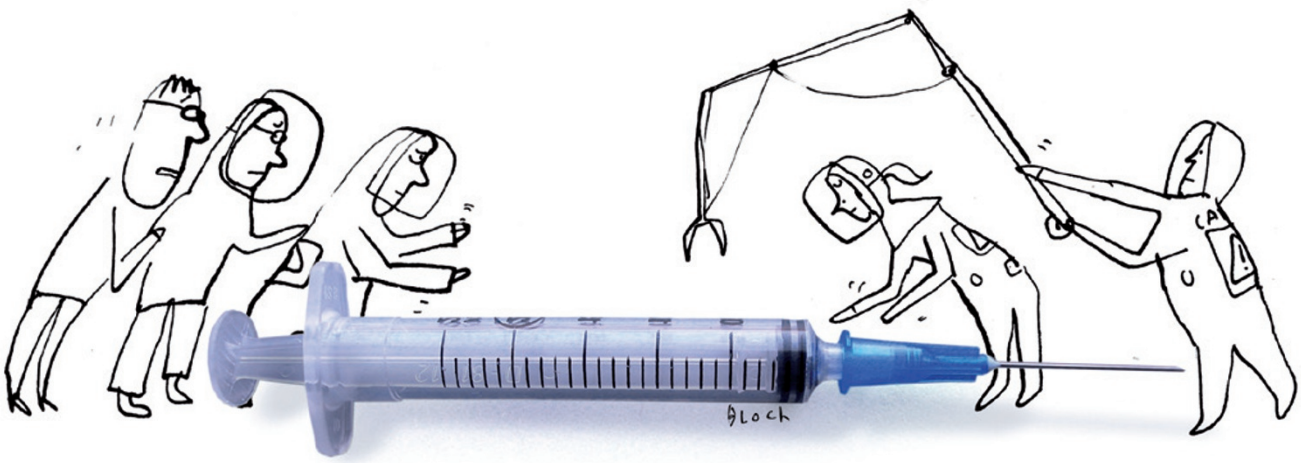

THE REAL ISSUES IN VACCINE SAFETY

Hysteria about false vaccine risks often overshadows the challenges of detecting the real ones.

BY ROBERTA KWOK

SERGE BLOCH

John Salamone is not a vaccine sceptic. He has never been persuaded by spurious claims that vaccines are toxic to children and responsible for autism or a host of other ailments. But tragically, Salamone found out first-hand that vaccines do have real, rare side effects when he saw his infant son, David, become weak and unable to crawl shortly after receiving the oral polio vaccine in 1990. After about two years of physical therapy and doctors' visits, Salamone learned that owing to a weakened immune system, David had contracted polio from the vaccine. "We basically gave him polio that day," says Salamone, who has retired from a position as a non-profit executive, and lives in Mount Holly, Virginia.

That was a known risk of the vaccination, which causes roughly one case of the disease per 2.4 million doses, often in people with an immune deficiency. A safer, inactivated, polio vaccine was available at the time, but the oral vaccine was cheaper, easier to administer and thought to be more effective at controlling outbreaks. But by the 1980s, polio had been all but eliminated in the United States; all cases originating in the country came from the vaccine. Salamone and other parents successfully campaigned for the United States to shift to the safer version in the late 1990s.

Vaccines face a tougher safety standard than most pharmaceutical products because they are given to healthy people, often children. What they stave off is unseen, and many of the diseases are now rare, with their effects forgotten. So only the risks of vaccines, low as they may be, loom in the public imagination. A backlash against vaccination, spurred by the likes of Andrew Wakefield — a UK surgeon who was struck off the medical register after making unfounded claims about the safety of the measles, mumps and rubella (MMR) vaccine — and a litany of celebrities and activists, has sometimes overshadowed scientific work to uncover real vaccine side effects. Many false links have been dispelled, including theories that the MMR vaccine and the vaccine preservative thimerosal cause autism[1]. But vaccines do carry risks, ranging from rashes or tenderness at the site of injection

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to fever-associated seizures called febrile convulsions and dangerous infections in those with compromised immune systems.

Serious problems are rare, so it is hard to prove that a vaccine causes them. Studies to confirm or debunk vaccine-associated risks can take a long time and, in the meantime, public-health officials must make difficult decisions on what to do and how to communicate with the public. Still, such work is necessary to maintain public trust, says Neal Halsey, a paediatrician at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. "If we don't do the research, there will be more people who don't believe in vaccines," he says.

VICTIMS OF THEIR OWN SUCCESS

Technological advances have made modern vaccines purer and safer than their historical counterparts. Most developed countries have switched to the inactivated polio vaccine and stopped using whole-cell pertussis (whooping cough) vaccines, which are made from killed bacteria and cause relatively high rates of arm swelling, febrile convulsions and periods of limpness or unresponsiveness.

Improved safety means that researchers are sometimes searching for vanishingly small risks. Although vaccines must undergo stringent safety tests before distribution, the trials typically don't enrol enough people to catch risks on the order of one case per 10,000–100,000 people (see 'Calculating risks'). The only way to find such side effects is to deploy the vaccine in the population and watch.

Officials have become increasingly vigilant. As worries about pandemic H1N1 influenza spread in 2009–10, several companies worked to prepare as many vaccine doses as possible. Meanwhile, health officials launched an unprecedented surveillance effort to monitor the vaccines' safety. US scientists and officials studied data from voluntary adverse-event reports, managed-care organizations, health-insurance companies, immunization registries, a network of neurologists and various health-care systems. European scientists linked data from 15 countries. And Chinese officials instructed health-care workers to report potential side effects within 24 hours; for the most serious events, they had two hours.

Scientists were specifically looking for Guillain-Barré syndrome, a paralytic disorder that is often treatable but can cause long-term disability or death. A 1976 swine-flu vaccine distributed in the United States was associated with between five and nine cases per one million vaccine recipients. Studies of subsequent flu vaccines have not shown a consistent link, but officials have been on the lookout for it. During the 2009–10 pandemic, something stranger turned up: some 60 cases of narcolepsy emerged among 4- to 19-year-olds in Finland. Most had received the H1N1 vaccine Pandemrix, made by GlaxoSmithKline in Brentford, UK. Another narcolepsy cluster showed up in Sweden. Scientists have yet to confirm whether the vaccine caused the rise in incidence.

Surveillance efforts have paid off for a variety of vaccines. A rotavirus vaccine was suspended in the United States in 1999 after public-health officials received 15 reports of intussusception, an infolding of the bowel, in vaccinated infants. The mechanism is uncertain, but the live-virus vaccine might cause swelling of bowel lymph nodes and increase contraction, leading to infolding. The vaccine is estimated to have caused about one case of intussusception per 10,000 recipients.

In 2007, Nicola Klein, co-director of the Kaiser Permanente Vaccine Study Center in Oakland, California, and her colleagues found that children aged between 12 and 23 months who had been immunized with a combination vaccine for measles, mumps, rubella and varicella (MMRV) had more febrile convulsions 7–10 days after vaccination than those receiving separate MMR and varicella vaccines. The finding prompted a US immunization advisory committee to withdraw its preference for the MMRV vaccine. A subsequent study[2] suggested that the combined vaccine resulted in one more febrile convulsion per 2,300 doses than the MMR and varicella vaccines given separately.

Efforts are under way to improve surveillance in low- and middle-income countries, some of which are gaining increased access to vaccines through an international programme called the GAVI Alliance (formerly the Global Alliance for Vaccines and Immunisation), based in Geneva, Switzerland. These areas could soon see new vaccines for diseases such as dengue and cholera. In 2006, the Pan American Health Organization, based in Washington DC, started a surveillance network among five Latin American countries. The World Health Organization (WHO) in Geneva is working with 12 countries, including Iran, Tunisia, Vietnam and India, to develop methods and tools for vaccine-safety monitoring, and half are already reporting to a global database, says Patrick Zuber, the WHO's group leader of global vaccine safety.

"If we don't do the research, there will be more people who don't believe in vaccines."

Researchers have also started conducting larger clinical trials. Pre-licensure trials for two new rotavirus vaccines, RotaTeq by Merck, based in Whitehouse Station, New Jersey, and Rotarix by GlaxoSmithKline, each enrolled more than 60,000 infants to evaluate safety[3,4]. But even these large trials cannot rule out rare events, so efforts would be better spent on well planned surveillance after licensing, argues Rino Rappuoli, global head of vaccines research at Novartis Vaccines and Diagnostics in Siena, Italy. With big pre-licensure trials, "you may feel better as a regulator, but you're not answering the scientific question", he says. Preliminary post-licensure studies in Mexico have detected a possible slight increase in intussusception risk after the first dose of Rotarix, and a similar pattern has emerged in Australia for both vaccines[5]. However, some researchers speculate that rotavirus vaccination may also protect against intussusception later.

DELAYED RESULTS, LOST TRUST

Even if a possible side effect is found, long periods of uncertainty can follow. To amass convincing evidence, scientists sometimes need to do controlled studies in multiple countries, covering hundreds of thousands or even millions of people. Scientists have not yet conclusively determined whether Pandemrix contributed to the European cluster of narcolepsy cases.

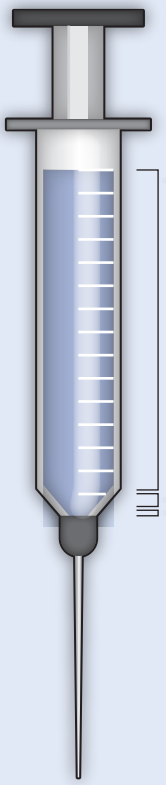
Scientists in the Vaccine Adverse Event Surveillance & Communication Consortium, a European research network, are examining narcolepsy diagnosis rates and comparing cases with matched controls across several European Union countries, some of which used different H1N1 vaccines. Data suggest that diagnosis rates rose slightly in several countries starting in 2008, before H1N1 vaccines were being distributed, but not enough to explain the episode in Finland, says principal investigator Miriam Sturkenboom, a pharmacoepidemiologist at Erasmus University Medical Center Rotterdam in the Netherlands. GlaxoSmithKline is also funding a study in Canada, where an H1N1 vaccine nearly identical to Pandemrix was used, but no rise in narcolepsy has been reported.

The increase in narcolepsy diagnoses might be explained by heightened disease awareness or infections with the H1N1 virus itself, says Jan Bonhoeffer, a paediatric-infectious-disease specialist at the University Children's Hospital Basel in Switzerland, and chief executive of the Brighton Collaboration, an international vaccine-safety research network. He says that the narcolepsy story fits a familiar pattern, similar to that seen with MMR and autism: people are eager to find an underlying cause for a serious, chronic, poorly understood disease.

Researchers need to investigate possible safety issues quickly, Bonhoeffer adds. Otherwise, by the time scientists conclude that a concern is unfounded, "no one cares, and it takes years to build up the trust again", he says. "So often, the widely communicated concern has caused more harm than it intended to prevent." A global vaccine-safety network would give scientists a faster way to test hypotheses with sufficient sample sizes, he says. In that spirit, the WHO is coordinating a global study on pandemic H1N1 flu vaccines and Guillain-Barré syndrome.

CALCULATING RISKS

Some vaccines have risks that are common but mild. A few have more serious risks, but these are very rare.



1 COMMON: MORE THAN 1 IN 100 DOSES
Redness, swelling or soreness at the site of an injection are common for many vaccines, as are mild fevers. Nausea, vomiting and diarrhoea have been reported for a few.

2 LESS COMMON: 1 IN 100 TO 1 IN 100,000
High fevers can occur in this range, as can fever-induced convulsions from vaccines such as that for measles, mumps and rubella (1 in 3,000 doses).

3 RARE: 1 IN 100,000 TO 1 IN 1 MILLION
Preliminary data suggest that current rotavirus vaccines are associated with intussusception, an infolding of the bowel, in about 1 in 100,000 first doses, but the overall risk is unclear. Severe allergic reactions to some vaccines are generally less common than this, in the order of 1 in 1 million.

4 INCONCLUSIVE: NOT ENOUGH DATA
Guillain-Barré syndrome, a paralytic disorder, has been associated with some seasonal influenza vaccines, but a causal link has not been firmly established. Serious disorders have been reported after other vaccinations, but many are so rare that determining causality is difficult.

Source: US Centers for Disease Control and Prevention. For more information, see go.nature.com/s7rfio

But strictly controlled randomized trials — the highest standard of evidence for determining causality — are often not possible because of the large number of participants needed. And randomized trials in one location will not prevent some researchers questioning whether the results apply in others, says Alfred Berg, a clinical epidemiologist at the University of Washington in Seattle.

Even if surveillance efforts became faster and more thorough, public-health officials still need to make quick decisions with incomplete data. Authorities often err on the side of caution, but warnings can make the public wary. In March, for example, Japanese officials suspended a vaccine for pneumococcal illnesses and one for *Haemophilus influenzae* type b when four children died shortly after immunization. Officials later concluded that there was no direct evidence of a link, but the episode still caused a scare, says Pier Luigi Lopalco, head of the vaccine-preventable-diseases programme at the European Centre for Disease Prevention and Control in Solna, Sweden. Suspending a vaccine tends to get more media attention than resuming one, he says, so people remember only the threat.

US government officials have drawn criticism for pushing for removal of thimerosal from vaccines, despite a lack of evidence that it poses a risk. "People said, why are you removing this if it's not a problem?" says Ken Bromberg, a paediatrician at the Brooklyn Hospital Center in New York. "It must really be a problem even though you say it's not." But inaction would have caused a loss of credibility, says Halsey. "That is not something I think the public would have accepted."

FINDING THOSE IN DANGER

Researchers have long known that some individuals are more susceptible to vaccine risks than others. Immunocompromised individuals have generally been discouraged from receiving live-virus vaccines. But other possible vulnerabilities are less clear. Some speculate that children with metabolic disorders might be prone to vaccine side effects, but two studies published in April suggest otherwise. Klein and her colleagues reported[6] that children with inherited metabolic disorders do not show an increase in emergency-department visits or hospitalizations in the 30 days after being immunized. The other study found that children with one type of metabolic disorder — urea cycle disorders — did not have more serious metabolic problems than usual within 21 days of vaccination[7].

Some researchers hope that doctors will eventually be able to screen people for genetic predispositions to vaccine side effects. Gregory Poland, a vaccinologist at the Mayo Clinic in Rochester, Minnesota, says that once predispositions have been identified, genetic screening would at least make the risks and benefits explicit. Scientists have begun studying predispositions to side effects from smallpox vaccination: Kathryn Edwards, a vaccinologist at Vanderbilt University in Nashville, Tennessee, and her colleagues have reported[8] two genes that might be associated with reactions such as rashes, and Poland's team is searching for genetic risk factors for myopericarditis — inflammation of the heart muscle and surrounding tissue.

Even if immunization does prove risky for certain children, withholding the vaccine could pose a greater threat. Vaccine-preventable diseases can be particularly severe or even fatal for patients with metabolic disorders, says Marshall Summar, chief of the division of genetics and metabolism at the Children's National Medical Center in Washington DC.

Edwards and her colleagues have been studying how children with mitochondrial disorders, a group of metabolic disorders, respond to vaccines and natural infections. If vaccines present a risk, doctors could take steps to counteract possible effects, for example by ensuring that the child is well nourished after immunization, says Edwards.

Safer vaccines and manufacturing processes are also in the works. A Novartis plant in Holly Springs, North Carolina, will produce influenza vaccine doses in cell culture, rather than the industry-standard chicken eggs. This process will improve reliability and reduce allergic reactions to egg proteins, says Rappuoli. The plant will be ready to make pandemic-flu vaccine this year if needed, he says.

Researchers are also developing replacements for vaccines that can be risky for vulnerable groups. These include current smallpox vaccines that cannot safely be given to immunocompromised people; the tuberculosis vaccine, which is not recommended for HIV-positive infants; and the yellow-fever vaccine, which puts elderly people at particular risk of a yellow-fever-like illness. The challenge will be to make safer vaccines just as effective: James Cherry, a paediatric-infectious-disease specialist at the University of California, Los Angeles, speculates that an outbreak of whooping cough in California in 2010 might have occurred partly because the safer acellular pertussis vaccines now in common use in developed countries tend to be less effective than the best whole-cell vaccines.

Researchers are quick to emphasize that the benefits of vaccines still greatly outweigh the risks. But as diseases recede from the public's memory, the population's tolerance for side effects will drop even further. "If you don't know the diseases and you haven't seen them, then you really aren't willing to accept any risk," says Edwards. Despite scientists' best efforts, eliminating risk is impossible. Vaccines are biological products with biological effects, says Juhani Eskola, deputy director general of Finland's National Institute for Health and Welfare in Helsinki. "We can never make them 100% safe." ■ SEE EDITORIAL P.420

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