CME

Navigating Parental Vaccine Hesitancy

CME EDUCATIONAL OBJECTIVES

1. Explain the processes to ensure vaccine safety in the United States.
2. List strategies to allay concerns regarding the purported connection between vaccines and autism in vaccine-hesitant parents.
3. Identify parents' understanding of the risks of alternative vaccine schedules.

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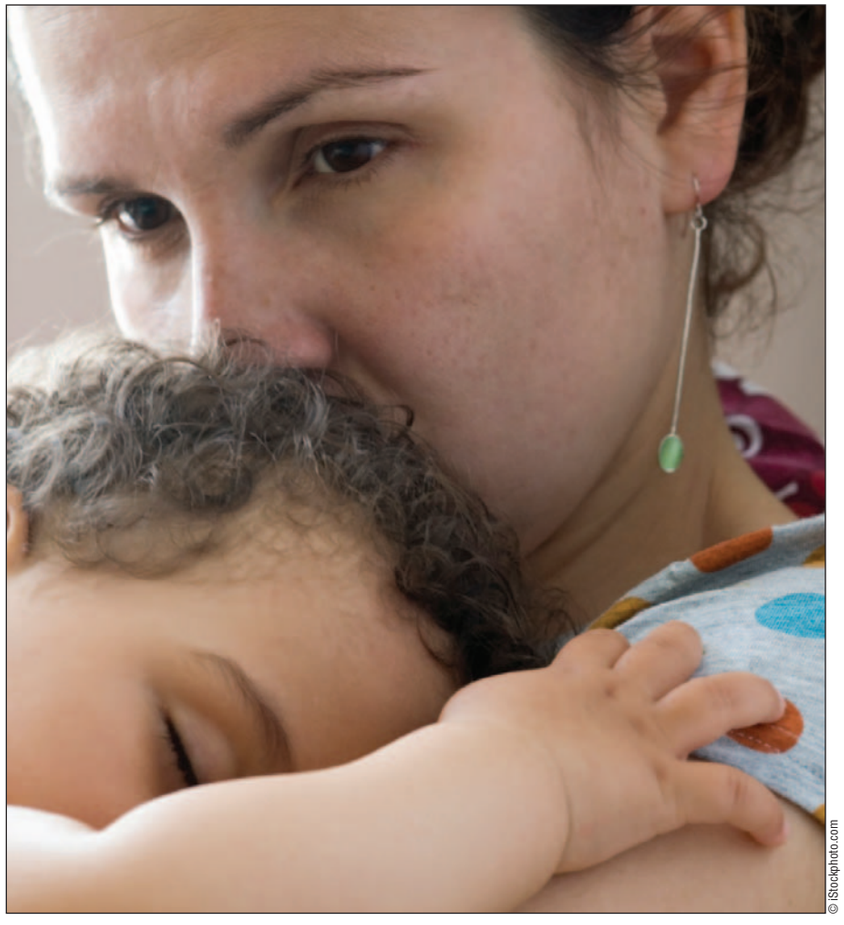


Pediatricians routinely encounter families who question the safety and necessity of childhood immunizations. Responding effectively to this begins with understanding the basis for concern and addressing each issue in a straightforward, comprehensive manner. This article reviews some of the common themes underlying vaccine hesitancy, delineates the processes that are in place to ensure vaccine safety, and explains the science behind the most common vaccine safety concerns.

Michael J. Smith, MD, MSCE and Gary S. Marshall, MD

TABLE 1.

Fear of Vaccines Can Lead to Public Harm

Vaccine[a]	Event or Finding	Evidence that Event Resulted From Willful Refusal to Vaccinate
DTwP	Outbreaks of pertussis in the U.K., late 1970s	Intense media coverage of anecdotal reports of neurologic reactions resulted in a a decrease in vaccination rates from 81% to 31%. Outbreaks were not seen in countries without anti-vaccine movements.
DTaP	Higher risk of pertussis in certain states	Risk correlates with availability of personal belief exemptions and the ease with which such exemptions are granted.
DTaP	Pertussis cases and controls in Colorado, 1996-2007	Odds of vaccine refusal 23 times higher among cases. Virtually all cases among refusers, and 11% of cases in the whole population were caused by refusal itself.
MMR	Measles eliminated from the U.K. in 1994 but endemic again in 2008	Immunization rates fell dramatically after Wakefield's 1998 article suggesting a causal link with autism.
MMR	33 cases of measles among members of a church in Indiana, 2005	31 cases occurred among members who refused vaccination because they feared adverse reactions.
MMR	Measles outbreaks in the U.S., 2008	The vast majority of cases were unvaccinated or vaccination status unknown. Of eligible persons, 66% not vaccinated because of religious or personal beliefs.
MMR	Measles outbreaks in Japan, mid 1990s	Measles vaccine made optional in Japan, resulting in more than 100,000 cases and 50 to 100 deaths per year.
Hib	*H influenzae* disease in Minnesota in 2008–highest number of cases since 1992	Three of the five cases were intentionally not immunized, including one who died.
Varicella	Varicella cases and controls in Colorado, 1998-2008	Odds of vaccine refusal 9 times higher among cases. Five percent of cases in the whole population were caused by refusal itself.

[a] In some cases, the concern may have been about all vaccines, or multiple vaccines, rather than the one cited.

Adapted from Marshall GS. The Vaccine Handbook: A Practical Guide for Clinicians. *3rd ed. Professional Communications, Inc., West Islip, NY: 2010.*[20]

VACCINE CONCERNS

It is difficult to measure exactly how many parents have serious concerns about vaccine safety. As recently as 2008, National Immunization Survey (NIS) data show coverage rates well above 90%, implying that most parents have their children vaccinated.[1] However, this is a national estimate that may not account for clustering of unvaccinated children; 90% coverage may mean that nine in every 10 children across the county are vaccinated, or that all children are vaccinated in nine communities and none in another. The recent measles outbreaks in the United States, which were for the most part limited to communities with low MMR uptake, suggest the latter.[2]

The best way to understand vaccine hesitancy may be to ask parents about it directly. Here's the good news: In a nationally representative survey of 1,552 parents, 90% of respondents stated that vaccines were a good way to protect their children.[3] But 54% also reported that they had concerns about serious adverse effects of vaccines; 25% believed that vaccines cause autism; and 11.5% had refused at least one vaccine.

Vaccines have been one of the most effective public health interventions of all time. Because vaccines have done their job, and vaccine-preventable diseases are no longer as prevalent as they once were, many parents do not see these diseases as a threat. However, the threat is real. The United States recently experienced the largest measles outbreak in more than a decade — with more than 90% of cases occurring in unvaccinated patients, mostly because of a specific choice made by parents.[2] Although there were no deaths during this outbreak, children actually do die of vaccine-preventable diseases in the United States.

In 2008, for example, an unvaccinated child died of *Haemophilus influenzae* type b (Hib) meningitis, which had been virtually eliminated by the introduction of Hib conjugate vaccines in the late 1980s.[4] Table 1 offers other examples of the public health consequences attributed to the fear of vaccines.

Will scattered disease outbreaks and occasional deaths be enough to restore public faith in our immunization program? At a minimum, they should serve as powerful reminders that not vaccinating is risky business. The question is, why has it come to this — a public that needs to witness disease and death before accepting a safe and effective preventive measure?

VACCINE SAFETY: FROM SCIENCE TO LAW

It is clear that vaccine-preventable diseases still exist, and explaining this to parents is the cornerstone of effective vaccine risk-benefit communication. Although vaccines are among one of the most thoroughly tested substances that are put into people's bodies for medical purposes, physicians must also be prepared to discuss the fact that vaccines are not 100% safe. Similar to any other pharmaceutical products, they have potential side effects.

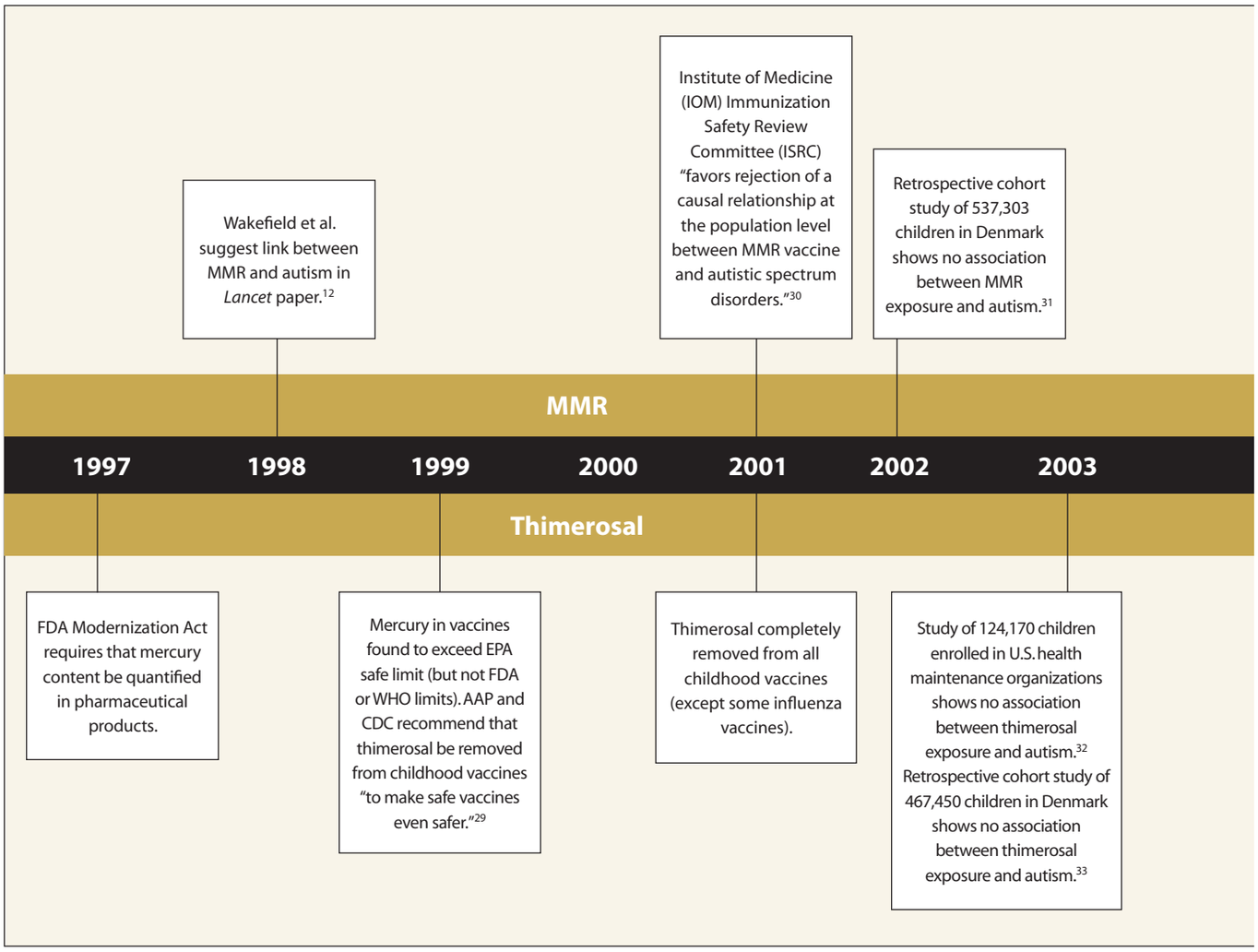


Figure. Vaccines and autism timeline.

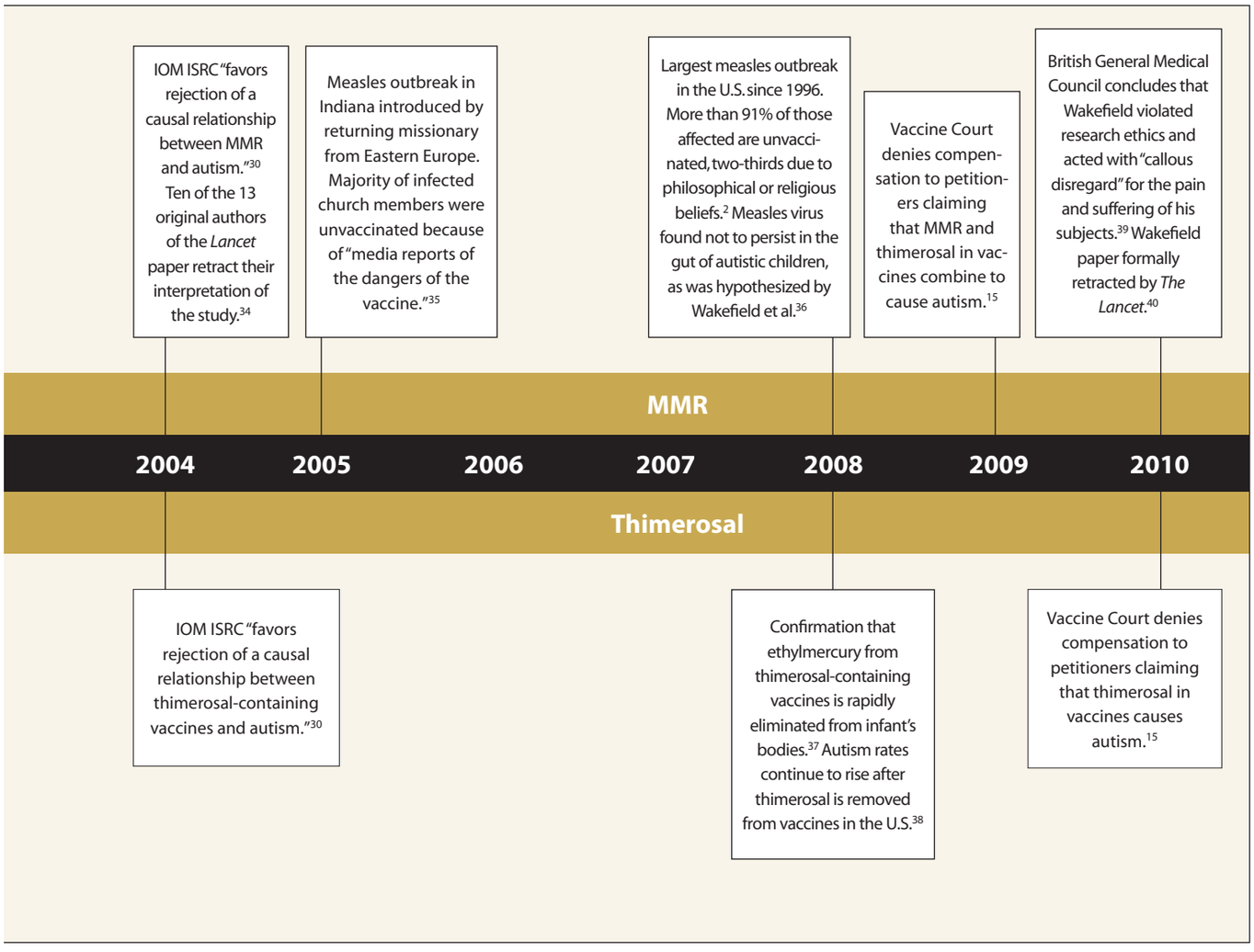
Fortunately, most of these are minor, such as fever and pain, erythema, or swelling at the injection site.

However, unlike medicines, which treat diseases and are given to sick people, vaccines are given to healthy people to prevent disease, so the threshold for establishing safety must be very high. The proof required by the Food and Drug Administration (FDA) before licensure is granted is daunting, involving thousands of people enrolled in rigorous clinical trials. The most reliable data come from large, randomized, controlled, phase 3 clinical trials that compare efficacy and safety of a new vaccine to a placebo (if there isn't already a vaccine for the disease) or to a currently licensed vaccine (if one exists). Occasionally, these studies are not large enough to detect rare vaccine adverse events.

For instance, a four-valent rhesus rotavirus vaccine (RotaShield, Wyeth) was approved for use in the United States in 1998 but was withdrawn within a year because of an association with intussusception, which occurred in approximately one of every 10,000 vaccine recipients.[5] This association was not detected in the prelicensure trials because, even though more than 10,000 children had been studied, those trials were not powered to detect such a small risk.

Because of the RotaShield experience, each of the current rotavirus vaccines (RotaTeq, Merck and Rotarix, GlaxoSmithKline) was studied in about 70,000 children before licensure. How do we know how many people to include in a clinical trial to detect a rare side effect? Parents (and providers) need to appreciate the mathematics behind the answer to this question.

Let's say, for example, that a given event occurs at a background rate of one in 100,000 people. To detect a twofold in-



crease in the rate of that event in a vaccinated population, 1,238,000 people would have to be enrolled in a randomized, controlled clinical trial.[6] The cost and logistics of conducting such a trial would be prohibitive. Researchers are therefore compelled to establish a reasonable balance between risk tolerance and feasibility to bring vaccines to the public in a timely manner.

Our obligation to ensure safety begins with prelicensure trials but continues after a vaccine is released, when the number of people vaccinated increases exponentially.

This is where postmarketing surveillance systems come in. The Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system jointly maintained by the FDA and Centers for Disease Control and Prevention (CDC), serves as an early warning system, encouraging reports to be filed by anyone about anyone who might have suffered an adverse event after vaccination. In fact, such systems picked up the intussusception problem with RotaShield. This all-inclusive approach maximizes sensitivity and generalizability. However — and this is key — it does nothing to establish causation.

VAERS cannot distinguish temporal associations from true cause-and-effect relationships because it only includes data about people who received the vaccine and had the adverse event of interest. It does not include reports of vaccinated individuals who have no adverse events, or unvaccinated people who experience the same adverse events (eg, autism in children who never received the MMR vaccination). Demonstration of causation requires population-based study designs that compare risk among vaccine-exposed and unexposed individuals.

The Vaccine Safety Datalink (VSD), which incorporates data from eight large managed-care organizations, is a good

TABLE 2.

Organizations Offering Credible Information About Vaccines and Vaccine Safety

Professional Organizations	
American Academy of Family Physicians (AAFP)	www.aafp.org
American Academy of Pediatrics (AAP)	www.cispimmunize.org
Association for Prevention Teaching and Research (APTR) (formerly the Association of Teachers of Preventive Medicine)	www.atpm.org
Centers for Disease Control and Prevention (CDC)	www.cdc.gov/vaccines
Infectious Diseases Society of America (IDSA)	www.idsociety.org
Pediatric Infectious Diseases Society (PIDS)	www.pids.org
Advocacy and Safety Assessment	
All Kids Count	www.allkidscount.org
Allied Vaccine Group	www.vaccine.org
Every Child by Two (ECBT)	www.ecbt.org
Global Alliance for Vaccines and Immunization (GAVI)	www.gavialliance.org
Immunization Action Coalition (IAC)	www.immunize.org
Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health	www.vaccinesafety.edu
National Foundation for Infectious Diseases (NFID)	www.nfid.org
Sabin Vaccine Institute (SVI)	www.sabin.org
For Parents	
Children's Hospital of Philadelphia Vaccine Education Center	www.vaccine.chop.edu
National Network for Immunization Information (NNii)	www.immunizationinfo.org
Parents of Kids with Infectious Diseases (PKID)	www.pkids.org
Vaccinate Your Baby	www.vaccinateyourbaby.com
Voices for Vaccines	http://www.voicesforvaccines.org

example of this. Because it includes data on those who did/did not receive specific vaccines and did/did not experience given events, the VSD allows calculation of true incidence rates and relative risks. Approximately 9 million people are included in the VSD, so even very rare events can be captured.[7]

Ultimately, the benefits of routine childhood immunization far outweigh the risks of serious adverse events, which, fortunately, are extremely rare. However, from time to time, children may be injured by a vaccine. In these cases, families may file a claim for compensation from the federal government through the National Vaccine Injury Compensation Program (VICP); in fact, they are required by law to pursue remedy through the VICP first, rather than through the tort system. If the injury is included on a list of scientifically validated vaccine injuries (listed in the Vaccine Injury Table),[8] the family is awarded compensation from a trust fund created from an excise tax on all vaccines. If the injury is not listed in the Vaccine Injury Table, the petitioner may be compensated by demonstrating that an injury was caused by the vaccine, or that the vaccine aggravated a pre-existing condition. Unlike the scientific rigor of epidemiologic studies, causation in the "vaccine court" relies on a "preponderance of the evidence," or proof of "more likely than not."[9] As a result, neither biological plausibility nor epidemiologic data are needed for favorable adjudication. Since its inception, the VICP has awarded 2,400 petitioners more than $1.8 billion.[10]

VACCINES AND AUTISM

As highlighted by recent studies of parents[3] and pediatricians,[11] the putative association between vaccines and autism has been the most prominent vaccine safety concern over the last decade. Most prominent has been the now disproven association between MMR and autism claimed by Andrew Wakefield and colleagues in a 1998 article in *The Lancet*.[12] The mercury-containing preservative thimerosal also has been subject to claims implicating it as a cause of autism, although thimerosal has not been added to routine childhood vaccines as a preservative for nearly a decade. Key moments in the parallel evolution of the hypothetical association between autism and MMR or thimerosal are outlined in the Figure (see page 478-479).

Many rigorous epidemiologic studies involving hundreds of thousands of person-years of exposure (and non-exposure) have failed to detect an association between vaccines and autism.[13] Providers and parents alike would be well-served to read Dr. Paul Offit's book on this topic.[14] Unfortunately, and in a sad commentary on the state of scientific thinking in modern America, the science supporting this simply hasn't gotten much traction, especially when it has been juxtaposed against the personal beliefs of celebrities who are given much television airtime.

What may grab the public's attention, however, are the two recent landmark decisions made by the vaccine court. In what has been called the Omnibus Autism Proceedings, designed to expedite the 5,200 autism cases filed with the VICP, countless hours of testimony and thousands of pages of scientific articles pertaining to several "test cases" were reviewed by Special Master Judges.[15] On Feb. 12, 2009, the Vaccine Court formally rejected claims that thimerosal and MMR combine to cause autism. On March 12, 2010, the court like-

wise rejected claims that thimerosal alone causes autism. The judges did not mince words: Special Master Vowell, in *Dwyer v. Secretary of Health and Human Services* (No. 03-1202V), wrote, "The witnesses setting forth this improbable sequence of cause and effect were outclassed in every respect by the impressive assembly of true experts in their respective fields who testified on behalf of respondent." Hopefully, these findings will serve to solidify in the court of public opinion what was decided in the court of science long ago — namely, that vaccines do not cause autism.

TOO MANY, TOO SOON?

A decade ago, nearly a quarter of parents reported the concern that children receive too many vaccines.[16] Since then, the number of vaccines routinely given to children has increased, which is a good thing, or so it would seem, as a wider spectrum of infections are prevented. Unfortunately, the increased shot burden has fueled a concern that infants' immune systems are being overwhelmed and that this may lead to a host of conditions, from autism (yes, the hypothesis has shifted yet again) to diabetes, allergies, and autoimmune diseases. In fact, "alternative schedules" that "space out" routine childhood immunizations have been offered.[17]

Although this may seem like a reasonable compromise to maintain adequate immunization coverage, there are many reasons it is a bad idea.

First, the notion of "immune overload" is not valid scientifically. An infant can (and does, in the course of everyday life) respond to thousands of antigenic challenges at the same time.[18] The 14 vaccines included in the official 2010 vaccination schedule[19] prevent 16 diseases but represent only 177 separate antigens spread out over 18 years.[20] In contrast, the three vaccines included in the 1980 vaccination schedule prevented eight diseases but represented about 3,041 separate antigens.

Second, delaying vaccines not only increases the risk of contracting infectious diseases but forces prioritization. Which shots should be delayed? It is not a good idea to delay the diphtheria/tetanus/acellular pertussis vaccine (DTaP), given the prevalence, morbidity, and mortality of pertussis among young infants.[21] But, then, do we delay the pneumococcal conjugate vaccine in deference to DTaP? What if the child develops pneumococcal meningitis in the interim — without question a terrible, utterly preventable event? For that matter, should we defer measles vaccination until 3 years, as has been suggested?[17] That is not a good idea when measles is just a plane flight away.

Third, delaying vaccination makes it more likely that a given series will not be completed.[22]

Finally, "spreading out" immunizations increases the number of visits needed to protect children. Who is going to pay for those extra visits, and how much extra work will it be to track down the children who don't show up for each of those visits?

There are many reasons delaying vaccines has negative consequences, but no evidence that it has any benefits.[23] In fact, a recent study demonstrated that children who received all vaccines on time during the first year of life performed the same or better on neuropyschologic testing at 7 to 10 years than children with delayed receipt of vaccines.[24]

MOVING FORWARD

Some parents will find these scientific arguments reassuring. However, science alone will not convince others. According to Michael Specter, author of *Denialism: How Irrational Thinking Hinders Scientific Progress, Harms the Planet, and Threatens Our Lives*, distrust of vaccines is part of a broader cultural trend that favors "science by consensus" — if many people make the same claim, it must be true.[25] Unfortunately, modern technology has made it difficult to determine exactly how many people are in the crowd.

Near universal access to the Internet and other social media make it surprisingly easy to find stories of children who were completely normal until they were vaccinated. Given that most children in the United States are completely vaccinated, any adverse event that occurs in the first year of life is likely to occur within weeks of a vaccination. Now that all adults are recommended to receive a flu vaccine every year, the perception that vaccination is temporally associated with adverse events is also likely to increase.

Let's put this into perspective. For instance, if 10 million women are given a vaccine, 86 will develop optic neuritis in the next 6 weeks.[26] If all 10 million are pregnant, 16,684 will have a spontaneous abortion. All of this is true — even if the shot is a placebo. This illustrates two things. First, as epidemiologists know but the public may not, sequence does not mean consequence. More importantly, as human beings, we have trouble grasping the big numerical picture — it is more natural to assume a relationship with the shot than to contemplate thousands of lost pregnancies (or cases of autism or SIDS) caused by chance alone (or to something other than the shot).

Yet, anti-vaccine websites are replete with personal stories of alleged vaccine injury, exploiting this human tendency to believe anecdote.[27,28] Unfortunately, Internet users may reach such sites accidentally using standard search engines. In a sense, we need to psychologically "immunize" parents against anecdotal thinking, giving them a firm foundation in probabilistic reasoning and scientific evidence. We can also direct them to reliable websites with science-based information about vaccines, vaccine safety, and vaccine-preventable diseases (see Table 2, page 480).

Don't be surprised, however — some of these websites tell their own anecdotal stories about children with bad outcomes from vaccine-preventable diseases. This is, in essence, fighting fire with fire. For those parents who distrust the pharmaceutical industry and the government agencies that study and approve vaccines,

stories from other parents may be seen as more trustworthy.

In the final analysis, the most important factor in effective vaccine risk-benefit communication is a trusting relationship with you, the primary care pediatrician. And one way to help parents understand that the risk-benefit equation comes out strongly in favor of vaccination is your own personal advocacy. Pediatricians recommend vaccines because they care about children. Even their own children and grandchildren are vaccinated. The approach begins with listening to parents and respecting their concerns, but it ends with a strong, evidence-based recommendation to strap the children into their "vaccine car seat" before they head out onto the highway of life.

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