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EDITORIAL COMMENTARY

Toward a Controlled Human Infection Model of Pertussis

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(See the Major Article by de Graaf et al on pages 403–11.)

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Pertussis is a highly contagious disease caused by *Bordetella pertussis,* spread by respiratory droplets [1, 2]. *B. pertussis* is a strict human pathogen with no other known reservoir. The disease has an initial catarrhal phase of 1–2 weeks followed by several weeks of paroxysmal coughing. The severe coughing bouts are often followed by post-tussive vomiting and an inspiratory whoop for which the disease is named [1, 2]. Other more severe signs can include apnea, cyanosis, seizures, encephalopathy, and weight loss [1, 2]. The disease is milder in older children and adults and most severe in infants, with half of all deaths in the United States occurring in infants under 2 months of age [3]. Pertussis was common in the prevaccine era, with an average of 162 000 cases per year in the United States with an average case fatality rate of 4% (1926 and 1929 Annual Reports of the Surgeon General of the Public Health Service of the United States). Introduction of whole-cell pertussis (wP) vaccines in the 1940s led to a rapid decline in the incidence of reported pertussis [4]. However, the wP vaccine was commonly associated with mild injection site pain and swelling, low-grade fever, and fretfulness and less commonly with convulsions and hypotonic–hyporesponsive episodes [5–8]. This reactogenicity led to reduced acceptance of the wP vaccine and declining vaccination rates in most high-income countries [9]. In response to public concerns about the wP vaccines, less reactogenic acellular pertussis (aP) vaccines were developed and licensed for use in the 1990s. These aP vaccines, consisting of purified bacterial antigens combined with aluminum adjuvant, were less reactogenic than the wP vaccines they replaced and demonstrated comparable efficacy against disease over the first 5 years following vaccination [8, 10–14]. The US Advisory Committee on Immunization Practices (ACIP) recommends the combined diptheria, tetanus, and acellular pertussis (DTaP) vaccine adsorbed be administered at 2, 4, and 6 months of age, between 12 and 18 months of age, and between 4 and 6 years of age [15]. A booster dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed (Tdap) is recommended between 11 and 12 years of age [15].

In the United States, approximately 95% of children receive at least 3 doses of aP vaccine by school entry, and >80% of children receive the adolescent booster dose by middle school enrollment [16, 17]. Despite these near universal rates of vaccination, the United States has experienced a steady increase in reported cases of pertussis since 2000 (Centers for Disease Control and Prevention, Pertussis Surveillance and Reporting website; URL: http://www.cdc.gov/pertussis/surv-reporting.html). Several factors likely contribute to this resurgence, including more rapid waning of protective immunity following aP vaccination, evolution of *B. pertussis* to escape aP vaccine-mediated immunity, and increased carriage and asymptomatic transmission from individuals vaccinated with the aP vaccines [18, 19].

Studies conducted using a baboon model of pertussis demonstrated that infection results in a strong immunity that prevents reinfection and disease upon a second exposure [20]. Baboons vaccinated with aP vaccines were protected against disease but were heavily colonized and remained colonized longer than unvaccinated animals [20]. Despite a lack of symptoms, infected, aP-vaccinated baboons were able to transmit to cohoused animals [20]. Examination of the immune response to vaccination in baboons demonstrated that infection with *B. pertussis* as well as vaccination with wP vaccine induced Th1 and Th17 responses, but both the Th1 and Th17 responses induced by infection were stronger than those seen following wP vaccination [20–22]. Neither infection nor wP vaccination induced Th2 responses. In contrast, the aP vaccines induced strong Th2 responses without significant Th1 or Th17 responses [20–22]. Taken together, these results indicate that Th2 responses induced by aP vaccination are sufficient to protect against disease but Th17 and possibly Th1 responses are likely required to prevent *B. pertussis* colonization, persistence

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and subsequent transmission. The results of immunogenicity studies in children following immunization or infection revealed that aP vaccination induced strong Th2 responses and weak Th1 responses while wP vaccines induced strong Th1 responses [23–25]. Th17 responses were observed in wP-primed adolescents but not in aP-primed adolescents following the adolescent booster vaccination, providing evidence of induction of Th17 memory in children following wP vaccination [26]. These results mirror those observed in the baboon model.

Epidemiological studies following pertussis outbreaks indicate rapid waning of immunity following the primary aP vaccination series. The efficacy of DTaP is >85% following the first 3 vaccinations and >98% following the fifth dose [8, 10, 27]. However, the risk of acquiring pertussis rises 4- to 15-fold by 5 years after the fifth dose [27–30]. Very rapid waning of protection was observed following booster vaccination with Tdap vaccine. Although initial vaccine efficacy for the Tdap booster was estimated to be 70–75%, efficacy was estimated to wane to as low as 10–12% 4 years post booster vaccination [31–34].

The available evidence suggests that the resurgence of pertussis in high-income countries is due to increased asymptomatic carriage in aP-vaccinated populations, leading to increased pertussis exposure in those populations, in combination with reduced duration of immunity induced by aP vaccines relative to that induced by wP vaccines. Despite these shortcomings, it is important to recognize that aP vaccines were developed in response to a significant need as acceptance of wP vaccination fell in high-income countries. The licensed aP vaccines have excellent safety profiles and protect vaccinated individuals from disease. The comparison of pertussis rates in high-income countries today with rates in the prevaccine era demonstrates that a significant level of control of pertussis is being maintained by aP vaccination. However, pertussis remains the most common vaccine-preventable disease, and we continue to observe increasing levels of pertussis in the face of high rates of vaccination. Next-generation vaccines are needed that combine the safety profile and protection against disease conferred by aP vaccines with protection against colonization and enhanced duration of immunity. To accomplish this goal, next-generation pertussis vaccines will likely be designed to induce different, or additional immune responses than the current aP vaccines and may also include a broader set of antigens.

A significant hurdle to the introduction of next-generation pertussis vaccines lies in the challenge of developing strong scientific evidence of effectiveness. The aP vaccines currently in use were shown to protect against disease in prospective, clinical-endpoint, efficacy studies conducted in populations with high incidence of pertussis [8, 10–14]. Comparable studies would be difficult and likely are not possible today. Although the incidence of pertussis is on the rise in high-income countries, the incidence is likely too low for a prospective clinical-endpoint study to be feasible. The difficulty of conducting prospective pertussis vaccine studies is compounded by the fact that pertussis incidence is cyclical, with peaks of infection alternating with troughs and different regions experiencing peaks and troughs of pertussis incidence in different years. The baboon model of pertussis provides a powerful tool for evaluating the ability of new antigens and adjuvants to protect against disease, and the baboon model may be used to provide supportive proof of concept for vaccines before their study in human clinical trials. However, clinical data will be required to demonstrate effectiveness in humans.

Multiple alternative approaches will likely be required to demonstrate substantial evidence of effectiveness of next generation vaccines. One component of such an approach may be the use of a pertussis controlled human infection model. In 2016, the US Food and Drug Administration licensed Vaxchora® for active immunization against disease caused by *Vibrio cholerae* in the United States. The primary evidence supporting the effectiveness of Vaxchora® was derived from human challenge studies [35]. A human challenge model of pertussis could be used to study early stages of infection, identify immune responses to infection and vaccination in humans, evaluate the effectiveness of novel antigens and adjuvants in preventing infection, down-select vaccine formulations and, depending on the clinical endpoints, possibly provide clinical efficacy data for a next-generation pertussis vaccine.

There are significant challenges in developing a pertussis controlled human infection model. Pertussis is transmitted by airborne respiratory droplets; therefore, appropriate containment facilities and study design are required to prevent transmission to contacts within the clinical center, and effective antibiotic treatment is required to ensure clearance of pertussis prior to discharge at the end of the study to prevent accidental transmission to subject contacts outside the clinical center. Antibiotic treatment provides an effective therapy for pertussis when administered early in infection. However, antibiotics have limited or no efficacy when administered late in infection, presumably due to damage to the host and/or residual toxin resulting in prolonged disease despite clearance of the organism [36]. This point of no return with respect to rescue therapy and the potential for severe disease may limit a pertussis challenge model to the study of establishment of infection and evaluation of early mild disease symptoms. Even a pertussis controlled human infection model limited to evaluating the initial infection would be valuable, particularly for the evaluation of vaccines intended to prevent colonization.

In this issue of *Clinical Infectious Diseases*, Haans de Graaf, Robert Read, and colleagues describe the early steps in the development of a human challenge model using fully virulent *B. pertussis*. Healthy adult subjects were inoculated intranasally with escalating doses of *B. pertussis* strain

B1917, a clinical isolate representative of strains currently circulating in Europe [37]. In order to avoid enrolling subjects with recent exposure to pertussis, antipertussis toxin titers were measured, and only subjects with titers below 20 international units were admitted to the study. Following inoculation, subjects were followed in an inpatient setting for disease symptoms, colonization, and shedding of *B. pertussis*. All subjects were treated with azithromycin starting on day 14 to ensure clearance prior to discharge and to limit development of symptoms. In this study, the authors demonstrated that human subjects can be safely and asymptomatically colonized with *B. pertussis* and defined a challenge dose that resulted in colonization of 80% of subjects. Nonspecific symptoms were reported in a minority of participants. Azithromycin eradicated colonization within 48 hours in 88% of colonized individuals, and antipertussis toxin immunoglobulin G seroconversion occurred in 47% of colonized participants. These results demonstrated that *B. pertussis* colonization can be deliberately induced in a controlled manner that leads to a systemic immune response without causing pertussis symptoms. The development of a *B. pertussis* human challenge model will allow researchers to confirm many important observations from animal models, will be useful in the evaluation of next-generation pertussis vaccines that will likely be designed to reduce or eliminate carriage and, critically, may allow for controlled pertussis vaccine efficacy studies and the exploration of correlates of immunity in humans.

Notes

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References

1. Kilgore PE, Salim AM, Zervos MJ, Schmitt HJ. Pertussis: microbiology, disease, treatment, and prevention. Clin Microbiol Rev **2016**; 29:449–86.
2. Pinto MV, Merkel TJ. Pertussis disease and transmission and host responses: insights from the baboon model of pertussis. J Infect **2017**; 74(Suppl 1):114–9.
3. Chu HY, Englund JA. Maternal immunization. Clin Infect Dis **2014**; 59:560–8.
4. Klein NP. Licensed pertussis vaccines in the United States: history and current state. Hum Vaccin Immunother **2014**; 10:2684–90.
5. Cody CL, Baraff LJ, Cherry JD, Marcy SM, Manclark CR. Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. Pediatrics **1981**; 68:650–60.
6. Decker MD, Edwards KM, Steinhoff MC, et al. Comparison of 13 acellular pertussis vaccines: adverse reactions. Pediatrics **1995**; 96:557–66.
7. Englund JA, Glezen WP, Barreto L. Controlled study of a new five-component acellular pertussis vaccine in adults and young children. J Infect Dis **1992**; 166:1436–41.
8. Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. N Engl J Med **1996**; 334:349–55.
9. Plotkin SA. The pertussis problem. Clin Infect Dis **2014**; 58:830–3.
10. Greco D, Salmaso S, Mastrantonio P, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. Progetto Pertosse Working Group. N Engl J Med **1996**; 334:341–8.
11. Gustafsson L, Hessel L, Storsaeter J, Olin P. Long-term follow-up of Swedish children vaccinated with acellular pertussis vaccines at 3, 5, and 12 months of age indicates the need for a booster dose at 5 to 7 years of age. Pediatrics **2006**; 118:978–84.
12. Olin P, Rasmussen F, Gustafsson L, Hallander HO, Heijbel H. Randomised controlled trial of two-component, three-component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. Ad Hoc Group for the Study of Pertussis Vaccines. Lancet **1997**; 350:1569–77.
13. Simondon F, Preziosi MP, Yam A, et al. A randomized double-blind trial comparing a two-component acellular to a whole-cell pertussis vaccine in Senegal. Vaccine **1997**; 15:1606–12.
14. Trollfors B, Taranger J, Lagergård T, et al. A placebo-controlled trial of a pertussis-toxoid vaccine. N Engl J Med **1995**; 333:1045–50.
15. Liang JL, Tiwari T, Moro P, et al. Prevention of pertussis, tetanus, and diphtheria with vaccines in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep **2018**; 67:1–44.
16. Hill HA, Elam-Evans LD, Yankey D, Singleton JA, Kang Y. Vaccination coverage among children aged 19–35 months - United States, 2017. MMWR Morb Mortal Wkly Rep **2018**; 67:1123–8.
17. Walker TY, Elam-Evans LD, Singleton JA, et al. National, Regional, state, and selected local area vaccination coverage among adolescents aged 13–17 years - United States, 2016. MMWR Morb Mortal Wkly Rep **2017**; 66:874–82.
18. Althouse BM, Scarpino SV. Asymptomatic transmission and the resurgence of *Bordetella pertussis*. BMC Med **2015**; 13:146.
19. Lapidot R, Gill CJ. The Pertussis resurgence: putting together the pieces of the puzzle. Trop Dis Travel Med Vaccines **2016**; 2:26.
20. Warfel JM, Zimmerman LI, Merkel TJ. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. Proc Natl Acad Sci U S A **2014**; 111:787–92.
21. Warfel JM, Merkel TJ. *Bordetella pertussis* infection induces a mucosal IL-17 response and long-lived Th17 and Th1 immune memory cells in nonhuman primates. Mucosal Immunol **2013**; 6:787–96.
22. Warfel JM, Zimmerman LI, Merkel TJ. Comparison of three whole-cell pertussis vaccines in the baboon model of pertussis. Clin Vaccine Immunol **2016**; 23:47–54.
23. Brummelman J, Wilk MM, Han WG, van Els CA, Mills KH. Roads to the development of improved pertussis vaccines paved by immunology. Pathog Dis **2015**; 73: ftv067.
24. Mascart F, Hainaut M, Peltier A, Verscheure V, Levy J, Locht C. Modulation of the infant immune responses by the first pertussis vaccine administrations. Vaccine **2007**; 25:391–8.
25. Mascart F, Verscheure V, Malfroot A, et al. *Bordetella pertussis* infection in 2-month-old infants promotes type 1 T cell responses. J Immunol **2003**; 170:1504–9.
26. da Silva Antunes R, Babor M, Carpenter C, et al. Th1/Th17 polarization persists following whole-cell pertussis vaccination despite repeated acellular boosters. J Clin Invest **2018**; 128:3853–65.
27. Misegades LK, Winter K, Harriman K, et al. Association of childhood pertussis with receipt of 5 doses of pertussis vaccine by time since last vaccine dose, California, 2010. JAMA **2012**; 308:2126–32.
28. Klein NP, Bartlett J, Fireman B, et al. Waning protection following 5 doses of a 3-component diphtheria, tetanus, and acellular pertussis vaccine. Vaccine **2017**; 35:3395–400.
29. Tartof SY, Lewis M, Kenyon C, et al. Waning immunity to pertussis following 5 doses of DTaP. Pediatrics **2013**; 131:e1047–52.
30. Witt MA, Katz PH, Witt DJ. Unexpectedly limited durability of immunity following acellular pertussis vaccination in preadolescents in a North American outbreak. Clin Infect Dis **2012**; 54:1730–5.
31. Acosta AM, DeBolt C, Tasslimi A, et al. Tdap vaccine effectiveness in adolescents during the 2012 Washington State pertussis epidemic. Pediatrics **2015**; 135:981–9.
32. Klein NP, Bartlett J, Fireman B, Baxter R. Waning Tdap effectiveness in adolescents. Pediatrics **2016**; 137:e20153326.
33. Koepke R, Eickhoff JC, Ayele RA, et al. Estimating the effectiveness of tetanus-diphtheria-acellular pertussis vaccine (Tdap) for preventing pertussis: evidence of rapidly waning immunity and difference in effectiveness by Tdap brand. J Infect Dis **2014**; 210:942–53.
34. Skoff TH, Martin SW. Impact of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccinations on reported pertussis cases among those 11 to 18 years of age in an era of waning pertussis immunity: a follow-up analysis. JAMA Pediatr **2016**; 170:453–8.
35. Ramanathan R, Stibitz S, Pratt D, Roberts J. Use of controlled human infection models (CHIMs) to support vaccine development: US regulatory considerations. Vaccine **2019**; 37:4256–61.
36. Wood N, McIntyre P. Pertussis: review of epidemiology, diagnosis, management and prevention. Paediatr Respir Rev **2008**; 9:201–11; quiz 11–2.
37. Bart MJ, van der Heide HG, Zeddeman A, Heuvelman K, van Gent M, Mooi FR. Complete genome sequences of 11 *Bordetella pertussis* strains representing the pandemic ptxP3 lineage. Genome Announc **2015**; 3:e01394–15.