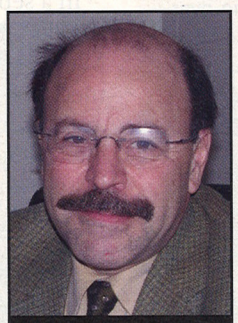
EDITORIAL

Fallout From MMR Vaccine Study Continues

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]).



BY STEPHEN I. PELTON, M.D.

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 anti-vaccine 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 through 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 from their study.

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." I also recommend an online analysis of the Wakefield paper by Professor Trisha Greenhalgh of University College London, a regular reviewer for the British Medical Journal and the Lancet: http://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. It has long been recognized that negative results are often challenging to publish. 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 criteria for publication and not political agendas.

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I do not have the insight to claim knowledge of what went awry at the Lancet in 1998 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." I have read published manuscripts in prestigious journals that failed to satisfy the rules of scientific evidence but appear to promote a politically correct agenda. This episode should remind us that scientific rigor should be the gold standard that investigators, reviewers, and editors rely on. ■

DR. PELTON *is chief of pediatric infectious disease and also is the coordinator for the maternal-child HIV program at Boston Medical Center. He disclosed that he has received grants for investigator-initiated research from, and has served on advisory boards for, GlaxoSmithKline, Pfizer (formerly Wyeth), and Novartis in the last 3 years.*

Disclosure: *Both the Lancet and this newspaper are published by Elsevier.*

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FDA responds:

Although FDA has not, to date, taken any regulatory action to remove unapproved oral colchicine products from the market, we have been in long-term communication with all manufacturers of unapproved drugs.

Of note, there are no "generic" colchicine products. By definition, generic drugs are those evaluated and approved by FDA to demonstrate bioequivalence to a brand name reference product. These colchicine products have not been evaluated and approved by FDA. They are therefore unapproved drugs, not generic medications, and neither their safety nor their efficacy can be ensured.

Only Mutual/URL has submitted an application to FDA for the approval of single-ingredient oral colchicine. We have discussed with the American College of Rheumatology (ACR) the importance of unapproved oral colchicine products obtaining FDA approval. ACR informed us that it would reach out to the unapproved manufacturers to encourage them to become engaged in the FDA approval process. FDA has an Unapproved Drugs Coordinator in the Office of New Drugs who is available to assist manufacturers in applying.

U.S. Needs an Antitobacco Stamp

In a recent letter, Dr. Alan Blum discussed Dr. James Lutschg's remarkable postage stamp collection related to smoking ("It's Time for Recognition," Feb. 1, 2010, p. 8).

I would like to update a statistic in his letter and let readers know that 65 countries have issued antitobacco postage stamps or other postal items such as postcards. It is ironic that Jan. 11, 2014, will be the 50th anniversary of the release of Surgeon General Luther Terry's landmark report on smoking and health, and yet the United States is not among the many countries that have issued an antitobacco postage stamp.

I plan to introduce a resolution at next month's annual meeting of the Medical Association of the State of Alabama (Dr. Luther Terry's home state) and subsequently to the American Medical Association asking them to urge the U.S. Postal Service's Citizens' Stamp Advisory Committee to recommend that such a postage stamp be issued. The resolution also will urge the AMA to encourage other national medical specialty societies and state medical associations to add their voices of support to this effort. I am hopeful that the American Academy of Family Physicians will take up this cause.

W. Jeff Terry, M.D.
Mobile, Ala.

Dr. Terry reports that he is the cousin of Dr. Luther Terry and that he is chair of Alabama's delegation to the AMA.

Corrections

A story "Genetic Test Is Validated for CAD Assessment" (FAMILY PRACTICE NEWS, Jan. 1, 2010, p. 12) referred incorrectly to a test marketed under the name Corus. The test is genomic, not genetic, and the precise name of the test is Corus CAD.

The article "Congenital Heart Disease Survival to Age 18 at 89%" (FAMILY PRACTICE NEWS, Jan. 1, 2010, page 20) should have stated that survival (not mortality) in the 1990-1999 group during follow-up was 99% in patients with mild congenital heart disease, 90% in those with moderate disease, and 59% in patients with a complex abnormality.