The power of 'box a'

'...if parents are to make the best choices for their children's health, facts about vaccines and the diseases they prevent must be presented in a manner that is at once informative and compelling.'

Paul A Offit, MD
Division of Infectious Disease, University of Pennsylvania School of Medicine, USA
Tel.: +1
Fax:
E-mail:

"Popular induction depends upon the emotional interest of the instances, not on their number," Bertrand Russell (1927).

On April 6 2000, the US Committee on Government Reform convened to discuss the growing rates of autism in the USA. The chairman of the committee opened the session with the following statement: "I can't believe that that's just a coincidence – that the shot is given and that within a very short time, he got nine shots in 1 day, the MMR (measles–mumps–rubella vaccine) and the DTaP (diphtheria–tetanus–acellular pertussis vaccine) and within just a matter of a few days instead of being the normal child that we played with and talked and everything else, he was running around and banging his head against the wall flailing his arms," [1]. The congressman was convinced that the MMR vaccine had caused his grandson to be autistic. Data from a study in England were presented at the same meeting showing that when autism followed receipt of MMR vaccine, it occurred at a rate that would be predicted by chance alone [1]. But the congressman remained unconvinced. He knew what he had seen.

On November 7 2002, *The New England Journal of Medicine* published a paper titled 'A population-based study of measles, mumps and rubella vaccination and autism,' [2]. The authors performed a retrospective, cohort study of all children born in Denmark between 1991 and 1998. The study included 537,303 children representing 2,129,864 person-years. The results were clear. The relative risk of autism in the group of vaccinated children as compared with unvaccinated children was 0.92 (95% confidence interval, 0.68–1.24). Further, there was no association between the age at the time of vaccination, the time since vaccination, or the date of vaccination and the development of autism.

Determination of whether the MMR vaccine causes autism requires four separate pieces of data (TABLE 1). These data allow one to determine the risk of autism in a vaccinated group and compare it with that in an unvaccinated group.

'The study using data from 'boxes a, b, c and d', was able to determine that the relationship between the MMR vaccine and autism was coincidental, not causal.'

The observation by the congressman included information from 'box a' and could not determine whether vaccines had caused autism in his grandson. The study reported in *The New England Journal of Medicine*, using data from 'boxes a, b, c and d', was able to determine that the relationship between the MMR vaccine and autism was coincidental, not causal.

It is difficult to conceive of a larger, better-constructed, more definitive study than that performed in Denmark. Furthermore, the Denmark study confirmed the findings of other studies performed in England, Finland and the USA [3–9]. However, many parents of autistic children remained unconvinced and some parents of young children are still frightened that MMR vaccine might cause autism. Why?

The answer to this question may lie in the work of Daniel Kahnemann who won the Nobel Prize in Economics in 2002. Over the past several decades Kahnemann and others studied the manner in which people make judgements under uncertainty.

 ISSN 1476-0584

Kahnemann found that people do not follow the laws of probability theory when judging the likelihood of uncertain events. Rather, they rely on a limited number of intuitive or speculative rules (heuristics) that sometimes yield reasonable judgements but often lead to severe and systematic errors. Furthermore, even the most 'rational' among us are subject to these biases.

For example, suppose you want to buy a midsize car [10]. As a prudent and sensible buyer, you read *Consumer Reports* and learn that 1000 owners and experts of each of ten midsized cars were interviewed and that theVolvo was recommended because it was mechanically superior and had an excellent repair record. Excited about your choice, you attend a party that evening and tell a friend that you have decided to buy a Volvo. Your friend reacts in disbelief: "A Volvo! You've got to be kidding. My brother-in-law had a Volvo. First, the fancy fuel injection thing went out. 500 bucks! Next he started having trouble with the transmission. He had to replace it. Finally, he sold it 3 years later for junk." Your enthusiasm for the Volvo drops precipitously. But the logical status of this information is that now, instead of having 1000 available data points about the Volvo, you have 1001. The mean frequency of repair for the Volvo would change marginally with the addition of your friend's new information and would not affect the conclusions of the report. But who among us would process that encounter in such a manner?

Kahnemann and others found that we are influenced to a greater extent by information that is emotional, direct and personal than by statistical arguments. The congressman and many parents saw their children receive vaccines and watched over the next few weeks as they developed their first symptoms of autism. Although vaccines do not cause autism, the power of their direct experiences was far more compelling than any statistical argument.

The power of personal and emotional evidence works at many levels. For example, several years ago an advisory committee to the Food and Drug Administration (FDA) heard testimony from people who claimed to suffer from chronic arthritis following receipt of the Lyme disease vaccine. The relationship between the Lyme disease vaccine and chronic arthritis had been tested previously in two excellent, prospective, placebo-controlled studies that included about 21,000 subjects followed for 2 years [11,12]. No significant differences in the type or frequency of joint symptoms in vaccine and placebo recipients were observed. However, the testimony to the FDA advisory committee was direct, heart-felt and compelling and the committee, recognizing the importance of 'maintaining the public's trust' in immunizations, recommended that the Lyme disease vaccine be tested further. Many people who read or watched news reports about this hearing were frightened by the possibility of getting arthritis from the Lyme disease vaccine. Sales of the Lyme disease vaccine dropped and the vaccine was eventually discontinued by the manufacturer.

Unfortunately, people with Lyme disease did not also testify in front of the committee. This wasn't because patients permanently harmed by Lyme disease were hard to find. Lyme disease affects about 15,000 people every year in the USA. About 60% of untreated adults with Lyme disease develop acute arthritis and about 10% of these patients develop chronic arthritis that is resistant to treatment with antibiotics [13].

The notion of 'maintaining the public's trust' bears a closer look. How do people learn about vaccines and by extension, come to trust vaccine immunization programs? For the most part, people learn about vaccines from newspapers, magazines, radio, television and the Internet. The news media are, at best, an imperfect window to the truth about vaccines. An example of the media's influence on the choice to be vaccinated was seen in 1974 when Kulenkampff and coworkers published a series of cases of children with mental retardation and epilepsy following receipt of the whole-cell pertussis vaccine [14]. This report received a great deal of attention from the media even though it only provided data from 'box a'. Children with seizure disorders, clad in protective headgear, were placed in front of the camera. Mothers told stories of children who were perfectly well until they were vaccinated. The rate of pertussis immunization in England dropped from 81 to 31% and resulted in more than 100,000 cases and 36 deaths from pertussis [15]. Media coverage of the Kulenkampff report also caused decreased immunization rates and increased pertussis deaths in Japan, Sweden and Wales [15]. Subsequent well-controlled studies found that whole-cell pertussis vaccine was not a cause of chronic neurologic disease [16–22]. However, studies that failed to show an association between pertussis vaccine and permanent brain damage, as well as stories of children hospitalized and killed every year by pertussis infection did not receive much media attention and were less available to the public. In October 2002, Daniel Kahnemann stated: "People take risks because they don't know the risks they are taking."

'People take risks because they don't know the risks they are taking.'

The work of Daniel Kahnemann and others suggests that if parents are to make the best choices for their children's health, facts about vaccines and the diseases they prevent must be presented in a manner that is at once informative and compelling. Otherwise, people seeking to be 'fully informed' about vaccines will be unlikely to receive all the information they need and will, as a result, make choices that are not in the best interest of their children.

Table 1.

	Disease	No disease
Vaccine	a	b
No vaccine	c	d

Paul A Offit MD is Chief of the Division of Infectious Diseases and Director of the Vaccine Education Center at the Children's Hospital of Philadelphia. He is also a Professor of Pediatrics at the University of Pennsylvania School of Medicine and a member of the Advisory Committee on Immunization Practices.

References

1 Autism: present challenges, future needs – why the increased rates? Committee on Government Reform, House of Representatives, 106th Congress, April 6th, (2000).

2 Madsen KM, Hvid A, Vestergaard M *et al.* A population-based study of measles, mumps and rubella vaccination and autism. *N. Engl. J. Med.* 347, 1477–1482 (2002).

3 Taylor B, Miller E, Farrington P *et al.* Autism and measles, mumps and rubella vaccine: no epidemiologic evidence for a causal association. *Lancet* 353, 2026–2029 (1999).

4 Farrington CP, Miller E, Taylor B. MMR and autism: further evidence against a causal association. *Vaccine* 19, 3632–3635 (2001).

5 Dales L, Hammer SJ, Smith NJ. Time trends in autism and in MMR immunization coverage in California. *JAMA* 285, 1183–1185 (2001).

6 Kaye JA, Melero-Montes M, Jick H. Mumps, measles and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis. *Br. Med. J.* 322, 460–463 (2001).

7 Taylor B, Miller E, Lingam *et al.* Measles, mumps and rubella vaccination and bowel problems or developmental regression in children with autism: population study. *Br. Med. J.* 324, 393–396 (2002).

8 Fombonne E, Chakrabarti S. No evidence for a new variant of measles–mumps–rubella-induced autism. *Pediatrics* 108, e58 (2001).

9 Mäkelä A, Nuorti P, Peltola H. Neurologic disorders after measles–mumps–rubella vaccination. *Pediatrics* 110, 957–963 (2002).

10 Nisbett RE, Borgida E, Crandall R, Reed H. Popular induction: information is not necessarily informative. In: *Judgment under uncertainty: heuristics and biases*. Kahnemann D, Slovic P, Tversky A (Eds). Cambridge University Press, Cambridge, UK (1982).

11 Steere AC, Sikand VK, Meurice F *et al.* Vaccination against Lyme disease with recombinant *Borrelia burgdorferi* outer-surface lipoprotein A with adjuvant. *N. Engl. J. Med.* 339, 209–215 (1998).

12 Sigal LH, Zahradnik JM, Lavin P *et al.* A vaccine consisting of recombinant *Borrelia burgdorferi* outer surface protein A to prevent Lyme disease. *N. Engl. J. Med.* 339, 216–222 (1998).

13 Steere AC, Gross D, Meyer AL, Huber BT. Autoimmune mechanisms in antibiotic treatment-resistant Lyme arthritis. *J. Autoimmunity* 16, 263–268 (2001).

14 Kulenkampff M, Schwartzman JS, Wilson J. Neurological complications of pertussis inoculation. *Arch. Dis. Child.* 49, 46–49 (1974).

15 Gangarosa EJ, Galazka AM, Wolfe CR *et al.* Impact of antivaccine movements on pertussis control: the untold story. *Lancet* 351, 356–361 (1998).

16 Cody CL, Baraff LJ, Cherry JD *et al.* Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. *Pediatrics* 68, 650–660 (1981).

17 Pollock TM, Morris J. A 7-year survey of disorders attributed to vaccination in Northwest Thames Region. *Lancet* 1, 753–757 (1983).

18 Walker AM, Jick H, Perera DR *et al.* Neurologic events following diphtheria-tetanus–pertussis immunization. *Pediatrics* 81, 345–349 (1988).

19 Griffin MR, Ray WA, Schaffner W *et al.* Risk of seizures and encephalopathy after immunization with diphtheria–tetanus–pertussis vaccine. *JAMA* 263, 1641–1645 (1990).

20 Shields WD, Nielsen C, Buch D *et al.* Relationship of pertussis immunization to the onset of neurologic disorders. *J. Pediatr.* 113, 801–805 (1988).

21 Gale JL, Thapa PB, Wassilak SGF *et al.* Risk of serious acute neurological illness after immunization with diphtheria–tetanus–pertussis vaccine: a population-based case-control study. *JAMA* 271, 37–41 (1994).

22 Golden GS. Pertussis vaccine and injury to the brain. *J. Pediatr.* 116, 854–861 (1990).