AFP Journal Club

The Story Behind the Study

Autism and Childhood Vaccinations: Debunking the Myth

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Purpose

Each month, three presenters review an interesting journal article in a conversational manner. These articles involve "hot topics" that affect family physicians or "bust" commonly held medical myths. The presenters give their opinions about the clinical value of the individual study discussed. The opinions reflect the views of the presenters, not those of *AFP* or the AAFP.

This Month's Article

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

For more information on EBM terms, see the EBM Toolkit at http://www.aafp.org/afp/ebmtoolkit.

Are childhood vaccinations associated with subsequent development of autism?

Bob: In 1998, a British gastroenterologist, Dr. Andrew Wakefield, published a report in the *Lancet* on eight children who developed symptoms of autism within one month of receiving the measles, mumps, and rubella (MMR) vaccine.[1] Since then, the media, advocacy groups, and celebrities have promulgated the link between childhood vaccinations (particularly the MMR vaccine) and the development of autism. But, is it true?

This month's article clearly outlines the epidemiologic and biologic studies that should reassure physicians and parents that there is no connection between childhood vaccinations and autism.[2] For the family physician, the data in this article are impressive and can be used to counter most parental concerns.

What does this article say?

Bob: This article reviews the three most commonly proposed hypotheses for vaccine-induced development of autism: (1) the MMR vaccine damages the intestinal lining, allowing the entrance of encephalopathic proteins; (2) thimerosal induces central nervous system toxicity; and (3) multiple vaccinations overwhelm and weaken the immune system. This article looks at the genesis of each theory and the data that debunk them.[2]

In regard to the MMR vaccine, Dr. Wakefield noted lymphoid nodular hyperplasia on endoscopy in eight children with gastrointestinal symptoms and signs of autism within one month of receiving the MMR vaccine. He then postulated that this intestinal inflammation allowed nonpermeable peptides into the bloodstream, subsequently affecting brain development.[1]

There are many holes in this argument. First, this was a self-referred cohort without a control group. Second, in Great Britain, approximately 50,000 children one to two years of age receive the MMR vaccine each month; this is a time when autism typically presents, making this likely a coincidental association. Third, the MMR vaccine has not been found to cause chronic intestinal inflammation. Fourth, no toxic encephalopathic proteins traveling from the intestine to the brain have ever been identified. Instead, genes that code for endogenous proteins, which influence neuronal synapse function, have been identified in children with autism.[3]

Mark: The most glaring flaw in the argument connecting an MMR-induced intestinal hyperplasia and subsequent autism development is assigning cause and effect to a potential association. Association should not be confused with causation.

Without a control group in the original study by Dr. Wakefield, it is imprudent to even suggest that there is an association between the MMR vaccine and intestinal lymphoid hyperplasia. Large-scale studies ▶

are often needed to demonstrate whether an association is statistically present.

Bob: The authors of this month's article reviewed 13 such large-scale studies that demonstrate no association between the MMR vaccine and autism.[2] These are separated into three types of studies:

- Ecologic (studies comparing vaccination rates with autism diagnosis). In California and the United Kingdom, the diagnosis of autism increased through the 1980s and 1990s, yet MMR vaccination rates remained stable during this time.[4,5] In Quebec, Canada, autism rates increased despite a decrease in MMR vaccination.[6]
- Retrospective observational (studies comparing vaccination status with autism diagnosis using national registries). The best study was one conducted in Denmark in which 440,655 children born between 1991 and 1998 who received the MMR vaccine were compared with 97,648 children born during the same years who were not given the MMR vaccine. There were no differences in autism rates between the two groups.[7]
- Prospective observational (a long-term vaccination project allows researchers to prospectively record adverse events associated with the MMR vaccine). In Finland, 1.8 million children were prospectively followed after MMR vaccination, and no cases of vaccine-induced autism were recorded.[8]

Andrea: To further refine the concept of association and causation, there are times when an association does represent a cause and effect. A good example is smoking and lung cancer rates. Clearly, smoking is associated with increased lung cancer rates, and a randomized, placebo-controlled trial is not needed to prove this. The association between smoking and lung cancer meets all of the following criteria: strength and consistency of the scientific data; existence of a temporal relationship (between smoking history and lung cancer); existence of a biologic gradient (increased exposure results in increased risk); a scientifically plausible association; and experimental interventions that work (smoking cessation decreases cancer rates).[9] However, in the case of MMR vaccine–induced autism, none of these criteria are present. The data, in fact, overwhelmingly support no association.

Bob: Let's briefly look at the second hypothesis of thimerosal-induced neurotoxicity. Thimerosal is an antibacterial agent that has been used in multidose vaccine preparations for more than 50 years. It is 50 percent ethyl mercury by weight. However, mercury poisoning has a distinctly different presentation than autism. The CDC has also demonstrated that the mercury in vaccines has not resulted in any subtle signs or symptoms of mercury poisoning.[10] The authors of this month's article review seven large-scale studies—again, ecologic, retrospective, and prospective studies—all demonstrating no association between thimerosal and autism.[2]

Mark: And, by the way, live vaccines like MMR do not contain thimerosal.

Bob: The third and final theory suggests that the simultaneous administration of multiple vaccines overloads the immune system, triggering autism in a susceptible host. However, because of advances in protein chemistry and DNA technology, the immunologic load has decreased from more than 3,000 immunologic components in the seven available vaccines in 1980 to less than 200 in the 14 recommended vaccines today.[2]

Andrea: Two more points: (1) an infant's immune system is capable of handling the thousands of antigens it is exposed to early in life; and (2) autism is not an autoimmune disease. Therefore, this theory has no credibility.

Should we believe this study?

Bob: This month's article clearly provides the science and statistics to dispel the theory that childhood vaccinations induce autism.[2] A Cochrane review came to the same conclusion in October 2005.[11]

Andrea: Large-scale studies, smaller studies, retrospective studies, prospective studies, and case-control studies (you name it) all come to the same conclusion: there is no connection between vaccines and autism. The only outlier is Dr. Wakefield's study, which suggests this possible link.[1]

Mark: Lo and behold, 10 of the 13 authors of Dr. Wakefield's *Lancet* article have since publicly retracted the interpretation they reported.[12] The editor of the *Lancet* has acknowledged that, had they appreciated the full context of Dr. Wakefield's study, "… publication would not have taken place the way that it did."[13] On further review, the *Lancet* also recently published an official retraction of Dr. Wakefield's study (http://press.thelancet.com/wakefieldretraction.pdf).

What should the family physician do?

Bob: Get this month's article. It's an easy read. Keep it handy for when parents are apprehensive about immunizing their child.

Andrea: A national survey conducted in 2003 to 2004 indicated that more than one fourth of all U.S. parents were either unsure of vaccine safety or refused or delayed vaccination of their children because of safety concerns. However, the most important take-home point from that survey was that the parents who changed their minds and immunized their children did so because of information and assurance provided by their health care professional.[14] Indeed, we do make a difference!

Mark: Understand the consequences if we just give in to fear and myths. In 2008, only three fourths of preschool children in the United Kingdom received two doses of the MMR vaccine. The result: measles infection rates have reached more than 1,000 cases per year, the highest since monitoring began in 1995.[15]

Main Points

- There are no epidemiologic or biologic studies that support a connection between childhood vaccinations and autism.

EBM Points

- An association does not confer causation.
- Multiple criteria should be examined when considering if an association implies causation, including strength, consistency, specificity, temporality, dose-response relationship, plausibility, coherence, experimental evidence, and analogy.[9]

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