

ENTRY POINT



Whooping cough resurgence: Two-month-old Saoirse Ball, held by her mother, Erinne, gets the whooping cough vaccine at Massachusetts General Hospital.

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As Immunity Wanes, Whooping Cough Returns

Protection from the most widely used pertussis vaccine is fading far sooner than expected—with few solutions in sight.

BY TERESA L. CHIN

Earlier this year, on what seemed to be an ordinary summer day, Leilah Gilligan's eight-year-old son, Max Paul, started coughing. At first Leilah didn't think much of it—Max has seasonal allergies, and he had been spending a lot of time outside on pollen-filled trails near their home north of San Francisco in Marin

County, California. Naturally, she had flashes of the normal parental concerns—just four years ago, their county had been the epicenter of one of the biggest US whooping cough epidemics in the past sixty years.¹ But Leilah and her husband had fully vaccinated Max before his sixth birthday with the recommended five doses of DTaP—the immunization most commonly used today to

protect against whooping cough. He wasn't due for a booster for another three years.² The family decided to wait.

Days went by. It was the middle of June, just a few weeks into a summer already packed with plans for summer camps, play dates, and a big upcoming family vacation to Disneyland in Southern California. Everyone was looking forward to the trip. They had bought tickets for the entire family: Leilah's husband, Josh; her parents; Max; and their young daughter, Charlotte. But as the departure date neared, Max's cough only seemed to be getting worse, particularly in the evenings. The once energetic second grader grew tired and listless. He gagged on his food at night. He lost sleep. Five days before they were set to leave for Disneyland, Leilah decided it was time to call her son's doctor. He told her to bring Max in right away.

Hours later, Max tested positive for whooping cough.

Leilah was shocked and angry at her son's diagnosis. "My first thought was, 'But he's fully vaccinated,'" she says. "I mean, it's 2014. He had his shots less than three years ago. I had just assumed that [whooping cough] wasn't a possibility."

More than just possible, the Gilligan family's experience is far from unique. Since the 1980s, despite high levels of vaccine coverage in children, outbreaks of whooping cough—also known as pertussis—have occurred every three to five years, with an increase in the peak incidence with each successive outbreak. Several factors may be at play, including genetic changes in *Bordetella pertussis*, the bacterium that causes whooping cough,³ and better diagnostic tools that may have resulted in increased recognition of existing cases.⁴ However, much of the scientific evidence points to waning immunity associated with acellular versions of the vaccine—those derived from only part of a dead *Bordetella pertussis* cell—as opposed to first-generation, whole-cell vaccines that are made using the entire inactivated organism.

The acellular pertussis vaccines, which were adopted widely in the 1990s,

are now used by national vaccine programs in most industrialized countries. Before that time, whole-cell pertussis vaccines were the norm—and still are in many developing countries around the world.

While pertussis vaccines were never expected to confer lifelong immunity, several studies published over the past four years have suggested that people who have been vaccinated with acellular pertussis may lose more than 40 percent of their protection every year, resulting in unanticipated gaps in population-level immunity. This effect is most evident in people, such as Leilah Gilligan's son Max, who received all five childhood immunizations using an acellular pertussis vaccine, rather than the older, whole-cell version. This cohort now spans in age from infants to twenty-somethings; its members are at increased likelihood of developing whooping cough even as adults. As these people go on to have families of their own, pertussis may become an even more serious public health issue, as sick parents may inadvertently infect infants, who are at the greatest risk of dying from the disease.

As cases of whooping cough become more frequent and severe, patients, parents, and providers are asking: Why doesn't a third generation of pertussis vaccines yet exist? And how, if at all, are researchers and policy makers moving toward a solution?

20/20 Hindsight

In order to understand why there is not yet a new pertussis vaccine, one must first understand how the current second-generation, acellular version came to be in the first place.

The original pertussis vaccine was first licensed in the United States in 1914, the same year Babe Ruth made his major league debut and Britain declared war on Germany at the outset of World War I. These first-generation vaccines were developed from killed whole-cell *Bordetella pertussis* organisms. In the late 1940s that whole-cell pertussis vaccine was combined with diphtheria and tetanus toxoids, forming the DTP vaccine.

The DTP vaccine was considered to be, for the most part, highly effective—between 80 and 98 percent. By the 1980s the number of annual cases of whooping

cough in the United States had fallen below 4,000, compared to more than 115,000 cases per year in the pre-vaccine era.⁴ But not all DTP vaccines were created equal. Although several versions of the vaccine were licensed by the United States based on a standard potency, not all of them produced the same level of protection. One version, used exclusively in Canada in the 1980s and 1990s, was subsequently found to be significantly less effective—between 49 and 61 percent.⁵ In Sweden DTP manufacturing process changes were associated with the country's pertussis resurgence in the 1970s.⁵ In 1993 an outbreak of pertussis occurred in the United States among a population that had been widely immunized with the DTP vaccine.⁵

And then there was the issue of reactogenicity—the likelihood that a vaccine will produce common adverse side effects. Whole-cell DTP vaccines were frequently associated with undesirable reactions, such as redness, swelling, and pain at the injection site.⁶ Many infants developed fevers and, less commonly but more seriously, seizures, persistent crying, and whole limb swelling. There were even concerns that DTP might be rarely associated with long-term neurological problems in children (pertussis vaccine encephalopathy), although subsequent studies have found no true association between the vaccine and permanent brain damage.⁷ But in the late 1980s and early 1990s, increasing public concern about the safety of the DTP vaccine led to a push for a second generation of vaccine that would produce fewer adverse reactions.

Developing a new vaccine, however, is easier said than done. It requires a combination of public desire, scientific consensus, and favorable financial incentives, to justify the enormous costs associated with research and development. These factors came to a head in the United States in the 1980s, when lawsuits related to vaccine safety led several manufacturers to withdraw their DTP vaccines. Soon afterwards, the United States enacted the National Childhood Vaccine Injury Act of 1986, which limited some of the liability borne by vaccine makers by setting aside government funds to compensate families for adverse events following immunization. Meanwhile, researchers began

looking into the possibility of developing acellular versions of the pertussis vaccine, which, because it would contain only part of the *Bordetella pertussis* organism, might maintain the effectiveness of their whole-cell predecessors without the associated adverse reactions.

“Development and licensure of a vaccine is of such an undertaking and requires a level of cost that can only be undertaken by private pharma industry,” says Jan T. Poolman, senior vice president of bacterial vaccines at Crucell Holland B.V. Poolman worked on the development of some of the first acellular pertussis vaccines in the 1980s. He says that it usually takes companies ten to fifteen years to develop a vaccine, after which public regulatory authorities typically request proof of efficacy measured over a period of only a few years. “There is a public-private consensus that it is undoable to measure vaccine efficacy for a decade or longer pre-licensure,” Poolman says. Spending more time on these studies “would be impractical... and block the development of vaccines.”

Trials of the new vaccines were conducted throughout the 1980s, and initial results seemed to suggest that their efficacy and safety profile were substantially better than that of at least some older DTP vaccines. These successes were based on only a few years of follow-up and did not look at long-term duration of protection. Still, the results of the trials were promising, and in the early-to-mid-1990s many industrialized countries began moving toward exclusive use of a new acellular vaccine, which, when it is again combined with diphtheria and tetanus vaccines, is known as DTaP (the lowercase *a* stands for acellular).

From start to finish, the move from whole-cell pertussis vaccines to acellular vaccines took more than twenty years. And it took another decade for a critical mass of children who had been vaccinated exclusively with DTaP to reach school age. That is when public health officials and researchers began to realize that there were issues with the vaccines' long-term immunity. In 2012 nearly 50,000 cases of pertussis were reported to the Centers for Disease Control and Prevention (CDC), including twenty pertussis-related deaths.⁸ This was the

highest number of reported cases in the United States since 1955. In the past year there have been pertussis outbreaks in California; Maryland; and Washington, D.C.⁸ And until a new vaccine is formulated, the CDC says that it's likely that countries using DTaP will experience whooping cough resurgences every three to five years.

Poolman, who recently edited a special issue of the journal *Vaccines* focused on the need for a third generation of pertussis vaccine, says the stage is being set for a new formulation. There is already a clear medical need, a public outcry, and a consumer base big enough to justify the research and development costs. But he cautions that the wait is far from over.

"Vaccine development in itself is a very long process," he says. "No private company is going to take on the risks of developing a new vaccine until there is academic consensus on how to do so... and for now, we are still in thinking mode."

Thinking Mode

In the years since researchers first became aware of problems with the DTaP vaccine, several ideas have emerged on how to best address the challenge of waning immunity. These ideas generally fall into three camps: developing a brand-new, whole-cell pertussis vaccine; purifying or adding other substances to the current acellular vaccine; or using a policy-based solution to adjust immunization schedules again, while continuing to use the current acellular vaccine.⁷

There are several barriers to developing a new whole-cell version of pertussis vaccine. Reactogenicity and potency of whole-cell pertussis vaccines seem to be linked, meaning that it will be difficult to develop a vaccine that maintains efficacy while reducing the adverse side effects once considered unacceptable. Further complicating the matter is cost: Developing a third-generation vaccine using a brand-new strain of the bacteria will require vigorous testing and be significantly more expensive to license compared to the option of adapting the existing acellular vaccine. Yet there have been some promising new developments on the whole-cell front. One new attenuated strain of *Bordetella per-*

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tussis known as BPZE1 is being investigated for intranasal administration at birth,⁹ and an adaptation of a different strain has shown early evidence of tolerability in mice.¹⁰

Instead of searching for a new strain, some researchers are looking into the possibility of adapting the current acellular vaccine by incorporating substances called adjuvants, such as aluminum hydroxide gels, that enhance the body's immune response to an antigen.⁷ Another promising strategy would be to swap the currently used pertussis toxin for a genetically purified version that may provide better long-term coverage.¹¹ While the option of adapting the familiar second-generation vaccine may alleviate some of the costly and time-consuming challenges associated with a new whole-cell version, such an approach may feed some parents' persistent, yet unproven, fears of the effects of adjuvants when vaccinating infants.

All three potential solutions are further undermined by the fact that scientists still don't fully understand the reasons for the current vaccine's substandard protection over time. "No one has been able to identify what exactly correlates with protection," says Nicola Klein, codirector of the vaccine study center at Kaiser Permanente Northern California. She adds that even if you have an idea of how to improve the pertussis vaccine, it would be difficult to determine whether that new version was significantly better than the old version from an immunological perspective—key evidence necessary for regulatory approval. "You could do an actual classic clinical trial, but [nearly] everyone is vaccinated," she says.

In an ideal world, one approach to developing a third-generation vaccine would emerge from academia as the clear frontrunner in balancing reacto-

genicity and long-term efficacy. Then pharmaceutical companies would immediately begin the process of developing and getting approvals for a new version. If that were the case, a new pertussis vaccine could be expected to emerge in a decade or so. At this point, however, the jury is still out on which approach will yield the best results. And until "thinking mode" yields a consensus among researchers, public health departments will have to continue shaping new policies around the current second-generation vaccine.

Since the large US pertussis outbreaks of the past five years, federal health officials have changed several vaccination recommendations to incorporate "cocooning," a strategy focused on people who are likely to be in close contact with infants, the age group most at risk of dying as a result of contracting whooping cough. In 2010 the Advisory Committee on Immunization Practices (ACIP) expanded its tetanus/diphtheria/pertussis booster shot recommendations to cover both undervaccinated children and senior adults.¹² Previous ACIP policies recommended only tetanus and diphtheria booster (Td) for adolescents and adults. ACIP now also recommends that all health care personnel who have not yet received a dose of the triple booster combo, regardless of age, should be vaccinated and that women should receive a booster with every pregnancy.¹²

If there's one thing public health officials, researchers, and providers agree upon, it's that widespread immunization is more important than ever. "At this point, we know the acellular vaccines are not as long lasting as we'd like, but they do work," says Klein. "It's very important to vaccinate kids. We know this is the cohort that is the most vulnerable."

The Wait Continues

This past June, four years after the first big US outbreak of pertussis and right on schedule with CDC predictions, Marin County, California, experienced a resurgence in whooping cough. This is when eight-year-old Max contracted the disease. After he was diagnosed, Max spent five days on antibiotics, indoors, and isolated from his peers. His mother, Leilah, had to take the week off

work to care for him, shuttling Max back and forth from doctors' appointments and sitting by his bedside as he coughed so hard he would sometimes vomit. Following standard county health department protocol, the entire family was put on antimicrobial prophylaxis, with special attention given to monitoring Max's infant sister.

Leilah notified the leaders at Max's summer camp that he had been diagnosed with whooping cough and urged that other families get their children tested if they began showing signs of illness. She said she never heard back

that anyone had gotten sick, though she says it's possible she just never found out.

"I'm shocked that he didn't give it to others," Leilah says. "He was in camp with hundreds of kids. I still have no idea where he might have picked it up. It could have been a classmate, a friend, a neighbor. Who knows?"

In the end, the family was fortunate. No one else became sick, and they even got to keep their Disneyland vacation plans. But Leilah says the experience has left her anxious to know how she can protect her family in the future.

"Would I be willing to vaccinate more often? Yes, of course," she says. "I'd be fine with a new vaccination, a new schedule, whatever. Knowing this vaccine doesn't protect as long as I thought was a shock." Yet, she says, even with the vaccine's waning coverage, "I would have vaccinated my kids anyway. I just wish everyone I talked to was on the same page." ■

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NOTES

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