelson KB, Bauman ML (2003) Thimerosal and autism? *Pediatrics* 111(3):674–679.

6 Offit PA, et al. (2002) Addressing parents' concerns: Do multiple vaccines overwhelm or weaken the infant's immune system? *Pediatrics* 109(1):124–129.

7 DeStefano F, Price CS, Weintraub ES (2013) Increasing exposure to antibody-stimulating proteins and polysaccharides in vaccines is not associated with risk of autism. *J Pediatr* 163(2):561–567.

8 Smith MJ, Woods CR (2010) On-time vaccine receipt in the first year does not adversely affect neuropsychological outcomes. *Pediatrics* 125(6):1134–1141.

9 Ault A (August 17, 2015) Survey: More parents accepting vaccine use. *Medscape Medical News*. Available at www.webmd.com. Accessed August 18, 2015.