

Conflicts of Interest in Vaccine Safety Research

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Conflicts of interest (COIs) cloud vaccine safety research. Sponsors of research have competing interests that may impede the objective study of vaccine side effects. Vaccine manufacturers, health officials, and medical journals may have financial and bureaucratic reasons for not wanting to acknowledge the risks of vaccines. Conversely, some advocacy groups may have legislative and financial reasons to sponsor research that finds risks in vaccines. Using the vaccine-autism debate as an illustration, this article details the conflicts of interest each of these groups faces, outlines the current state of vaccine safety research, and suggests remedies to address COIs. Minimizing COIs in vaccine safety research could reduce research bias and restore greater trust in the vaccine program.

Keywords: adverse effects of vaccines, autism, conflicts of interest, vaccine research, vaccine safety

INTRODUCTION

How safe are vaccines? Health officials caution that no vaccine is 100% safe, but they sponsor studies that conclude the benefits of vaccines far outweigh the risks. Yet conflicts of interest (COIs) cloud the study of adverse effects of vaccines, and public skepticism about vaccine safety information is widespread (ASTHO, 2010). Investigation into the possible link between childhood vaccines and autism provides an illustration of the competing interests that sponsors of vaccine safety research face that could affect their objectivity in choosing which studies to support. Much research is sponsored by vaccine manufacturers and public health bodies, who have financial and bureaucratic interests that could impede the objective study of vaccine safety. These companies and agencies adamantly deny a link between vaccines and autism, and argue that vaccines are one of the most important innovations in disease reduction in the 20th Century (CDC, 1999). They cite several studies that conclude a

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link between vaccines and neurological disorders cannot be established (Offit, 2008). Such research is often disseminated by medical journals that have financial reasons to promote the views of the research sponsors. Conversely, research promoted by some autism advocacy groups presents several overlapping and interwoven theories that link vaccines to autism. Researchers suggest that live viruses and the neurotoxins mercury and aluminum in some vaccines may be associated with neurological disorders (Jepson and Johnson, 2007).

This article examines COIs among people who conduct vaccine safety research as well as institutions that support the research. Using the investigation into the possible link between childhood vaccines and autism as an illustration, this article discusses the current state of vaccine safety research. Gaps in current research are discussed as well as the low level of public trust in the research. To address COIs, Resnik's (2004) framework is used to determine which conflicts to prohibit, which to manage, and which merely to disclose. The existence of COIs does not necessarily mean that the research is fraudulent or that the system that sponsors the research is wholly corrupt. To be sure, many honest and unbiased researchers are examining vaccine safety. However, COIs are widespread, and research consumers cannot know the extent of the problem. Thus, the reliability of any of the information generated is uncertain. If an unbiased researcher bases his or her work on biased research, the result could be an unintentional perpetuation of the bias. Acknowledging and ameliorating the COIs could lead to better and more trusted vaccine safety research.

COIS AMONG SPONSORS OF VACCINE SAFETY RESEARCH

Funding for research on vaccines and vaccine safety comes from several sources. Vaccine developers must provide regulators with studies showing the safety of their products, and they sometimes sponsor similar studies for the medical community at large. Public health agencies, such as the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) in the United States, sponsor studies that promote public health. Other sponsors of research include Congressional committees, special medical panels, advocacy groups, and indirectly, medical journals. All of these sponsors face competing interests that could affect their objectivity in determining which research to promote.

Vaccine Manufacturers

Vaccine manufacturers have a COI related to the tension between making profits and studying the negative side effects of their products. Vaccines are a big and growing business: Worldwide sales of pediatric vaccines in 2009 were about \$11.5 billion, and sales are expected to reach close to \$20 billion by 2014 (Sahoo, 2010). Once manufacturers have met the expensive regulatory hurdles

of vaccine approval, they have little incentive to research the safety of their products. Although postlicensure analyses are typically undertaken to ensure the safety of the products, such analyses in the United States, for example, are performed by the same regulatory agencies that initially approved the vaccines (Salmon et al., 2004). Moreover, vaccine manufacturers do not face the threat of lawsuits that might motivate other industries to seek to improve safety. The National Childhood Vaccine Injury Act of 1986 protects vaccine companies in the United States from being sued. The protection was deemed necessary, because vaccine manufacturers were facing increasing tort litigation and an adequate supply of vaccines at stable costs was considered essential for public health (Supreme Court, 2011). One implication of the legislation was to provide incentives for the development of new vaccines, which typically earned smaller profit margins per dose than other drugs. Citizens in the United Kingdom may sue vaccine manufacturers, but no plaintiff has ever been successful (Hanson, 2007).

Concern about adverse effects of vaccines on sales is evident in intra-office correspondence at Merck, a vaccine manufacturer. In a 1991 internal memo to executives at Merck, Maurice Hilleman, a vaccine researcher, reported that some countries were considering banning thimerosal, the mercury-containing preservative. He admitted he did not know whether thimerosal was dangerous, but he warned that sales could be affected by public perceptions. He suggested reducing the thimerosal content of vaccines being exported. In the memo, Dr. Hilleman gave no indication that he would investigate whether the thimerosal in vaccines could harm infants and young children despite his stated concern (Hilleman, 1991).

Compounding the COIs inherent in the business of manufacturing vaccines is the fact that vaccine manufacturers sponsor research. The influence of industry is wide-spread: It affects individuals as well as institutions and study outcomes as well as research initiatives. In a survey of faculty at top U.S. medical research institutions, Tereskerz et al. (2009) found over two-thirds of researchers (338 out of 506) received some support from industry. Studies show that the financial interests of researchers are positively associated with outcomes favorable to the sponsor in medical studies (Friedman and Richter, 2004; Jefferson et al., 2009; Yank et al., 2007). Not only individual researchers, but also research institutions can be influenced by industry sponsorships such as grants, endowed chairs, and other gifts (Tereskerz, 2003). Industry sponsorship can influence not only outcome, but research initiatives as well: The Tereskerz et al. (2009) survey mentioned above also found 35% of respondents knew of industry-sponsored researchers who compromised their research agenda because the researchers were sponsored by industry. Where industry support was important to the research unit, over half of respondents knew of researchers who compromised their research initiatives. The same study noted that industry support tended to go to senior or well-established researchers,

so industry influence on research agenda could reach younger researchers who work with or for their more established mentors.

Although authors of research articles are supposed to declare COIs, authors do not always fully disclose important information. For example, the tobacco industry was adept at recruiting medical researchers to refute any link between smoking and cancer without having the researchers reveal their sources of the funding (Drope and Chapman, 2001). Few consequences seem to be in place for authors who do not declare COIs, and at least one major medical journal, *Journal of the American Medical Association (JAMA)*, has modified its policy to make the investigation of COIs less transparent (DeAngelis and Fontanarosa, 2009). Besides receiving research funds from industry, researchers are sometimes paid to put their names on articles they did not write. The true industry-sponsored author is not revealed, so the reader is often not aware of the industry influence on these ghost-written articles (Ngai et al., 2005).

U.S. FDA

The U.S. FDA faces at least three COIs when it considers sponsoring research into the possible link between vaccines and autism. The first is the mission of the FDA, which is to protect “the public health by assuring the safety, efficacy, and security of human and veterinary drugs. . . . The FDA also helps the public get the accurate, science-based information they need to use medicines and foods to improve their health” (FDA, 2009). The FDA evaluates and approves vaccines for safety and efficacy. Sponsoring research that finds a link between autism and vaccines that the FDA has approved could greatly damage the Administration’s reputation and reduce public trust in the FDA.

A second major COI in the FDA lies in the way the Administration is funded. In 1992, the Prescription Drug User Fee Act was adopted whereby pharmaceutical companies paid fees to have their drugs evaluated. The intent of the legislation was to enhance the resources of the FDA and thereby speed up evaluations. However, industry funding could result in industry influence (Angell, 2004). While the Act refers only to prescription drugs and not vaccines, many vaccine manufacturers also produce prescription drugs. The user fees paid by drug manufacturers provide incentives for the FDA to be more friendly to the industry since it is dependent upon industry funding.

A third conflict involves the National Vaccine Injury Compensation Program. Parents who believe their child may have been injured by a vaccine can file a claim in the Division of Vaccine Injury Compensation (DVIC). Both DVIC and the FDA are divisions of the U.S. Department of Health and Human Services (DHHS). If the information that the FDA is mandated to provide the public includes studies that show vaccines could be related to autism, it would be providing evidence for claims being filed within its own agency.

As of December 2011, over 5,600 autism claims have been filed in DVIC. The average payout for vaccine-related injuries is close to \$825,000 (DHHS, 2011), so the autism claims could cost the Program over \$4.6 billion. Additionally, more parents would seek compensation if DVIC recognized autism as a vaccine injury.

U.S. Centers for Disease Control and Prevention (CDC)

After a vaccine receives approval from the U.S. FDA, the U.S. Centers for Disease Control and Prevention (CDC) decides whether to add a vaccine to its recommended schedule for the U.S. civilian population. The CDC also sponsors research on vaccine safety. It has at least three major COIs that could hamper its ability to provide objective research about vaccines. The first is the nature of the CDC's mandate, which is to prevent and control disease, injury, and disability (CDC, 2012). Thus, the CDC is obligated to prevent disease, which it does largely by promoting vaccination. It is also charged with controlling disabilities. If the research it sponsors were to identify vaccines as being hazardous and if the vaccination schedule it recommends is associated with autism, it would be forced to concede that its policies did not support its goals and actually promoted disabilities. Since the CDC is charged with promoting vaccination programs as well as assessing vaccine risks, it might be reluctant to sponsor research that uncovers risks it may have created.

An example of the CDC being concerned about research into a problem it may have created occurred in 2000, when the CDC commissioned the Institute of Medicine (IOM) to evaluate vaccine safety, particularly the possible links between the mumps-measles-rubella vaccine and the mercury-containing preservative thimerosal with autism. In a discussion concerning the proposed study (IOM, 2001), Dr. Marie McCormick, then Chair of the Immunization Safety Review Committee of the IOM, said (p. 33), “[The CDC] wants us to declare, well, these things [vaccines] are pretty safe on a population basis.” Later in this planning discussion, Dr. McCormick decided (p. 97), “[W]e are not ever going to come down that [autism] is a true side effect [of vaccines]”, thereby declaring a conclusion before the study was undertaken. In its final report, the IOM stated that although a link between vaccines and autism was possible theoretically, epidemiological studies favored no causal link and suggested funds be channeled to more promising areas of research (IOM, 2004). Other researchers who receive grants from the CDC may also be leery of investigating problems their benefactor may have created.

A second conflict involves the National Vaccine Injury Compensation Program. Parents who believe their child may have been injured by a vaccine can file a claim in the DVIC, which, along with the CDC, is part of DHHS. Thus, if the CDC sponsored research that found vaccines had side effects such as autism, it would be providing evidence for claims filed against its own agency.

Finally, officials at the CDC may see working for the government as a stepping stone to employment at a vaccine manufacturer. A year after leaving as director of CDC in 2009, Dr. Julie Gerberding took a position as president of Merck Vaccines. During her tenure as CDC director from 2002 to 2008, Dr. Gerberding supported the above-mentioned IOM study as well as other studies that concluded no link between vaccines and neurological disorders could be found (see CDC, 2010, for an overview of the studies). Another former CDC employee, Dr. Thomas Verstraeten, began working for GlaxoSmithKline when he was in the process of completing a major study on the potential negative side effects of thimerosal at the CDC (Verstraeten, 2004); the study found no consistent significant associations between thimerosal and negative neurological outcomes (Verstraeten et al., 2003). While the studies may have been good analyses, the COI regarding research emphasis or conclusion is unavoidable when a public official takes a lucrative position in the industry that s/he previously regulated.

U.S. Congress

While U.S. Congressional committees have undertaken a few investigations into the possible link between vaccines and autism (US HR, 2000a,b, 2003), they have not actively pursued the issue. Members of Congress may be reluctant to sponsor research into vaccine safety for at least two reasons: contributions and prospects of future employment. According to the Center for Responsive Politics, the pharmaceutical/health products industry spent over \$2.3 billion between 1998 and 2011 to lobby elected officials and candidates, more than any other industry (CRP, 2011). CRP also reports that the number of lobbyists increased steadily from 729 in 1998 to a peak of 1,803 in 2008, declining to 1,612 in 2010 (CRP, 2010). Since 2005, the industry employed at least three lobbyists for every member of Congress. Additionally, a revolving door exists between Congress and the pharmaceutical industry. Over half of the lobbyists employed by the pharmaceutical industry in 2008 had worked in Congress or another branch of the federal government, and 35 had been former members of Congress (Beckel, 2009). Mandating a study that could hurt major contributors or future employers could result in fewer contributions or no offers of employment or both.

Special Medical Panels

Special panels in the medical community can sponsor vaccine safety studies. One special panel that could provide grants for vaccine safety studies is the U.S. Interagency Autism Coordinating Committee (IACC), which coordinates the various agencies within the DHHS that explore autism. Part of IACC's mandate is to fund research into possible causes of autism. In January

2009, Dr. Thomas Insel, chair of the Committee, called a surprise re-vote on whether to support the funding of two studies that were to have investigated the possible link between vaccines and autism. Although the committee had voted in December 2008 to support the studies (IACC, 2008), the committee decided against conducting the studies in the re-vote. Dr. Insel said DHHS' Health Resources and Services Administration (HRSA), which administers both the grants for IACC as well as the vaccine-injury compensation funds, faced at least the appearance of a COI:

So the optics of having HRSA vote on issues related to autism and vaccines, when they have a large court case, the optics of having people who could be perceived to have or to represent those who have a financial investment in this issue. It takes it out of the realm of a scientific question, a research question, and it raises the possibility that some could see whatever comments we make as being biased by non-scientific issues. . . . If we say, yes, we think it's important to look at this and to provide additional information, it implies that we believe that there's a relationship between autism and vaccines . . . If we say we don't think that this needs to be pursued, it opens us up to the possibility, at least the optics, that we were trying to keep HRSA from having to go down this road legally. (IACC, 2009)

Advocacy Groups

Some independent advocacy groups are skeptical of vaccines and are interested in exposing the dangers of vaccines. These non-profit organizations sponsor research into the possible association between vaccines and autism. Groups such as the Autism Research Institute (ARI), the National Vaccine Information Center (NVIC), and Sensible Action for Ending Mercury-Induced Neurological Disorders (SafeMinds) provide limited grants for the study of vaccine safety. These groups consider that vaccines or vaccine ingredients may be associated with autism and have a reputational interest in the outcome of the research. Some members of these organizations also have a legislative agenda that includes enacting laws to allow vaccination choice and allocating more resources to the study of vaccine side effects (Habakus and Holland, 2011). Parents of children with autism or other neurological disorders founded many of these groups; some of the parents have filed claims under the U.S. Vaccine Injury Compensation Program. Therefore, some individuals associated with these groups have a financial interest in seeing research that establishes a link between vaccines and autism. These organizations sponsor relatively small projects: ARI grants average about \$20,000 (ARI, 2012), and SafeMinds grants range from \$5,000 to \$75,000 per year (SafeMinds, 2012); the entire research budget for NVIC is roughly \$100,000 (NVIC, 2012). While these organizations are not as well-staffed or well-funded as government agencies or vaccine manufacturers, their main task is to generate information to refute agency

or industry claims. In so doing, they are known to fund research to help bolster their position. Although there is limited oversight concerning the general information these groups disseminate, the research they sponsor goes through the same vetting process as any other research that appears in peer-reviewed journals.

Medical Journals

While medical journals do not sponsor vaccine safety research directly, they disseminate research and thereby influence the type of research that is sponsored. If an area of research is sponsored, but not published, sponsors will not continue to fund the area.

Medical journals should be the repository of objective, unbiased research. However, some authors of articles as well as publishers of journals have COIs concerning the dissemination of research on vaccine safety. An author who is a paid consultant for or receives grant money from a vaccine manufacturer has a COI when publishing a paper analyzing the safety of vaccines. This COI does not mean that the analysis is incorrect, but the conflict could influence the analysis. An editorial in the *New England Journal of Medicine (NEJM)* noted generally:

What is at issue is not whether researchers can be 'bought' in the sense of a quid pro quo, it is that close and remunerative collaboration with a company naturally creates goodwill on the part of researchers and the hope that the largesse will continue. This attitude can subtly influence scientific judgment. (Angell, 2000)

Medical journal authors' ties to vaccine manufacturers are pervasive, as revealed in a review of authors of vaccine safety articles published in top journals. Table 1 reports the number of articles found by searching in EBSCOhost for the terms 'vaccine' and 'safety' in the abstracts of original research articles of selected journals from 2006 to 2010. Lundh et al. (2010) have identified the following as major medical journals based on their impact factors: *Archives of Internal Medicine (Archives)*, *Annals of Internal Medicine*, *British Medical Journal (BMJ)*, *JAMA*, the *Lancet*, and the *NEJM*. All these journals were searched as well as *Pediatrics*, because of its emphasis on children's health. *Archives* had no studies meeting the search criteria, but the remaining journals contained a total of 39 studies that did meet the criteria. Thirty-one studies, or 79.5%, included at least one author who declared a COI with a vaccine manufacturer, and 24 studies, or 61.5%, included at least three authors with COIs.

Not only authors, but also journals themselves can be conflicted. Washington (2011) details the reliance of medical journals on advertising from pharmaceutical companies, which can account for up to 99% of a journal's advertising revenue. Fugh-Berman et al. (2006) point out that some journals

Table 1: Original research articles with “vaccine safety” in abstract, 2006–2010.

Journal	Total number	At least 1 author discloses COI	At least 3 authors disclose COI
<i>Annals of Internal Medicine</i>	1	1	0
<i>BMJ</i> (international edition)	1	1	1
<i>JAMA</i>	3	3	2
<i>Lancet</i>	9	9	7
<i>New England Journal of Medicine</i>	11	9	7
<i>Pediatrics</i>	14	8	7
Total	39	31	24

accept advertising revenue only from companies that sell products relevant to medicine, thereby increasing the reliance of the journal on drug companies. In testimony before the U.K. House of Commons Science and Technology Committee, Dr. Fiona Godlee, editor-in-chief of the *BMJ*, further characterized the relationship between journals and drug companies as follows:

Even on the peer-reviewed side of things, it has been said that the journals are the marketing arm of the pharmaceutical industry. That is not untrue. To a large extent, that is true. (UK HC Science and Technology Committee, 2011)

Additionally, pharmaceutical companies provide funds to medical journals by purchasing article reprints and subscriptions that the companies distribute to physicians. Although information on the amount of revenue generated through reprints is not publically available, Lundh et al. (2010) queried six major medical journals to determine the influence of reprints on their total revenue in 2005–2006. The two journals that responded were *BMJ*, which reported that the selling of close to one million reprints represented 3% of its income, and the *Lancet* for which the selling of over 11 million reprints represented 41% of its income. Lundh et al. determined from public sources that the American Medical Association, which publishes *Archives* and *JAMA*, earned approximately 12% of its revenue from reprints. Testimony by Dr. Richard Horton, editor of the *Lancet*, to the U.K. House of Commons Health Committee provides further evidence of the importance of reprint income. Horton discussed his experience with calls from investigators about their research. If Horton expressed interest in the work, the investigator might indicate the article could generate reprint revenue. Horton explained:

Then the conversation might go: ‘It is likely that the company will want to buy several hundred thousand reprints’ and of course several hundred thousand reprints might translate into half a million pounds, a million pounds revenue to the journal. There is an implicit connection between the submission of a paper and the revenue that comes into a journal. (UK HC Health Committee, 2005)

Horton further testified that if a reviewer were too critical of an article, the research sponsor might call Horton and demand that the journal be less critical. The company representative might threaten to pull the paper and point out that if the paper were pulled, there would be no reprint income for the journal.

VACCINE SAFETY RESEARCH TODAY

Resnik (2004) points out that COIs can lead to biased research, injuries and low trust. While we cannot know with certainty whether the COIs discussed above have influenced the current state of vaccine safety research, we do know that gaps exist in research, reports of vaccine injuries are not studied, and public trust is low. Effectively addressing these issues involves minimizing the COIs that vaccine safety researchers face. However, unlike other medical researchers, almost all vaccine safety researchers face some kind of COI.

Most Researchers Face COIs

Typically, COIs in medical research are confined to industry influence. For example, industry-sponsored research showed smoking was safe. Researchers who wrote on the dangers of smoking wanted to refute the industry safety studies, but, until the desire to enact laws to ban smoking arose, the researchers did not have a political agenda. However, some vaccine skeptics have formed organizations (see *Advocacy Groups* above) and have a legal agenda: They want vaccination choice and they want compensation for alleged victims (Habakus and Holland, 2011).

The fact that COIs exist for sponsors of research that promote vaccines as well as those who are skeptical of vaccines could contribute to several trends in vaccine research today. One trend is the increased interest in research concerned with vaccine safety since the 1990s, when a link between vaccines and autism was first hypothesized. Table 2 shows the steady growth in the proportion of vaccine articles indexed in PubMed that include safety. Of the articles indexed in PubMed that contained the term “vaccine” in the abstract, a little over 2% also contained the term “safety” in 1980. This percentage grew to 5% in 1990 and 7% in 2000. By 2010, the percentage was close to 10%.

Another trend is the increase in contradictory research. Some studies show that a link between autism and vaccines cannot be established, while others conclude the question is open and more study is needed. Parents, typically the ultimate decision makers concerning vaccines, are confused, yet they can find more information to assist in answering their questions. Moreover, the search for information is an on-going process. Even if parents decide to fully vaccinate their infants, they may decide later to delay or refuse shots, especially if their

Table 2: Articles indexed in PubMed concerning vaccine safety.

Year	“Vaccine” in abstract (#)	“Vaccine” and “safety” in abstract (#)	“Vaccine” and “safety” in abstract (%)
1980	1,131	24	2.1%
1990	2,118	105	5.0%
2000	3,988	281	7.0%
2010	8,288	792	9.6%

child shows signs of neurological impairments. This course of action is easier to pursue since research exists on both sides of the vaccine safety question.

Consumers of medical research must in all likelihood accept that almost all researchers of vaccine safety face COIs, and discount accordingly. They already know how to discount industry-sponsored research, but they must learn how to discount research sponsored by groups that are skeptical of vaccines. Regardless of the research sponsor, consumers must be exceptionally vigilant in assessing the research questions being asked, the manner in which the study is designed, which data are collected and how, and whether the conclusion follows from the analysis. For example, epidemiological studies conclude that a link between vaccines and autism cannot be established (Hviid et al., 2003; Madsen et al., 2003; Smith and Woods, 2010), yet such studies are designed to create hypotheses, not determine causation or lack thereof (Washio et al., 2008).

Some vaccine safety researchers appear to have few, if any, connections with vaccine manufacturers, North American or Western European regulators or groups that question vaccine safety. Research is emerging from outside North America and Western Europe and appears to be written by people with few or no conflicts. Researchers such as Wu et al. (2010) from China, Dorea and Marques (2010) from Brazil, and Duszczynk-Budharthoki et al. (2011) from Poland declare in their publications that they have no COIs. The results of these vaccine safety studies are mixed: Wu et al. conclude the H1N1 vaccine is safe, while Dorea and Marques and Duszczynk-Budharthoki et al. conclude mercury and aluminum in vaccines can be harmful.

Gaps in Vaccine Safety Research Exist

While the safety of an individual vaccine is considered in the regulatory approval process, studies tend to observe the effects of a vaccine for only a few weeks after the administration of the shot, so long-term effects are unknown. Manufacturers and regulators are to perform postlicensure studies, but resources for such studies are limited: Cooper et al. (2008) report that the U.S. Immunization Safety Office has a budget of only \$20 million, which is a fraction of the close to \$3 billion allocated to the U.S. National Center

for Immunization and Respiratory Diseases, which distributes vaccines and monitors vaccine-preventable diseases. Moreover, no study of the safety of the entire U.S. vaccine schedule has ever been undertaken. That is, the safety of the combination of vaccines is unknown.

Additionally, questions about vaccine safety are not addressed. For example, questions surrounding the safety of thimerosal, which is half ethylmercury, persist. The typical influenza vaccine contains 50 micrograms of thimerosal, and the U.S. state of California classifies thimerosal as a mercury compound, which can cause developmental toxicity (CA EPA, 2004). However, no study offers guidelines for safe levels of injecting ethylmercury (FDA, 2011). Aluminum is another ingredient found in vaccines, yet the risks are not well understood (Dorea and Marques, 2010; Tomljenovic and Shaw, 2011a,b).

At least one public health official has raised concerns about the gaps in vaccine safety research. Dr. Bernadine Healy, former director of the U.S. National Institutes of Health, commented that public health officials were not pursuing a possible link between vaccines and autism out of fear for what they might find and the effects on the vaccination program:

There is a completely expressed concern that they don't want to pursue a hypothesis because that hypothesis could be damaging to the public health community at large by scaring people . . . I think the public's smarter than that. The public values vaccines. But more importantly, I don't think you should ever turn your back on any scientific hypothesis because you're afraid of what it might show. (Attkisson, 2009)

One doctor who explored the possible hazards of vaccines became the center of a storm of controversy. In a series of case studies, Dr. Andrew Wakefield and colleagues suggested a possible association between gastrointestinal issues—perhaps precipitated by the measles-mumps-rubella vaccine—and autism:

We have identified a chronic enterocolitis in children that may be related to neuropsychiatric dysfunction. In most cases, onset of symptoms was after measles, mumps, and rubella immunisation. Further investigations are needed to examine this syndrome and its possible relation to this vaccine. (Wakefield et al., 1998)

The U.K. General Medical Council, a professional self-governing body that licenses doctors, created a Fitness to Practice (FTP) hearing panel that found Wakefield guilty of serious professional misconduct (GMC, 2010) and revoked his license to practice medicine in the United Kingdom. Although some say the research is fraudulent (Deer, 2011), others point to research that substantiates Wakefield et al.'s conclusions (PR Newswire, 2011). Putting aside the hotly debated question of Wakefield's guilt or innocence, Wakefield's experience could have a chilling effect on any researcher considering the study of vaccine risks.

Reports of Vaccine Injuries Are Not Investigated

Although many parents report that vaccines have caused or are associated with autism, no research sponsor has launched a major investigation of the children who are alleged to have developed autism from vaccines. One study found at least 83 vaccine-injured people who received compensation from the U.S. Vaccine Injury Compensation Program (VICP) had autism along with other disabilities (Holland et al., 2011). Besides those compensated, more than 5,600 people have filed claims in VICP stating that vaccines triggered their child's autism (DHHS, 2011) and over 2,000 reports of autism or autism spectrum disorder as a vaccine reaction have been reported to the Vaccine Adverse Event Reporting System (VAERS), which collects information from people who believe they or their child have been injured by a vaccine. The system is an unreliable measure of vaccine reactions: Scott et al. (1990) note that such a passive system vastly underreports the true number of adverse events, whereas Ellenberg and Chen (1997) point out that reports could be mere coincidences so that overreporting could be a problem. Regardless of the accuracy of the claims or of the reporting system, many parents suspect vaccines caused their child's autism. One study found almost half of all parents of children with autism believe that vaccines triggered their children's disorder (Law et al., 2010). These parents could be wrong, but they have not yet been convinced by current research that vaccines are safe. Despite these reports and parental suspicions, no research sponsor has supported a large-scale study of the prevalence of autism among vaccinated versus unvaccinated children, nor are vaccination records included in prospective studies. For example, the Columbia Center for Children's Environmental Health sponsors studies that track pre- and post-natal exposures to a variety of environmental pollutants to determine possible adverse health outcomes, yet exposures to vaccines are not included (CCCEH, 2011). Nor are vaccinations included in the National Child Study, which also looks prospectively at the influence of other environmental factors on children's health (NCS, 2012).

Trust in Vaccine Safety Research Is Low

Some industry analysts have characterized public confidence in vaccines as a crisis (Black and Rappuoli, 2010). Kennedy et al. (2011) report that 77% of U.S. parents surveyed have at least one concern about vaccine safety. According to a CDC report, 39% of parents surveyed in the United States said they either delayed or refused vaccinations for their children (DeNoon, 2010). In a survey by WebMD, almost 70% of U.S. parents wanted information about vaccine risks, and 66% said they either questioned or refused a vaccination for their child (DeNoon, 2011). Almost half of all parents surveyed in the United States question the validity of vaccine safety data because of the influence

of pharmaceutical companies, and over 40% believe the government is covering up information about vaccine safety (ASTHO, 2010). In one study, parents reported being most concerned about the MMR, HPV, and influenza shots; parents' most common fears were autism, too many shots, and serious side effects (Tryon et al., 2011).

Not only parents, but health care workers including new doctors are also raising questions about vaccine safety. One study revealed that only 40% of health care workers received an influenza shot (King et al., 2006). In another study, reasons for refusal by health care workers included concern over adverse reactions (Clark et al., 2009). When the state of New York mandated the influenza and H1N1 shots for medical professionals, health care workers protested, citing safety concerns about the shots (Matthews, 2009). The mandate was withdrawn within two months of being issued and before it ever took effect (Chan and Hartocollis, 2009). In another study, new doctors were found to be more skeptical about vaccine safety than their older peers. They particularly questioned the safety of the polio, MMR, and varicella vaccines (Mergler and Omer, 2011).

DISCUSSION

Addressing the COIs among the people who conduct research and institutions that study vaccine safety could reduce bias while restoring public trust. Research suggests egregious COIs should be prohibited, while some COIs can be managed and others need only to be disclosed (Resnik, 2004). Such a framework is useful in determining how to address COIs in vaccine safety research.

Prohibit Agencies that Promote Vaccines from Overseeing Vaccine Safety

The U.S. airline industry offers a model for addressing the conflict of the CDC both promoting vaccines and overseeing vaccine safety (Salmon et al., 2004). Similar to the U.S. National Transportation Safety Board (NTSB), which oversees transportation safety issues of national importance, an independent agency to oversee vaccine safety could be established. The NTSB is an independent agency, which receives no funding or administrative support from the U.S. Department of Transportation. Likewise, separating a National Vaccine Safety Board from the DHHS would be important, based on the experience of the NTSB. Although the NTSB had been part of the Transportation Department, officials decided to separate the two entities for proper oversight, declaring ". . . No federal agency can properly perform such (investigatory) functions unless it is totally separate and independent from any other . . . agency of the United States" (NTSB, 2011).

However, creating a credible independent vaccine safety agency would be difficult since airline accidents differ from vaccine injuries in at least two crucial ways. First, an airline accident is obvious. The airline industry cannot sponsor studies that claim that the accident did not occur, nor can it suppress media reports of the accident. Vaccine injury, however, can be explained away as coincidence, especially if the injury does not manifest itself until several years after the administration of the shot. Since vaccine injury can be difficult to determine, it is all the more important that the agency that oversees vaccine risks should be separate from the agency that promotes vaccines. If a parent reports an injury to an agency that is specifically charged with vaccine risk, the agency has an incentive to investigate.

A second major difference stems from the first: Since accidents are so apparent in the airline industry, the industry is forced to promote safety. An airline with a bad safety record would lose customers and face ruinous lawsuits. The vaccine industry has no such constraints; the state mandates that children receive the industry's products and the only legal avenue of redress is a vaccine injury panel, not a court of law. Indeed, once a vaccine has gone through the expensive approval process, a vaccine manufacturer has a disincentive to study negative side effects. Admitting the existence of such side effects might compel the manufacturer to withdraw the vaccine, make improvements that reduce the side effect, and then seek regulatory approval once again, a very expensive process. A credible vaccine safety board could address some of these issues. Any report by a parent or doctor of an adverse reaction to a vaccine would be investigated. Moreover, this agency could compare the long-term health outcomes of children who were vaccinated versus those who were not vaccinated: No such study has yet been performed. If certain vaccines were found to be associated with autism, bad publicity would force vaccine manufacturers to be concerned about the risks of those vaccines.

Despite the difficulties, creating an independent vaccine safety agency would assist in restoring public confidence in the vaccine program. As Salmon et al. (2004) noted: "The public must know that vaccine safety concerns are taken seriously and investigated by independent professionals whose primary responsibility is safety, not financial gain, public image, or program goals."

Prohibit Government Officials from Working for Vaccine Manufacturers

Closing the revolving door between public office and vaccine manufacturers could help to restore confidence in the vaccine program. Parents would trust public health officials in the government if parents knew the officials could not use public service as a stepping stone to a lucrative position in private industry. Specifically, any person in a vaccine policymaking position or any member of a vaccine advisory committee could have no past funding or salary from a vaccine

manufacturer. Nor should they own stock in a vaccine company. Moreover, the vaccine policymakers and vaccine advisors would not be allowed to receive grants or salary from or purchase stock in vaccine manufacturers after leaving their posts. The same policy could be in effect for special masters who decide vaccine injury cases as well as legislators who enact laws that affect vaccine regulations.

Since finding qualified vaccine experts who have no past ties to pharmaceutical companies is very difficult (Drazen and Curfman, 2002), the implementation of this policy would be step-wise and long-term. The first step would be to prohibit vaccine policymakers from receiving funds after leaving their positions. Currently, in the United States, policymakers must wait one year before accepting a position in an industry they regulated. This waiting period should be extended to at least five years, or, ideally, ten years. The government officials could work in other industries or academia, but not in the industry they regulated or in an academic capacity where they would receive funds from industry. The prohibition of past funding could be phased in by setting caps on the amount a policymaker received in the past. The caps could be lowered over time, and ultimately reach zero. Phasing in this program might not take as long as one might expect: The American Medical Student Association launched a PharmFree Campaign in 2002 whereby medical students can pledge not to accept funds from pharmaceutical companies either as students or as doctors (AMSA, 2011).

Manage the Influence of Vaccine Manufacturers on Medical Journals

To ensure the objectivity of published medical research on vaccine safety, vaccine manufacturers should not influence medical journals. One way to improve the integrity of medical publications is for central repositories of research to require disclosure of ties between journals and pharmaceutical companies. PubMed, an on-line index of biomedical literature maintained by the U.S. National Institutes of Health, is such a repository. PubMed could require journals that it cites to disclose any COIs, including the amount of revenue the journal receives from pharmaceutical companies—including advertising and reprints—as well as whether owners or editors of the journal are stockholders or board members of pharmaceutical companies.

The benefits of information must be balanced with the costs of obtaining the information. Collecting and reporting information costs both time and effort. Institutions that request information should attempt to obtain information that is already being collected by the journals. Such institutions could work with the journals' accountants to determine which information is readily available and to create a standardized form—similar to the form that the International Committee of Medical Journal Editors (ICMJE) suggests its

member journals require of authors in the journals (ICMJE, 2011). The benefit of such an undertaking is similar to the benefit of requiring individual authors to disclose COIs: Knowing the extent of private industry involvement would go far in assuring an increasingly wary research consumer that major medical journals are not unduly influenced by pharmaceutical companies.

Disclose All Financial Payments to Doctors

One step to address COIs in the vaccine safety research in the United States is the Physician Payment Sunshine Act (PPSA). Beginning in 2012, drug manufacturers must report to the DHHS all payments they make to doctors or teaching hospitals. DHHS is then to make the data easily available to the public, including the names and addresses of doctors or hospitals as well as the types and amounts of payments. Such disclosures are particularly important for doctors who are researching vaccine safety or sponsoring such research.

Besides reports from drug companies, medical researchers themselves as well as research hospitals should disclose the financial ties they have with third parties. Disclosures should be easily available to the public and, to the extent possible, streamlined. Authors of articles published in journals that belong to the ICMJE must already report their funding sources and their financial ties with third parties; researchers and research institutions could post the same form on a central website. The form is electronic and can be easily up-dated. It should include not only that a money transfer to a doctor or institution has been made, but also the amounts that the researchers receive, since even small transfers can influence behavior (Katz et al., 2003). To present a complete profile of financial ties, medical researchers should also disclose stock holdings and stock options. Not only researchers, but also people who serve in national health offices such as DHSS or on special health panels such as IACC should openly disclose all financial ties to vaccine manufacturers.

Some may argue that having both companies and individual doctors or institutions report financial ties would be redundant. However, such a system is currently in place in the United States regarding income tax. Companies report how much they pay employees, and individuals report how much they earn as well as their income from sources other than working. Likewise, individual doctors may own stock in vaccine manufacturers or receive funds from non-U.S. manufacturers that are not covered under the PPSA. Therefore, both sources of information are needed.

Enforcing the disclosure requirements would be a challenge. Since vaccine manufacturers and public health regulators face COIs, the enforcement agency should be independent of industry and current regulators. In the United States, the Internal Revenue Service has experience auditing financial claims and could extend its work to ensure vaccine manufacturers, doctors, and medical institutions accurately disclose financial ties. Fines could be exacted for

non-compliance as well as banning researchers from publishing in journals for a period of time or receiving government grants for research or both.

Disclose All Data in Vaccine Safety Studies

Since the consumers of vaccine safety research must be exceptionally vigilant in understanding the studies (see section *Most Researchers Face COIs*), the readers should have easy access to the data used in the studies. The U.S. National Academies recognized the importance of sharing data when they created the Committee on Responsibilities of Authorship in the Biological Sciences. The Committee created the “uniform principle for sharing integral data and materials expeditiously (UPSIDE), which includes the following tenet:

An author’s obligation is not only to release data and materials to enable others to verify or replicate published finds (as journals already implicitly or explicitly require) but also to provide them in a form on which other scientists can build with further research. (NRC, 2003)

Data could be posted with the electronic version of studies or deposited with the journal as a requirement for being published.

Implementing this recommendation could be difficult. Although Public Library of Science (PLOS) journals require all authors to honor requests for data from independent researchers, Savage and Vickers (2009) found that most researchers did not comply. Only one of the ten authors Savage and Vickers contacted provided them with the raw data they requested. Some of the authors were not permitted to provide data, as they had changed institutions; other authors said providing annotated data would take too much time to prepare. These comments led Savage and Vickers to recommend that data be deposited at the time of publication. Their findings also suggest that the impetus for data sharing must come from the journals themselves.

SUMMARY

COIs can influence the objectivity of vaccine safety researchers. Using the vaccine-autism debate as an illustration, this article describes the COIs faced by various research sponsors. Vaccine manufacturers have financial motives and public health officials have bureaucratic reasons that might lead them to sponsor research that concludes vaccines are safe. Advocacy groups have members with legal and financial reasons to support studies that find adverse effects in vaccines. These conflicts do not mean the research is incorrect, but the research could be selective and biased. Currently, most vaccine safety researchers face conflicts, which contribute to consumer confusion as well as more studies concerned with vaccine safety. Reported injuries from vaccines

are not investigated and both the public as well as some health workers question vaccine safety research. Ameliorating the COIs—through bureaucratic restructuring and enforced transparency—could lead to less bias, more investigation into reported injuries and increased trust in vaccine safety research.

DISCLOSURES

The author has two daughters with pervasive development disorder, not otherwise specified. She has filed a petition in the U.S. Court of Federal Claims under the National Vaccine Injury Compensation Program for one of her daughters. The author is a former member of the board of directors of Sensible Action for Ending Mercury-Induced Neurological Disorders (SafeMinds).

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