

symptomatology.³ Larger, prospective, longitudinal studies would be particularly helpful in determining whether airway inflammation is chronic or intermittent and whether it is, in fact, clinically significant. The notion, however, that respiratory abnormalities in children following preterm birth are, in part, mediated by airway inflammation could open up a further avenue of research into the respiratory sequelae of preterm birth, and may lead to novel therapeutic approaches. ■

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Responding to Pertussis

In his textbook published in 1940, Holmes noted that the "prevention of whooping cough by ordinary public health measures is almost impossible."¹ Despite the advent and universal implementation of effective pertussis vaccines in the intervening half century, in this issue of *The Journal*, Winter et al² describe the largest statewide pertussis epidemic in California in more than 60 years, which is largely a recapitulation of this vexing problem.

Vaccines are licensed on the basis of safety and either demonstrated efficacy or immunogenicity known to correlate with efficacy in protecting individuals against disease. Yet, the greatest benefit of vaccines comes from applying them at public health scale to achieve both direct and indirect protection, or herd immunity. Childhood pneumococcal vaccination rapidly reduced the incidence of disease in adults, attributable to a reduction of nasopharyngeal carriage in children, who serve as a reservoir of transmission to adults.³ A shortage of *Haemophilus influenzae* type b vaccine resulted in a recommendation to defer the booster dose for a period of 18 months. Despite decreases in coverage, no increases in *Haemophilus influenzae* type b disease were observed. Although the booster dose is associated with long-term protection, sustained reductions in transmission achieved through vaccination effectively served as a blanket of pro-

tection for young children against reintroduction of the organism and return of disease.^{4,5} High coverage with measles vaccine protected a sufficiently high proportion of the population to reduce susceptibility and eliminate indigenous measles transmission in the Americas.⁶ In each example, transmission of the causative organism was disrupted to a sufficient degree to achieve a benefit greater than the sum of the individual level of vaccine effectiveness.

Pertussis has a high basic reproduction number (R_0)—on the order of 12 to 17, which is equivalent to the number of secondary cases resulting from one case introduced into a fully susceptible population.⁷ When R_0 is less than one, transmission will extinguish itself. If a sufficient proportion of the population has been infected, the effective reproduction number goes below one, and transmission dissipates. The goal of vaccination is to force this number to less than one; however, the level of protection necessary to achieve extinction of transmission in a population is essentially one minus the reciprocal of R_0 . Therefore, 92% to 95% of the population must be protected against pertussis to halt transmission. Although coverage with the childhood diphtheria/tetanus toxoids/acellular pertussis vaccine is 95%, the vaccines currently in use are approximately 85% effective overall, and evidence is increasing that immunity may wane more rapidly

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R_0	Reproduction number
Tdap	Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine

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than anticipated.⁸⁻¹⁰ Adolescent tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) coverage is approaching 70%, but the short-term effectiveness observed in field studies is approximately 70%.^{11,12} Adult Tdap coverage remains less than 10%.¹³ A notable feature of the epidemiology of pertussis—the peaks in incidence that occur every few years—has persisted since the pre-vaccine era, evidence that despite effectively protecting individuals against pertussis, vaccines may have only a minimal effect on transmission.

Notably absent in this description of outbreak control measures in California is the use of chemoprophylaxis, or antibiotics given to exposed persons to prevent the development of disease. Chemoprophylaxis can prevent pertussis in exposed persons, but a full course of treatment is required rather than a single dose or abbreviated course.¹⁴ The determination of who is exposed and who is actually at risk of infection is difficult. Secondary attack rates among susceptible household contacts are high, but transmission to others probably requires more than brief or casual contact. It is unclear whether chemoprophylaxis can interrupt transmission sufficiently and stop a community outbreak or epidemic such as the one described in California. Efforts to do so may result in far more people receiving antibiotics than is necessary.

Case investigation for disease surveillance and making prevention and control recommendations strains public health resources. At the peak of the California outbreak in July, case reports were being received at a rate of 50 per day. In an outbreak of 26 cases in a school in Nebraska, the investigation of each case required 42 regular person-hours and 1 hour of overtime.¹⁵ Contact tracing for chemoprophylaxis around each case required 21 phone calls. The total cost of the Nebraska outbreak was \$52 000, or more than \$2000 per case. The implications of sustaining this level of effort to investigate and respond to more than 9000 cases are staggering. A back-of-the-envelope calculation suggests that the cost to respond to the California epidemic could have totaled \$20 million and required 45 person-years. Costs of antibiotics, diagnostic testing, and indirect costs such as time lost from work would make the response far costlier.

The authors and their colleagues are to be commended for their sustained efforts to track and respond to this outbreak and their focus on preventing severe and fatal disease. With a high burden of disease and a high proportion of cases among fully vaccinated children, prevention strategies were limited. Although unvaccinated persons are at increased risk for disease and can develop severe disease at any age, vaccinated persons who acquire pertussis generally have milder symptoms and a shorter duration of illness, as well as reduced risk for hospitalization, complications, and mortality.^{16,17} Efforts were made to vaccinate the unvaccinated, and in consultation with the Centers for Disease Control and Prevention, the California Department of Health expanded Tdap vaccine recommendations to include immunization of pregnant women. They also supplied publicly purchased Tdap vaccine to providers of health care for pregnant and postpartum

women to facilitate their vaccination. The number of reported cases exceeded 800 per month in May and did not decrease below this level again until December, 8 months later, yet the case/fatality ratio did not exceed that of the US overall.¹⁸ Although 10 fatalities occurred, there were no deaths reported after September in this epidemic. Hospitalizations were relatively rare after infancy, length of stay generally was short among hospitalized cases, and neurologic complications were uncommon. Messaging to increase awareness among providers and the public, with special efforts to reach California's Hispanic communities, and guidance targeting chemoprophylaxis and vaccination for contacts of infants likely prevented cases and deaths.

Research should focus on the contribution of waning immunity from childhood vaccination to the re-emergence of pertussis and dramatic epidemics in California and elsewhere. However, limitations in the duration of vaccine protection do not imply limited vaccine impact. Vaccinated children largely are protected from severe and fatal disease. Furthermore, limitations in herd immunity do not argue against vaccination. To the contrary, reducing the overall burden of pertussis requires high compliance and timely receipt of vaccination according to the recommended schedule. There is an urgent need to improve adult vaccination coverage, especially among those who have close contact with infants. Full implementation of the recommendation for pregnant women to receive Tdap should be a priority, and its effectiveness should be evaluated to understand whether or not immunization during pregnancy represents the best strategy to prevent severe and fatal pertussis in infants.

Through epidemiologic week 30 in 2012, more than 20 000 cases of pertussis were reported in the US—more cases than were reported during the same period in any of the preceding 50 years. Pediatricians and public health providers would be well served by learning the lessons presented in this epidemic in California. ■

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