

Hairy situation. Sausage-shaped *B. pertussis* lodges into cilia in the respiratory tract.

PUBLIC HEALTH

The Pertussis Paradox

The introduction of a safer vaccine has inadvertently led to a frightening spike in the deadly disease commonly known as whooping cough

When California reported more than 9000 cases of whooping cough in 2010, public health alarm bells rang far and wide. A childhood disease vanquished decades ago by a vaccine was resurgent. Major outbreaks of the disease, properly known as pertussis, soon surfaced in several other states, including Minnesota, Washington, and North Carolina. Something was wrong, very wrong.

Kathryn Edwards, a vaccinologist at Vanderbilt University in Nashville, and many of her colleagues realized that the safer pertussis vaccines they helped usher in in the 1990s had come at a steep cost: They do not create immune protection as long-lasting as the vaccine they replaced. “It’s humbling and kind of depressing,” says Edwards, whose own daughter had suffered serious side effects from the old-fashioned vaccine. “I spent so much of my time and my life working on this. ... We were so excited that we had the answer, and now it isn’t really the answer.”

The old shot had cut the number of annual cases of whooping cough in the United States to a low of just over a thousand in 1976. But as the Centers for Disease Control and Prevention (CDC) in Atlanta prepares its final tally of U.S. cases in 2012, the number is closing in on 50,000, the highest since 1955, with at least 18 deaths and hundreds of hospitalized infants. Once-rare outbreaks

are also common among vaccinated children across Europe, Australia, and Japan.

The old whooping cough vaccine, known as DTP, contained killed whole pertussis bacteria—*Bordetella pertussis*—as well as detoxified diphtheria and tetanus particles to protect against those diseases. In the newer vaccines, the pertussis component includes only purified pieces of that organism. Intensive studies are under way to try to understand why the safer “acellular” vaccines, dubbed DTaP, don’t protect for as long. Already, the studies have uncovered features of both the bacteria and the immune response to it that may be to blame. Other efforts are focused on salvaging the long-term efficacy of the old vaccine without restoring its dangers. But vaccine researchers know that solving the problem will not be easy.

Less is less

The original DTP vaccine, introduced in the 1940s, has been administered to children billions of times. But it frequently caused high fevers and seizures, which rekindled an anti-vaccine movement that had been quiet for half a century. In the 1980s, parents who blamed DTP for harming their children successfully sued manufacturers, leading many vaccine-makers to leave the market, although studies showed that permanent brain damage suppos-

edly linked to the product was extremely rare and perhaps never directly caused by the vaccine. “People used to get up at scientific meetings and shout, ‘You’re killing our babies!’” recalls Alison Weiss, a microbiologist at the University of Cincinnati in Ohio.

The actual side effects were soon linked to a powerful immune stimulant called endotoxin, contained in the cell membrane of the pertussis bacteria. This substance was removed from all the DTaP vaccines, which replaced DTP in the United States and other wealthier nations in the late 1990s.

The new vaccines seemed just as effective, without the side effects. “Our nurses did home visits and administered randomized shots. They could tell with 100% certainty who got whole-cell and who got DTaP,” Edwards says. “It was pretty remarkable—they were much less reactive. And they made antibody responses that were comparable or even higher than the whole-cell vaccine.” Today, five doses are given to kids between the ages of 2 months and 5 years, and a booster shot (with a slightly reduced dose) is administered around age 12.

The mounting bad news about pertussis outbreaks has caused great consternation among health officials, who are acutely sensitive to public distrust of vaccines—in no small part because of the old DTP’s problems.

Bruce Gellin, director of the National Vaccine Program Office at the U.S. Department of Health and Human Services, emphasizes the irony. “The DTP shot was the origin of the modern antivaccine movement, which led to a whole cascade of events, including a new vaccine that was less reactogenic—but as it turns out, at a cost,” Gellin says. Adds epidemiologist Thomas Clark of CDC’s Meningitis and Vaccine Preventable Diseases Branch: “We have acellular vaccines because people doubted the safety of whole-cell vaccines. We don’t want them to doubt the effectiveness of our pertussis vaccines.”

It took several years after DTaP came to market before its limitations became clear. The reason: The immunity that it generates wanes slowly, as Clark’s group at CDC showed in *The Journal of the American Medical Association* last November. They found that the acellular vaccines were solidly effective in the first year. But protection steadily declined over 5 years—as other studies have also shown. They revealed that children who received even a single dose of whole-cell vaccine were more than twice as likely to remain disease-free during an outbreak as those who

received only acellular vaccines when they were infants. “These studies say the vaccine is the problem,” Weiss says.

Untangling why has been difficult, because researchers don’t fully understand how pertussis vaccines work. Even with the whole-cell pertussis shot, the bacterium often infected adults, blood sera studies have shown, but they usually did not get sick or did not realize that their coughs were due to pertussis. “It’s amazing how little we understand about pertussis and our immune response to it,” says microbiologist Tod Merkel, who heads the respiratory and special pathogens lab at the Food and Drug Administration (FDA) in Bethesda, Maryland.

The whole-cell shot contained more than a dozen different antigens, the particles that stimulate the creation of antibodies. Acellular vaccines in use around the world today contain between one and four of the antigens, including an important substance called pertussis toxin. The two vaccines now used in the United States also contain the pertussis surface proteins filamentous hemagglutinin antigen (FHA) and pertactin.

The acellular vaccines generate high levels of antibodies to these proteins—but not all of those antibodies seem to be crucial for immunity to the disease. In trials held in Sweden and Germany, for example, whole-cell vaccines proved effective at preventing disease even while producing lower antibody levels to pertussis toxin and FHA.

Pertussis “yanks the chains of the immune system,” says the University of Cincinnati’s Weiss. “It directs the immune system in the wrong way.” FHA, for example, stimulates production of interleukin-10, a chemical that stimulates antibody production but suppresses a healthy response to bacterial infections.

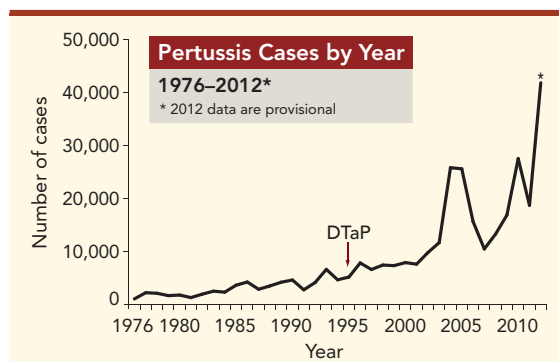
Endotoxin, in contrast, appears to be key to an effective vaccine. Although endotoxin triggers the high fevers and other adverse reactions caused by the whole-cell shot, it also sparks a hearty “innate” immune response. Unlike the adaptive immune system that produces antibodies against specific invaders, the more primitive innate immune system mounts attacks against, say, all Gram-negative bacteria like pertussis. So this nastier part of the bug may account for much of the old DTP vaccine’s longer-lasting effects.

Some studies suggest that *B. pertussis* is exacerbating a bad situation by mutating around DTaP, foiling the vaccine even during the period it stimulates a robust response. New pertussis strains recently found in the United States, France, and Australia, for example, lack pertactin, a key vaccine component. In a particularly concerning finding reported by

Clark’s CDC group in the 7 February issue of *The New England Journal of Medicine*, it found pertactin-negative strains in 11 of 12 infants hospitalized during a recent outbreak in Philadelphia, Pennsylvania. “You don’t find pertactinless isolates in our historic collection,” Clark notes.

DTaP 2.0

For now, public health officials are trying to deploy the existing vaccine more effectively. Because pertussis presents the most profound risk to unimmunized infants, CDC’s Advisory Committee on Immunization Practices (ACIP) last year recommended that pregnant women receive a booster version of DTaP. The hope is that the booster will help protect the babies for at least their first year by preventing infection in the mothers. Maternal antibodies may also pass through the placenta and breast milk and directly protect the baby, too. Unpublished British data show that an intensive maternal vaccination program begun there last October has protected infants well.



Reversal of fortune. U.S. pertussis cases have steadily climbed in the DTaP era.

But the recent outbreaks show that older children need longer-lasting immunity. A proposal to give adolescents a second booster—for a total of seven pertussis shots between birth and age 16—was tabled at the June meeting of ACIP because of a negative cost/benefit assessment. The most attractive solution is clearly an improved DTaP.

“We have to go back to research on pertussis, which has not been a priority in the recent past because we thought the problem was more or less solved,” says Stanley Plotkin, a renowned vaccinologist who consults with Sanofi Pasteur, a major producer of acellular vaccines. Although the number of labs working on pertussis has shrunk, a core of experienced researchers remains, and they have better tools than they did in the 1990s, including a new animal model. Merkel and his colleagues last year showed that the baboon

provides a far more accurate reflection of human immunity to pertussis—and a better testbed for vaccines—than the macaque monkeys in which earlier work was done.

Academic researchers and industry are pursuing a variety of approaches. New ingredients might include adenylate cyclase toxin, a protein that helps *B. pertussis* establish an infection. Novartis, of Basel, Switzerland, is looking into the reintroduction of a vaccine containing a genetically modified pertussis toxin. The vaccine performed well in trials in the 1990s, but was never licensed in the United States or most of Europe. Other researchers are eyeing the immune system stimulator, or adjuvant, in the current vaccine. It uses alum; perhaps a newer adjuvant could breathe life into the cell-free vaccine.

Some researchers want to refurbish the whole-cell vaccine so it packs a punch without causing harm. Microbiologist Camille Loch and his colleagues at INSERM, the French biomedical research agency, have developed a live pertussis vaccine in which three of the pertussis toxins have been genetically deactivated or removed.

Sprayed into the nose, the vaccine protected mice well and produced a healthier immune response than acellular vaccines. It has so far been safely tested in a small number of adults. James Cherry, an infectious disease specialist at the University of California, Los Angeles, with colleagues Rachel Fernandez of the University of British Columbia, Vancouver, and Peter Sebo of the Academy of Sciences of the Czech Republic in Prague, are working on a version

of the killed whole-cell vaccine that contains genetically detoxified endotoxin.

Formulating a new vaccine and getting it licensed for use in infants presents sobering challenges, however. Changing pertussis ingredients could alter the effectiveness of the tetanus and diphtheria components in the DTaP shot—which in some places also contains hepatitis B, inactivated polio, and *Haemophilus influenzae* type b antigens. All told, bringing a new vaccine to market could cost several years and hundreds of millions of dollars. Companies that profit from current pertussis vaccines may balk at the investment.

But until government and industry commit to the effort, CDC’s Clark and other epidemiologists suspect that pertussis cases in countries that use DTaP will continue to climb.

—ARTHUR ALLEN

Arthur Allen is a writer in Washington, D.C.