

# Current controversies in the USA regarding vaccine safety

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As a result of the vaccines discovered in the 20th Century, parents and many healthcare providers of the 21st Century have limited or no experience with the devastating effects of diseases such as polio, smallpox or measles. Fear of disease has shifted to concerns regarding vaccine safety. Scientific evidence has refuted many of the misconceptions regarding vaccine safety; however, parental refusal of vaccines is increasing. Here we review six of the most prevalent controversies surrounding vaccine safety: the proposed causal relationship between receipt of the measles–mumps–rubella vaccine and autism; thimerosal as a potential trigger for autism; religious objection based on some vaccine viruses being grown in cell lines from aborted fetal tissues; parental worries that use of the human papillomavirus vaccine may lead to youth promiscuity; fears regarding the purported association between pertussis vaccination and adverse neurological outcomes; and concerns regarding too many vaccines overloading or weakening the infant immune system. Healthcare providers are ideally positioned to correct these misconceptions, but they must recognize and acknowledge parents' concerns, educate themselves on the latest scientific research that addresses these, and dedicate sufficient time to discuss vaccine safety with worried parents.

**KEYWORDS:** controversies • immunizations • vaccine safety • vaccines

Historical evidence suggests that there is a predictable inverse relationship between the levels of vaccine-preventable diseases and safety concerns, with safety concerns likely to emerge as first-hand experience with vaccine-preventable diseases decreases [1]. Today, vaccines represent one of the most important medical advances of all time and are responsible for preventing several vaccine-preventable diseases, and untold human suffering and disability [101]. As a consequence of the vaccine discoveries of the 20th Century, parents and many healthcare providers of the 21st Century have limited or no experience with the devastating effects of diseases such as polio, smallpox or measles. This has contributed to an uneasy relationship between the lay public and stewards of public health. In a recent survey of pediatricians and family practitioners, 11% of the physicians did not recommend to parents that children receive all available vaccines [2]. **Thus, controversies surrounding safety have clouded the successes reaped by these life-saving vaccines.** Fear of disease has shifted to fear of vaccine safety. Ironically, vaccines have become victims of their own success.

Scientific evidence has refuted many of the misconceptions regarding the safety of vaccines [3]; however, a distressing increase in parental refusal of vaccines has been reported [4,5,6]. A 2001–2002

National Immunization Survey indicated that 1% of parents believe vaccines are unsafe and another 6% have a neutral opinion on vaccine safety. Both groups had similar low vaccination coverage [4]. The 2003–2004 National Immunization Survey revealed an increase in vaccine refusal rates to 6%, with a total of 28.3% of respondents indicating that they were unsure or delaying vaccines due to concerns about vaccine safety [7]. Recent outbreaks of measles, *Haemophilus influenzae* type b invasive disease and pertussis have been attributed to vaccine refusal resulting in under-immunized infants and children [8–11]. These outbreaks underscore the need for continued efforts to educate the community regarding the safety and efficacy of currently licensed vaccines.

In this review, current common vaccine controversies in the USA will be addressed. In addition, the extant scientific evidence will be discussed within the context of the ongoing public health debate regarding the recommended vaccination schedule for infants and children.

## Neurodevelopmental concerns: disconnecting autism

One of the most contentious vaccine controversies to date is the proposed causal relationship between the receipt of the measles–mumps–rubella

(MMR) vaccine and autism. Andrew Wakefield, a gastroenterologist in the UK, was the first to postulate the so-called 'leaky-gut' theory. Wakefield's theory was supported by studies that identified measles virus nucleic acid sequences in the blood cells and intestinal tissue of some children who had experienced severe behavioral regression [12,13]. A similar investigation with a larger sample failed to reveal persistence of measles virus nucleic acids in the peripheral blood of children with autism-spectrum disorder [14]. Subsequently, results of several large population- and ecologic-based studies have failed to provide any support for Wakefield's theory [15]. In light of the compelling evidence refuting Wakefield's contention, most of his coauthors have published a formal retraction of the findings of the original article and the journal *Lancet* has recently fully retracted the original publication based on several elements of the paper being proven to be false [16,17]. Further details about this controversy and autism research have been published in a recent book [18]. The Institute of Medicine (IOM) in a report on vaccine safety has stated that "the committee concludes that the evidence favors rejection of a causal relationship between MMR vaccine and autism" [19]. Although there are rare side effects such as immediate hypersensitivity reactions and febrile seizures, as well as mild fever and rash that occur relatively commonly in association with its use, the MMR vaccine continues to be safe, efficacious and recommended by the Advisory Committee on Immunization Practices (ACIP) of the US CDC, and endorsed by the American Academy of Pediatrics (AAP) and the American Academy of Family Practice (AAFP).

Thimerosal is another hot button issue that has been debated in relationship to the onset of autism. Thimerosal has served as a preservative in vaccines since the 1930s. It is added to multidose vaccine vials for its bactericidal properties to preserve the sterility of the contents. In the late 1990s, the government became aware of and concerned about mercury exposure in the general population and the Environmental Protection Agency (EPA) published standards of safe limits of methylmercury exposure [20]. Thimerosal contains 49.6% mercury by weight and metabolizes into ethylmercury and thiosalicylate [15]. The use of thimerosal came under fire as more thimerosal-containing vaccines were added to the recommended infant and child immunization schedule. The possibility of subsequent neurodevelopmental problems related to the cumulative amounts of thimerosal that a child was receiving in the first 2 years of life, the total amount of mercury being administered at a single clinic visit, especially for the very smallest of infants (including premature infants in whom safety data were unavailable at the time) were raised as concerns [20,21].

In 1999, the AAP and the US Public Health Service (USPHS) took a cautionary stance and issued a joint statement calling for the removal of thimerosal from pediatric vaccines [22]. At that time, the risks of low-dose ethylmercury in vaccines were unknown, although there was no evidence that thimerosal-containing vaccines contributed to toxic mercury levels. Studies conducted subsequently suggest that ethylmercury behaves very differently to the more concerning environmental neurotoxin methylmercury [21]. The action taken by the AAP and USPHS

had a significant ripple effect on the general public's acceptance of vaccine safety. The birth dose of hepatitis B vaccine, which at the time contained thimerosal, was subsequently withheld by many healthcare providers and the hepatitis B vaccination campaign experienced a serious setback. The removal of thimerosal from vaccine vials has also increased production costs, which are ultimately passed on to the consumer. At present, with the exception of some influenza vaccines, none of the routinely recommended pediatric vaccines contain thimerosal as a preservative.

In spite of overwhelming scientific evidence to the contrary, the debate rages on with media reports fueling the general public's fear and erosion of confidence in vaccines. In March 2008, the story of Hannah Poling, a 9-year-old child whose parents claimed that she developed severe neurodevelopmental problems after receiving the MMR and other vaccines, found its way to front page news. The MMR-autism 'link' and the hypothesis that multiple vaccines cause autism were given 'new life' when the Polings were successful in their litigation under the Vaccine Injury Compensation Program (VICP). The VICP was developed to fairly compensate individuals who feel they have been harmed by a vaccine. Unlike most US legal claims, the VICP only requires a biologically plausible theory and not irrefutable proof [23].

The following year on 12 February 2009, the US Court of Federal Claims denied damages for three families who were seeking redress for what they believed to be MMR vaccine-associated neurodevelopmental harm to their children. The three cases were considered 'test cases' for the almost 5000 families with pending claims. The hearings were conducted over 2 years and included 5000 pages of expert testimony and 939 medical articles [102]. This was a landmark decision that was criticized by antivaccine activists and lauded by the Department of Health and Human Services (DHHS). Once again, the purported link between MMR, as well as thimerosal, and autism had been disconnected.

### Moral & religious concerns

Some parents have refused certain vaccinations for their children based on religious objections. The moral opposition to these vaccines is due to the acquisition of the initial cell lines in which vaccine viruses are grown, from voluntarily aborted fetuses. The specific vaccines are:

- Single-antigen vaccines against rubella
- Multiantigen vaccines against MMR
- Single-antigen vaccine against chickenpox
- Vaccines against hepatitis A [24]

In response to these concerns, the US Conference of Catholic Bishops has issued statements relieving parents of the obligation to refuse this vaccine based on the Catholic Church's opposition to voluntary abortion. The Catholic Bishops have noted that the source of the cell line for the vaccines was not the choice of the parents and the only viable option to protect their child and the community from serious illness is to take the vaccine [25].

### Human papillomavirus vaccine: a battle between policy & parents

Human papillomavirus (HPV) is the most common sexually transmitted disease and is most widely known for its association with cervical cancer. There are more than 120 genotypes of HPV with approximately 30 affecting at least half of sexually active individuals. Of the 30 types, 12 can cause cervical cancer [26]. Four HPV genotypes have been targeted for vaccine development: 6, 11, 16 and 18. HPV-6 and -11 cause anogenital warts and, if transmitted vertically from a mother to her infant, may cause juvenile recurrent respiratory papillomatosis [26].

The first HPV vaccine was licensed by Merck, NJ, USA (Gardasil®) in 2006 and was heralded by many as the most important anticancer vaccine since the hepatitis B vaccine. A second bivalent (HPV types 16 and 18) vaccine, Cervarix® (GlaxoSmithKline, London, UK), has recently been licensed by the US FDA. However, controversies and questions concerning safety as well as parental attitudes have contributed to the relatively low HPV vaccine uptake – 17.9% of vaccine-eligible young women aged 13–17 years and 9.9% aged 18–26 years [27,103].

Gardasil is a quadrivalent vaccine (serotypes 6, 11, 16 and 18) and approved for use in females, ages 9–26 years. It has been recommended by the Advisory Committee on Immunization Practices (ACIP) of the CDC and endorsed by the AAP and the AAFP since 2007 [28].

Follow-up studies have revealed a 98–99% efficacy rate for Gardasil [29,30]. Post-licensure safety data for this vaccine as reported by the federal Vaccine Adverse Event Reporting Systems has been similar to other vaccine post-licensure data [31]. The question arises as to the acceptability of any vaccine risk with a disease that can be prevented by an active screening process. The answer lies within a medical system that has been unsuccessful in reducing the incidence of HPV-associated disease through routine screening [32].

Public health, politics and parents have clashed and created a significant obstacle to the widespread acceptance of the HPV vaccine. Shortly after the licensure of the HPV vaccine, several states began introducing legislation to mandate HPV vaccination for school-aged girls [33]. This action prompted a groundswell of opposition from the lay public and immersed the HPV vaccine in controversy. Parents and some healthcare providers argue that receipt of the HPV vaccine should be a matter of individual choice, particularly since the vaccine is designed to prevent a sexually transmitted infection. Opponents proclaim that the HPV vaccine promotes early initiation of sexual activity and/or increased promiscuity [104].

The reality is that young people engage in risky sexual behavior that can have devastating effects on their health well into adulthood [34]. A government study of abstinence-only education in middle schools revealed that within 4–6 years after the program, an equal number of participants versus controls had experienced sexual activity with the mean age of 14.9 years of age for first sexual activity [105]. The 2005 US Youth Risk Behavior Survey has reported similar findings with a median of 3.6% of females reporting experiencing their first sexual encounter before 13 years

of age [35]. The National Health and Nutrition Examination Survey (NHANES) interviewed adults regarding sexual behavior and reported that 20% of 20–29-year-olds had engaged in sexual activity before 15 years of age [106]. An even harsher reality is that young children can become infected with HPV after being subjected to involuntary sexual activity due to rape, incest or other unwanted genital contact [34].

### Nervous system disorders: encephalopathies

The licensure of whole-cell pertussis vaccines in the 1940s marked the beginning of a dramatic decrease in the morbidity and mortality associated with *Bordetella pertussis* infection. Prior to the widespread use of the pertussis vaccine, hundreds of thousands of children every year contracted this debilitating respiratory infection and thousands of infants died [36]. However, despite routine use of this vaccine and, subsequently, the less reactogenic acellular pertussis vaccines, pertussis remains endemic in the USA [37]. This situation can partly be attributed to an increase in vaccine refusals as well as the modest efficacy (70–90%) of these vaccines, and an increasing adolescent and adult pool of susceptible individuals in whom immunity has waned over time.

The history of the pertussis vaccine debate dates back nearly 35 years. This controversy was first ignited by a study published in 1974 suggesting neurological complications associated with the pertussis vaccine [38]. Reports of post-vaccine febrile seizures added fuel to the fire [39]. These vaccine safety studies created significant anxiety among the general public, so that pertussis vaccine coverage plummeted in the UK from over 70% to approximately 30% [39]. Japan and Sweden also observed dramatic decreases in pertussis vaccine uptake as national mandates were lifted. The benefit of the pertussis vaccine soon became apparent as these countries quickly experienced widespread pertussis epidemics [40]. A case–control study entitled the National Childhood Encephalopathy Study (NCES) was conducted in the UK from 1976–1979, that suggested that the risk of permanent brain injury from pertussis vaccination might not be zero but was still extremely low (1 in 300,000) [41]. Immunization rates began to recover after the NCES data were published. Unfortunately, the findings of the NCES were interpreted by some people as supporting a causal relationship between pertussis vaccine use and encephalopathy. Over time, this interpretation has been refuted [42,43]. In 1988, a London High Court of Justice ruling attempted to put an end to the speculation that pertussis vaccine caused serious neurological events but the damage had already been done in terms of pertussis vaccine acceptance [39]. Several well-designed studies have since been conducted that show no evidence of an association between the whole-cell diphtheria–pertussis–tetanus vaccine and encephalopathy [44,45].

### An overwhelmed or healthy immune system?

The number of recommended childhood vaccines has increased exponentially in the last 50 years. A fully immunized child by the age of 2 years will have received 14 different vaccines and up to 26 injections. Some healthcare visits may require five injections at a single visit. Understandably, parents have voiced concern about too many vaccines overloading or weakening the fragile

immune system of their infant [46]. This notion may be based upon reports that certain live viral vaccines, such as those containing attenuated measles virus, can cause a decrease in protective immune responses to varicella vaccine [47] and that the high-titered measles vaccine (Edmonston–Zagreb strain) can cause an excess of cases of invasive bacterial infections in developing countries [48]. It should be noted that current vaccines (including the highly attenuated Moraten strain of measles vaccine) do not appear to cause clinically relevant immunosuppression in healthy children [3].

The neonate's immune system begins to develop and is primed *in utero* [49]. There is evidence that fetuses have the capacity to form antibodies in the presence of intrauterine infections [50]. Infants can generate functional T cells as well as the full range of B-cell responses [51]. Continued maturation of the immune system is observed as the neonate, within hours of life, begins to colonize his/her intestinal tract and respond to a whole host of environmental antigenic stimuli. Infants in fact have an amazing capacity to respond to a vast array of antigens, including vaccines. However, the infant's immune system is not capable of responding with adult efficiency. Maturation of the immune response occurs in an orderly fashion from approximately 16 weeks gestation and slowly gains momentum in the first year of life. This, along with the presence of maternal antibodies provided passively, may account for the need for multiple injections to complete the primary series of several vaccines [49,50]. Data suggest that, theoretically, the intact immune system could respond to  $10^9$ – $10^{11}$  different antigens [51]. Today's vaccines contain far fewer antigens than the immune system is designed to respond to. Medical advances in vaccinology have contributed to the decline in the number of antigens in modern vaccines. For example, the whole-cell pertussis vaccine contained approximately 3000 proteins compared with the two to five proteins found in the current acellular pertussis vaccines [51].

Thus, parents and caregivers should be reassured based on these data that vaccines will not overwhelm or weaken the infant immune system.

### Expert commentary

Parents today are overwhelmed with the vaccine controversies and the decisions they face regarding their children's health and well being. They are inundated with media reports of profit-driven pharmaceutical companies that cannot be trusted, internet blogs hosted by antivaccine activists and internet misinformation. They are in need of trusted expert advice. Although some parents distrust the experts, a majority identify their healthcare provider as the person with the most influence over their decision to vaccinate their child [52]. Healthcare providers are positioned to correct misconceptions and alleviate anxieties; but first they must recognize and acknowledge parents' fears. They must educate themselves on the latest scientific research that addresses these issues. They also need to dedicate time to discuss concerns regarding vaccine safety with worried parents. To achieve these two things, training programs for healthcare providers need to include coursework on quality communication, and third-party payors need

to reimburse immunization providers for education related to vaccination [3]. Providers also need to familiarize themselves with programs such as the Vaccine Safety Datalink, a collaborative effort between CDC's Immunization Safety Office and eight managed-care organizations (MCOs) [107]. The Vaccine Safety Datalink project was established in 1990 to monitor immunization safety and address the gaps in scientific knowledge regarding rare and serious events following immunization. Ultimately, it is imperative for all stakeholders to recognize that the overall health and well-being of US children is dependent on a robust vaccination program in which parents and providers are partners, not adversaries.

### Five-year view

Although well-designed, statistically valid, scientific research studies have refuted many of the claimed adverse effects associated with vaccines, a portion of the public remains concerned regarding the safety of these life-saving products. Unfortunately, these controversial claims are not likely to disappear in the future. As medical science progresses and new vaccines are introduced, it is only to be expected that more controversies surrounding their safety will develop. Particular interest is likely to be focused on vaccine additives and adjuvants such as aluminum and squalene. While the vaccine–MMR/thimerosal debate appears to be abating, new concerns have arisen regarding the possible association between vaccine adjuvants/multiple vaccines given simultaneously and the development of autism spectrum disorders. Fears regarding vaccines and various disorders without clear-cut etiologies such as Alzheimer's disease, other forms of dementia, neuropsychiatric illnesses, learning disabilities, rheumatoid diseases, macrophagic myofasciitis and Gulf War Syndrome [108–110] are also gaining attention. It is, therefore, imperative that healthcare providers be prepared to respond to patient and parent anxieties related to these emerging concerns.

### Key issues

- The schedule of vaccines currently recommended for infants, children and adolescents has expanded in the USA within the societal context of increased concern with environmental risks.
- Incidence of vaccine-preventable diseases has declined dramatically in the last two decades.
- Fear of disease has been replaced by fear of vaccines.
- High vaccination coverage rates at the community level are necessary to protect individuals who cannot receive the vaccine(s) or those who are too young to be fully protected.
- Public health departments, government agencies and medical professional organizations have responded to parental concerns regarding immunizations via educational campaigns and by providing instructive materials in print and online.
- Healthcare providers need to be fully aware of the current scientific evidence and available educational material for lay people that support the currently recommended vaccine schedule.
- A trusting relationship must be forged between the consumer and healthcare provider that facilitates open communication.

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