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The Wakefield Paper

I'm very glad that the Lancet finally retracted the 1998 paper by Andrew J. Wakefield et al. that incorrectly suggested a link between the measles-mumps-rubella combined vaccine and autism. In my opinion, as well as others, the data did not warrant publication in 1998.

Following the judgment of the U.K. General Medical Council's Fitness to Practise Panel on Jan. 28, 2010, the Lancet editors said in a Feb. 2 statement, "it has become clear that several elements of the 1998 paper by Wakefield et al. are incorrect, contrary to the findings of an earlier investigation. In particular, the claims in the original paper that children were 'consecutively referred' and that investigations were 'approved' by the local ethics committee have been proven to be false. Therefore we fully retract this paper from the published record" (Lancet 2010 Feb. 2 [doi: 10.1016/S0140-6736(10)60175-4]). The Lancet cited information that they did not have at the time the manuscript was submitted—which also included an undisclosed patent and funding from antivaccine trial lawyers—as reasons for the retraction. In my mind, the study itself did not reach a credible standard and should never have even been published. I suspect that a high level of public interest in the topics of both autism and vaccine safety may have contributed to the journal's editors' enthusiasm for the submission even though the conclusions were not supported by the

data, and in retrospect, the basic elements of research were not upheld.

Indeed, the authors never established what they claimed to demonstrate: a link between the MMR vaccine and a phenomenon they called "autistic enterocolitis." The study was small—just 12 children—there was no control group, and the children had been specifically selected from among those referred to a pediatric gastroenterology clinic with both bowel symptoms *and* pervasive developmental disorder (Lancet 1998;351:637-41).

The study relied on parental report—8 of the 12 said that the onset of developmental delay symptoms was within 2 weeks of MMR receipt and the authors made no apparent attempt to confirm the reports. The study also relied on very sophisticated technology (in-situ hybridization, in-cell reverse transcriptase, and real-time quantitative TaqMan PCR) to demonstrate measles virus in the gut but failed to include a basic concept—a control population. Research by other investigators including a recent study of children with gastrointestinal syndromes with and without "autistic behavior" have failed to confirm Wakefield's findings.

At most, Wakefield and his colleagues showed a potential association. However, their final paragraph emphasizes the potential linkage ("In most cases, onset of symptoms was after measles, mumps, and rubella immunization") and in subsequent statements warned against the use of combined MMR vaccines. As a result, use of MMR vaccine plummeted in the United Kingdom, measles cases rose, and overall public confidence in immunization was severely damaged.

Unfortunately the fallout continues today, despite the accumulation of a vast literature contradicting Wakefield's conclusions, including an Institute of Medicine report ("Immunization Safety Review: Vaccines and Autism 2004") rejecting a causal relationship. One study particularly relevant to Wakefield's advocacy for using single dosing of measles vaccine is the unique situation in Japan, where, due to a problem with the mumps component, use of the MMR vaccine ceased completely in April 1993 and only monovalent vaccines were used thereafter (which, as it happens, is what Wakefield's group had recommended as a solution).

Despite the removal of the combination MMR vaccine from Japan's immunization program, the cumulative incidence of autism spectrum disorder (ASD) increased significantly up to age 7 among children born in Kohoku Ward (population approximately 300,000) in the years 1988-1996, with the most notable rise beginning with the birth cohort of 1993 (J. Child Psychol. Psychiatry 2005;46:572-9). "The significance of this finding is that MMR vaccination is most unlikely to be a cause of ASD, that it cannot explain the rise over time in the incidence of ASD, and that withdrawal of MMR in countries where it is still being used cannot be expected to lead to a reduction in the incidence of ASD," Dr. Hideo Honda and associates concluded.

Numerous additional studies from the United States, Scandinavia, and elsewhere have also conclusively shown a lack of any link between the vaccine, autism, and/or this supposed gastrointestinal syndrome. There's a good summary of all these data in Wikipedia, under "MMR Vaccine Controversy" (http://en.wikipedia.org/wiki/MMR_vaccine_controversy). I also recommend an online analysis of the Wakefield paper by Prof. Trisha Greenhalgh of University College London, a regular reviewer for the British Medical Journal and the Lancet (www.briandeer.com/mmr/lancet-greenhalgh.htm.

What are the lessons we learn from this 20-year episode? We all have biases that have the potential to color our view of scientific data. Recently, concern about undue influence from the pharmaceutical industry has become a hot topic, hopefully addressed by full transparency of potential conflicts of interest by authors. It is equally imperative for journal editors to be aware of their biases and to advocate for scientific rigor as the criterion for publication and not a political agenda.

I do not have the insight to claim knowledge of what went awry in the case of the Wakefield paper. I do know that I have heard colleagues say, "How could you believe the results of such and such study; it was sponsored by industry." This episode should remind us that scientific rigor should be the gold standard that investigators, reviewers, and editors rely on.

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