

100-Day Cough

By KATHLEEN FACKELMANN

Jane had a cough that just wouldn't quit. All through her pregnancy, she hacked and coughed. Nothing seemed to help. Days after delivery, her infant fell desperately ill and died. Only then did doctors make the connection between Jane's cough and *Bordetella pertussis*, the bacterium that causes whooping cough.

Is Jane's case a tragic anomaly?

New research suggests that infection with *B. pertussis* is far more common in adults than previously recognized. Researchers have reported that 12 to 31 percent of adults with a persistent cough have undiagnosed pertussis.

Do adults spread the whooping cough bug?

"Infections in adults are common," James D. Cherry of the University of California, Los Angeles (UCLA) School of Medicine told scientists attending a pertussis conference in Washington, D.C., last month.

For adults, the staccato cough often results in repeated trips to the doctor's office. A misdiagnosis, or no diagnosis at all, is the usual result. The adult version of pertussis rarely results in the telltale whoop that marks the disease in children. After months, the cough usually subsides on its own.

For unprotected infants, however, the disease is far more dangerous. Infection at first causes a runny nose, sore throat, and mild cough. But later, the cough can turn vicious. The babies cough spasmodically, then whoop as they try to catch their breath. They may vomit or turn purple. If the brain is deprived of oxygen, babies may suffer seizures or develop permanent brain damage. Some infected infants die. Pertussis is less likely to be fatal in older children, but they occasionally develop ear infections or pneumonia.

Most U.S. infants receive their first dose of the pertussis vaccine at age 2 months. The disease remains a threat, however, especially for younger infants and children who have not been vaccinated.

Since the 1980s, pertussis infection in the United States has surged cyclically,

with peaks every 3 to 4 years. The last upsurge occurred in 1993. If the pattern holds, public health officials expect another outbreak this year or next. Some researchers believe that undiagnosed pertussis infection in adults may fuel this sometimes deadly cycle in children.

Mary E. Nennig, a researcher at the Kaiser Permanente Pediatric Vaccine Study Center in San Francisco, realized a few years ago that several previous studies indicated a pertussis problem in U.S. teenagers and adults.

Chief among them was a 1992 study of 130 UCLA students who had sought help for a cough that lasted more than 6 days. Cherry and his colleagues found that 34 of them had undiagnosed infection with *B. pertussis* (SN: 11/25/95, p. 356.)

More recently, Seth W. Wright of the Vanderbilt University Medical Center in Nashville studied 75 adults who had visited a hospital emergency room complaining of prolonged coughing. Wright's team discovered that 16 had unrecognized pertussis (SN: 4/8/95, p. 214).

Nennig wondered if she would find similar rates of pertussis among adult members of a Kaiser health plan, who would more closely represent the general population. She and her coworkers studied 153 people age 18 and older who visited the San Francisco health facility complaining of a chronic cough.

Establishing a diagnosis of pertussis is notoriously tough. *B. pertussis* is a fickle organism, difficult to grow in culture or isolate in patients.

The problem is that most adults don't rush to the doctor the minute they develop a cough. In the Kaiser study, participants had suffered a cough for an average of 6 weeks before seeking help. By that time, the body's immune system may have already killed *B. pertussis*.

Yet this bug often leaves a nasty legacy of prolonged coughing. Some scientists theorize that one of several toxins exuded by *B. pertussis* damages airway cells involved in the cough reflex. Until those cells are repaired, the harsh cough continues. Indeed, folk legends refer to pertussis

as the 100-day cough, Nennig notes.

To solve the problem of diagnosis, the team relied on a blood test that looks for an antibody to a known pertussis toxin. Antibodies are proteins made by the immune system to fight an invader such as *B. pertussis*. Nennig and her colleagues assigned a diagnosis of pertussis to those people with a chronic cough who also had very high concentrations of this antibody.

The team discovered that 19 of the patients with a persistent cough had evidence of pertussis infection, translating into a disease prevalence of 12.4 percent. Nennig and her colleagues published the results of this study in the June 5 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION (JAMA).

To calculate the disease incidence in the general population, the team had to do some more homework. The investigators considered the total number of patients using the San Francisco facility during the study and then zeroed in on the number of Kaiser patients who had complained of a prolonged cough. Their calculations led them to estimate an incidence of at least 176 adult cases per 100,000 people per year. They concluded that adult pertussis is approximately as widespread as peptic ulcer disease.

That newly calculated rate of pertussis is significantly higher than local and national estimates, Nennig notes. The San Francisco Health Department reported an incidence of 1.6 cases per 100,000 people in all age groups during 1994. That translates to about 12 cases of pertussis in all of San Francisco. Nennig points out that her team found 19 just by looking at one Kaiser clinic.

Similarly, national figures appear to underestimate the scope of the pertussis problem. In the July 21, 1995 MORBIDITY AND MORTALITY WEEKLY REPORT, the Centers for Disease Control and Prevention (CDC) reported 1.8 cases per 100,000 people of all ages in the United States in 1994 and just 0.2 case per 100,000 for people age 20 and older.

Outside the research community, doctors rarely, if ever, recognize adult pertussis. Adults may experience mild, coldlike symptoms and a cough. "It's a very prolonged cough without being productive," Cherry says, in contrast to bronchitis, whose victims often cough up mucus.

In Cherry's study of the 34 pertussis-infected UCLA students, none had been correctly diagnosed when they sought treatment for the cough.

When Nennig and her colleagues went back to the Kaiser medical records, they found that not a single chart had noted pertussis infection as a possible cause of the persistent cough, even though some patients had gone to the clinic as many as nine times for cough symptoms. Three of the 19 patients whom researchers later

diagnosed as having pertussis infection had been sent to a specialist, such as an allergy or asthma doctor.

The Kaiser doctors—following what appears to be standard medical practice—attributed their patients' coughs to a variety of ills, including sinus infection, reactive airway disease, bronchitis, asthma, allergy, and viral syndrome. In some cases, no diagnosis was made.



A 3-week-old infant suffering from whooping cough.

"The average physician doesn't have a clue about pertussis [in adults]," Cherry says. "They don't recognize the illness."

Even if a physician were to suspect pertussis in an adult, there's no easy way to test for the bug, Nennig says. The antibody test used by the Kaiser team remains a research tool and is not available to physicians.

For the adult with pertussis infection, misdiagnosis can result in expense and anxiety. Patients, and insurers, end up paying for unnecessary, sometimes risky tests and medication. If the tests turn up nothing, the patient is left with the worry of a chronic cough.

"It can be a nightmare for the physician and the patient," Nennig says.

For public health experts, the greatest significance of adult pertussis may be its link to children.

"Adults and adolescents are an important reservoir for pertussis in the United States," says Peter M. Strebel, an epidemiologist at the Atlanta-based CDC. They are often the first in a household to suffer a pertussis infection, Strebel told scientists attending the pertussis conference, which was sponsored by the National Institutes of Health. Moreover, *B. pertussis* does not appear to cause disease in animals other than humans.

During the early, most contagious stage of pertussis infection, adults may notice what they think is an insignificant cough. But infants who inhale microscopic droplets of the extremely infectious sputum can develop full-force whooping cough, Strebel says.

If doctors can stop pertussis in adults and teens, they might be able to quench the outbreaks of pertussis that kill or disable many infants.

Although in some countries vaccination is not routine, most U.S. adolescents and adults were vaccinated as children. Researchers now know that pertussis protection wears off in about a decade, leaving people vulnerable to infection. However, bouts with *B. pertussis* in such people tend to be mild and thus go unrecognized.

The development of a new crop of pertussis vaccines has spurred talk of a booster program for adults. The vaccine currently in clinical use contains whole, killed bacteria that spur immunity against *B. pertussis*. These whole-cell pertussis vaccines sometimes cause painful swelling and other unpleasant reactions.

The new, so-called acellular vaccines rely on the pertussis proteins, rather than a whole bacterium, to spark immunity and are therefore thought to be safer. Two studies of infants published in the Feb. 8, 1996 *NEW ENGLAND JOURNAL OF MEDICINE* demonstrated that the acellular pertussis vaccines provide disease protection and provoke fewer reactions than the whole-cell vaccine.

The Food and Drug Administration is expected to approve the acellular vaccines for infants shortly. The adult version requires further testing.

In theory, adults and teenagers would get booster shots of a pertussis vaccine

every decade or so. But nobody really knows how long such vaccines would hold *B. pertussis* at bay. If the shield lasted just a year, the cost of giving the vaccine to adults would prove prohibitive.

The NIH plans to launch a clinical efficacy trial to see how well the acellular vaccines perform as adult boosters, according to David Klein of the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Md. That trial is scheduled to last about 3 years, he says.

Rather than vaccinate the entire population, some researchers advocate focusing on certain groups. For example, scientists know that adults can unknowingly spread pertussis to unvaccinated infants. NIAID plans an initial study in which researchers would give the acellular pertussis vaccine to pregnant baboons in hopes of establishing immunity in their offspring. If all goes well, they might launch a similar test in pregnant women, Klein says.

Will U.S. adults submit to a booster shot for an infection that causes a cough? That's a big question, researchers admit. But the most compelling reason to vaccinate adults is to stop the lethal spread of *B. pertussis* in children, says Nennig's coauthor Kathryn M. Edwards of Vanderbilt.

Some researchers advocate an all-out war against *B. pertussis*. "I think we ought to think about vaccinating adults," Edwards says.

Cherry adds, "Our ultimate goal should be the elimination of the organism." □

A link between pertussis and crib death

Preliminary research supports a link between *Bordetella pertussis* and some cases of sudden infant death syndrome (SIDS). It is the first time this bacterium has been associated with the syndrome, which causes apparently healthy infants to die in their sleep.

James D. Cherry of the University of California, Los Angeles School of Medicine, Ulrich Heininger of the University Hospital in Erlangen, Germany, and others began to investigate the link after they had worked on a case in which a German baby nearly died in its sleep. The baby survived, and the team later diagnosed a pertussis infection. Cherry and his colleagues began to wonder if *B. pertussis* causes other episodes in which breathing stops.

The German baby, for example, didn't suffer from a recognizable cough. Yet it exhaled a lot of air without drawing in enough to replace it, Cherry noted. Rather than the cough and whoop of an older child, a newborn with pertussis infection may simply appear to hold its breath periodically, he says.

The researchers decided to investigate additional cases of crib death. From

December 1990 to November 1993, the team collected nose and throat secretions from infants who had died of SIDS, but tests for *B. pertussis* gave uniformly negative results. Because of the difficulty of growing this bacterium in culture dishes, the team decided to try a different tack.

They used polymerase chain reaction, a powerful molecular test, to search out the DNA that codes for a known toxin produced by *B. pertussis*. The team studied 51 additional babies who had died of SIDS. This time, they hit pay dirt.

At the time of death, 18 percent had evidence of pertussis infection, the researchers reported in September 1995 at the annual meeting of the Infectious Diseases Society of America held in San Francisco. Cherry notes that *B. pertussis* attacks the airway cells in young infants, who may not be strong enough to cough. Only when an infant abruptly stops breathing does the illness show itself, he adds.

Still, this study remains preliminary. Cherry cautions that further research is needed to demonstrate the link, if any, between pertussis and crib death.

—K. Fackelmann