Vaccines and Related Biological Products Advisory Committee Meeting
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FDA Briefing Document

Use of Controlled Human Infection Models to Support Licensure of Pertussis Vaccines

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Glossary

ACIP	Advisory Committee on Immunization Practices
aP	acellular pertussis
CHIM	controlled human infection model
CFU	colony-forming unit
D	Diphtheria Toxoid
DTaP	Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed
FDA	U.S. Food and Drug Administration
FHA	filamentous hemagglutinin
FIM	fimbriae
HBsAg	hepatitis B surface antigen
IPV	inactivated poliovirus
PRN	pertactin
PRP	*Haemophilus influenzae* type B capsular polysaccharide polyribosyl-ribitol-phosphate
PT	pertussis toxoid
T	Tetanus Toxoid
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed
T_H	helper T cells
U.S.	United States
WHO	World Health Organization
wP	whole cell pertussis

Section 1: Overview

Pertussis is an acute respiratory disease caused by the Gram-negative bacterium *Bordetella pertussis.* The severity of the disease manifestations depends on age, prior infection, and vaccination status, with unvaccinated infants presenting with the most severe disease. The classical presentation is characterized by spasmodic coughing associated with post-tussive vomiting, inspiratory whoop, and cyanosis.

Diphtheria, tetanus, and whole cell pertussis (wP) vaccines were developed and introduced in the 1940s–1950s in several countries. Currently, global pertussis vaccine coverage is approximately 86%, according to the World Health Organization (WHO, 2015b; WHO, 2019). Approximately 64% of countries worldwide use wP vaccines, accounting for all the countries in the WHO Southeast Asia Region and 96% of the African Region (WHO, 2015a). In high-income countries, acellular pertussis (aP) vaccines replaced wP vaccines due to concerns over the reactogenicity of wP vaccines. Despite near universal vaccine coverage in infants, the incidence of reported pertussis has steadily increased following the introduction of aP vaccines in these countries. U.S. postmarketing effectiveness data corroborate prelicensure efficacy estimates for DTaP vaccines with regard to prevention of pertussis in the relative short term. However, national pertussis surveillance data and findings from postmarketing effectiveness studies are consistent with a progressive decrease in vaccine effectiveness with each year after the fifth dose of DTaP vaccine (Misegades et al., 2010; Klein et al., 2012; Tartof et al., 2013) and suggest relatively early waning of protection after the adolescent dose of Tdap vaccine.

On 6 March 2013, pertussis experts from academia, government agencies, and pharmaceutical companies met during a Working Group Meeting on Pertussis held in Bethesda, Maryland (Burns et al., 2014). The working group identified potential causes for the increased reports of pertussis, including (1) short-lived adaptive immunity following immunization, (2) suboptimal balance of immune response (e.g., skewed towards a T-helper 2 [Th2] response), (3) need for additional vaccine antigens for optimal protection, (4) insufficient quantity or incorrect balance of antigens, (5) antigen mismatch with circulating strains, (6) suboptimal schedule or population coverage, (7) differential effectiveness of the vaccines in current use, and (8) increased awareness, better diagnostics, and/or more complete reporting.

The working group's consensus was that long-term solutions were needed to effect a fundamental change in pertussis epidemiology, and that the optimal vaccine would afford long-term protection against both disease and transmission. Potential strategies identified to improve control of pertussis included changes in vaccination schedules with already licensed combination vaccines, development of acellular pertussis (aP)-only vaccines for additional doses, and development of new vaccines that might confer longer lasting protection and reduce transmission. A significant challenge to the introduction of new pertussis vaccines lies in demonstrating substantial evidence of effectiveness, since prospective clinical endpoint efficacy studies are likely infeasible due to the unpredictable and sporadic occurrence of pertussis disease and the large sample sizes required. Therefore, alternative approaches will likely be required to provide substantial evidence of effectiveness of new pertussis vaccines. One component of such an approach may be the use of a pertussis controlled human infection model (CHIM). The purpose of this VRBPAC meeting is to

discuss the use of pertussis CHIMs in clinical studies to demonstrate effectiveness of new pertussis vaccines.

Section 2: Pertussis Disease and Epidemiology

B. pertussis infection may be asymptomatic or may present as a respiratory illness of varying severity. The severity of disease is likely modulated by host factors including age, vaccination status, and prior exposure. The classic presentation, most common in younger children, is typically divided into three stages: the catarrhal phase, the paroxysmal phase, and the convalescent phase. The catarrhal phase, 1–2 weeks in duration, is characterized by nonspecific prodromal coryzal symptoms with onset of a mild progressive cough. The paroxysmal phase (also known as whooping cough) is the most severe and is characterized by intense and spasmodic cough associated with post-tussive vomiting, inspiratory whoop, and cyanosis. This phase can last 4–6 weeks, with a gradual improvement after the first 3 weeks. In the convalescent phase, patients experience gradual improvement, with a decrease in the frequency and severity of the cough paroxysms and an eventual resolution of symptoms. Depending on the setting and timing, the diagnosis can be made clinically, or with analysis of properly collected nasal secretions by culture or PCR, or serologically. Antimicrobial treatment is indicated for most patients in the catarrhal and paroxysmal phases of the disease, and for household contacts regardless of vaccination status.

Complications of pertussis can occur in all age groups, but serious complications occur most commonly in very young infants. The most common complications in infants are apnea (50–76%), pneumonia (20–23%), and weight loss (12%). Infants require hospitalization in approximately 50% of cases. The most common complications in adolescents and adults are apnea (27–86%), weight loss (3–33%), and urinary incontinence (3–28%) (Kilgore et. al., 2016 and Wood et.al., 2008). Neurological complications, such as convulsions, are more common in infants. Pertussis can be fatal, with death occurring most commonly in infants under two months of age. Several other risk factors for fatal pertussis in infants were described by Winter et al., 2015: lower birth weight, smaller gestational age, younger age at time of the beginning of cough, and higher counts of white blood cells and lymphocytes.

B. pertussis is a strictly mucosal pathogen that establishes itself on ciliated cells in the conducting airways of the respiratory tract, where it replicates to high numbers. Typically, *B. pertussis* is limited to the respiratory tract. Disseminated disease is only observed in highly immunocompromised patients. Systemic impacts of infection are presumed to be due to the action of secreted bacterial toxins. Pertussis toxin is generally considered the main mediator of systemic effects, including pulmonary hypertension, shock, organ failure, and lymphocytosis.

The reservoir of *B. pertussis* is exclusively human, and the disease is transmitted via airborne droplets. The airborne transmission of *B. pertussis* was first hypothesized by Luttinger et al., 1916, but the first controlled study proving this hypothesis was performed by Warfel et al., 2012. The determination of pertussis attack rates in humans is challenging. Previous prospective studies showed that attack rates between household contacts are around 76% (64–86%), but the rates are highly variable among studies and are often confounded by variables such as population age and immune status, either due to vaccination or previous exposure. In school classroom contact studies, similar variability was

reported, with attack rates that varied from 0–36%. The differences in the attack rates between household and classroom studies is consistent with a need for close or prolonged contact for the disease to be transmitted, an event more likely to happen in a household than in a school setting (Mertsola et al., 1983; Isomura, 1991; Schmitt, 1997; Simondon, 1997; Storsaeter and Gustafsson, 1997; Heininger et al., 1998; Warfel et al., 2012).

Although pertussis outbreaks in high-income countries are well publicized, 95% of pertussis cases occur in low- and middle-income countries according to the WHO, with an estimated 16 million cases and 200,000 deaths worldwide attributed to pertussis each year. Pertussis is considered by WHO to be one of the leading diseases preventable by vaccines.

The incidence of pertussis appears to be cyclic, with peaks occurring every 3–5 years within a given region. This observed periodicity has been maintained from the pre-vaccine era through the wP and aP vaccine eras even when vaccine coverage rates have varied. This phenomenon is not completely understood. The length of inter-epidemic periods is likely driven by the percentage of susceptible individuals in a population, primarily non-vaccinated newborns and vaccinated individuals with waning immunity, relative to the number of individuals protected due to direct vaccination, maternal immunization, or immunity conferred by infection.

In the pre-vaccine era, *B. pertussis* was responsible for an average of 182,000 cases of pertussis and 5,633 deaths per year in the U.S. In 1943, the American Academy of Pediatrics recommended routine use of wP vaccines, and in 1948, the number of reported cases of pertussis in the U.S. dropped below 100,000. It reached its lowest point of 1010 cases in 1976. However, pertussis was never eliminated in the U.S., with between 1010 and 5000 cases reported per year from 1968 to 1990. Between 1990 and the present, a steady increase in pertussis reporting has been observed in the U.S. The potential cause of that increase is discussed below.

Section 3: Development of Pertussis Vaccines

The first pertussis vaccines to be widely used were wP vaccines that consisted of inactivated *B. pertussis* organisms, combined with tetanus and diphtheria toxoids, and adsorbed to aluminum salts. These vaccines were introduced in several countries in the 1940s–1950s. Although effective, the wP vaccines were reactogenic, and injection site tenderness, fever, and irritability were common. High fevers, febrile seizures, and hypotonic and hyporesponsive episodes, while much less common, were clearly associated with the vaccines. This reactogenicity resulted in reduced acceptance of wP vaccines in the 1970s, and the resulting reduced vaccination coverage was a decisive factor driving the development and introduction of less reactogenic aP vaccines in high-income countries.

Acellular pertussis (aP) vaccines consist of purified pertussis toxin and additional antigens adsorbed to aluminum salts. Several aP vaccines have been developed, differing in antigen content and amounts of each antigen. All aP vaccines contain chemically or genetically inactivated pertussis toxoid (PT), either alone or in combination with filamentous hemagglutinin (FHA), pertactin (PRN), and/or fimbriae (FIM). After clinical trials demonstrated efficacy of aP-containing vaccines and lower reactogenicity compared with wP-containing vaccines, high-income countries in Europe, North America, and Australia progressively introduced aP-containing vaccines during the 1980s and 1990s. Currently,

these vaccines remain the standard of care. In the U.S., Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) and Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Tdap) vaccines are recommended for use by the Advisory Committee on Immunization Practices (ACIP).

Despite high vaccination coverage with aP-containing vaccines, the U.S. has experienced a resurgence in reported pertussis cases. This rise may be due to a combination of factors: genetic adaptation of circulating strains to escape vaccine pressure; rapid waning of aP vaccine-induced immunity; and the failure of aP-containing vaccines to prevent *B. pertussis* colonization, carriage, and transmission (Warfel et.al. 2014 and Wilk et. Al., 2019). aP-containing vaccines induce helper T cells (T_H2) memory and neutralizing antibody responses that effectively prevent symptomatic disease but fail to prevent colonization and carriage. In contrast, infection and vaccination with wP vaccine induce both T_H1 and T_H17 memory and antibody responses against a wide array of bacterial antigens that result in prevention of symptomatic disease and reductions in colonization and carriage (Ross et. al., 2013 and Warfel and Merkel, 2013).

In Europe, Australia, and the U.S., the rise in the incidence of pertussis since the introduction of aP-containing vaccines has been associated with increases in both epidemic peaks and the interpeak baselines. In the U.S., several outbreaks occurred in the last decade, with peaks occurring in 2004-05, 2010, 2012, and 2014. The rates of disease were highest in children less than one year of age, with an incidence of 126.7 cases per 100,000 individuals. Vaccination coverage in the U.S. has been consistently high, varying between 94 and 95% for three doses and between 82.5 and 84.6% for four or more doses in 19 through 35-month-old children. WHO continues to recommend wP-containing vaccines in the low- and middle-income countries that still use wP-containing vaccines as part of their national immunization programs. Approximately 75% of children vaccinated around the world receive a wP-containing vaccine.

Widespread use of aP-containing vaccines continues to provide a significant public health benefit by preventing disease. Despite the resurgence of pertussis, current rates of disease are very low relative to the rates reported during the pre-vaccine era. A significant gap in vaccine-mediated protection exists between birth and completion of an infant's primary vaccination series. Maternal vaccination during the third trimester of pregnancy with U.S.-licensed Tdap vaccines has been shown to be effective in protecting newborns against pertussis in the first two months of life. However, coverage by maternal vaccination during pregnancy is low, with only approximately 50% of mothers choosing to be vaccinated.

Current U.S.-licensed pertussis vaccines

In the U.S., nine acellular pertussis antigen-containing vaccines are licensed and available for the prevention of pertussis as shown in the following table:

Table 1. Current U.S.-Licensed Acellular Pertussis Antigen Containing Vaccines

Vaccine Type/ Trade Name	Manufacturer	Pertussis Antigens	Other Antigens	Pertussis Data to Support Licensure
DTaP vaccines	--	--	--	--
Daptacel	SP	PT, FHA, PRN, FIM2/3	D, T	Efficacy with immunobridging to U.S. population
Infanrix	GSK	PT, FHA, PRN	D, T	Efficacy with immunobridging to U.S. population
DTaP-based combination vaccines	--	--	--	--
Kinrix	GSK	PT, FHA, PRN	D, T, IPV	Linked[a] to Infanrix efficacy and immunologic NI to Infanrix control
Pediarix	GSK	PT, FHA, PRN	D, T, HBsAg, IPV	Linked[a] to Infanrix and immunologic NI to Infanrix control
Pentacel	SP	PT, FHA, PRN, FIM2/3	D, T, PRP-T, IPV	Linked[a] to Daptacel and immunologic NI to Daptacel
Quadracel	SP	PT, FHA, PRN, FIM2/3	D, T, IPV	Linked[a] to Daptacel and immunologic NI to Daptacel
Vaxelis	SP[b]	PT, FHA, PRN, FIM2/3	D, T, IPV, PRP-OMP, HBsAg	Linked[a] to Daptacel and immunologic NI to Pentacel and Daptacel
Tdap vaccines	--	--	--	--
Adacel	SP	PT, FHA, PRN, FIM2/3	d, T	Linked[a] to Daptacel and immunologic NI to Daptacel
Boostrix	GSK	PT, FHA, PRN	d, T	Linked[a] to Infanrix and immunologic NI to Infanrix

Source: FDA.

Abbreviations: D and d=diphtheria toxoid (d, 2-2.5 Lf; D, 15-25 Lf); DTaP=diphtheria and tetanus toxoids and acellular pertussis vaccine; FHA=filamentous hemagglutinin; FIM=fimbriae types 2 and 3; GSK=GlaxoSmithKline Biologicals; HbsAg=hepatitis B surface antigen; IPV=inactivated poliovirus types 1, 2, and 3; OMP=outer membrane protein complex of *Neisseria meningitidis*; PRN=pertactin; PRP=*Haemophilus influenza* type B capsular polysaccharide polyribosyl-ribitol-phosphate; PT=inactivated pertussis toxin; SP=Sanofi Pasteur Limited; T=tetanus toxoid; Tdap=Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed.

a. The listed U.S.-licensed DTaP-based combination vaccines are either “linked to Infanrix” or “linked to Daptacel” because they contain the same pertussis antigens produced by the same manufacturer and process for the cited DTaP-only vaccine for which clinical efficacy against pertussis disease endpoints was demonstrated.

b. Vaxelis is manufactured by SP and is a product of MSP Vaccine Company, a joint venture of Merck and Sanofi Pasteur.

The U.S.-licensed DTaP-only vaccines (i.e., Infanrix and Daptacel) are approved for active immunization against diphtheria, tetanus, and pertussis as a five-dose series in infants and children 6 weeks through 6 years of age. They are administered intramuscularly at approximately 2, 4, and 6 months of age, at 15–20 months of age, and at 4–6 years of age. The pertussis antigens contained in Infanrix are PT, FHA, and PRN, and the pertussis antigens contained in Daptacel are PT, FHA, PRN, and FIM types 2 and 3. However, the role of each pertussis component in the pathogenesis of and immunity to pertussis is not clearly defined, and there is no well-established serological correlate of protection for pertussis.

Infanrix
Efficacy against pertussis following the first three doses of Infanrix was demonstrated in two clinical trials: a randomized, double-blind, active diphtheria and tetanus toxoids (DT)-controlled study conducted in Italy that assessed absolute protective vaccine efficacy and a prospective efficacy trial in Germany that employed a household contact study design. The Italian study demonstrated that protection against pertussis was sustained to 6 years of age, and the German study showed no indication of waning protection up to the time of the booster vaccination in the second year of life. In addition, the immune responses to each pertussis antigen contained in Infanrix were evaluated at one month after the third dose in these two efficacy trials and in a U.S. study. The antibody responses to the three pertussis antigens (PT, FHA, and PRN) in the U.S. population were similar to those achieved in the two populations in which efficacy of Infanrix was demonstrated.

Daptacel
Protective efficacy against pertussis following the first three doses of Daptacel was demonstrated in a randomized, double-blind, placebo-controlled efficacy trial conducted in Sweden (the Sweden I Efficacy Trial, Olin, 1991) in which sustained protection against pertussis was demonstrated for the 2-year follow-up period. To assess the antibody responses to the pertussis antigens contained in Daptacel in the U.S. population, the U.S. Bridging Study was conducted. In this study, two lots of Daptacel, including the lot used in the Sweden I Efficacy Trial, were administered to U.S. infants, and antibody responses in U.S. infants following three doses of Daptacel were compared to those from a subset of infants enrolled in the Sweden I Efficacy Trial. Antibody responses to all the pertussis antigens, except for those to PRN, were similar. Separate U.S. and Canadian studies in which children received four doses of Daptacel demonstrated antibody responses to all the pertussis antigens contained in Daptacel, and at least as high as those seen in the Swedish infants after three doses. Based on these data, the antibody responses to the four pertussis antigens contained in Daptacel in North American children following four doses were similar to those achieved in Swedish children in whom efficacy was demonstrated after three doses.

The U.S.-licensed DTaP-based combination vaccines listed in Table 1 are either “linked to Infanrix” or “linked to Daptacel” because they contain the same pertussis antigens produced by the same manufacturer and process for the cited DTaP-only vaccine for which clinical efficacy against pertussis disease endpoints was demonstrated, as indicated in footnote a to Table 1 above.

Section 4: Effectiveness of the Acellular Pertussis Component of DTaP-Based Combination Vaccines and Tdap Vaccines
Bridging from licensed DTaP-only vaccines to DTaP-based combination vaccines
Pertussis efficacy data from the relevant linked DTaP vaccine (i.e., Daptacel or Infanrix), along with data from comparative immunogenicity analyses demonstrating noninferiority of antibody responses to each of the pertussis antigens in recipients of the DTaP-based combination vaccine to those in recipients of the control DTaP vaccine, support the effectiveness of the pertussis component of the DTaP-based combination vaccines.

Bridging from licensed pediatric DTaP vaccines to adolescent/adult Tdap booster
To address the increase of reported pertussis among U.S. adolescents and adults that began in the 1980s, two Tdap booster vaccines (i.e., Adacel and Boostrix) were developed.

The acellular pertussis components of each vaccine were the same as those of the respective licensed DTaP vaccine from each manufacturer. Infant pertussis efficacy data from the relevant linked DTaP vaccine supported the effectiveness of the pertussis component of the respective Tdap vaccine. Antibody responses to each of the pertussis antigens in recipients of the Tdap vaccines were compared to antibody responses of the infants who received a primary series of the (linked) DTaP vaccine in the pertussis efficacy trials described above. In addition, based on prespecified definitions and success criteria, the proportion of Tdap-vaccinated adolescents and adults who demonstrated a booster response to each pertussis antigen was also determined. These immunogenicity data, along with the pertussis efficacy data on the relevant linked DTaP vaccine, supported the effectiveness of the pertussis components of the Tdap vaccines.

Challenges to bridging from licensed acellular pertussis vaccines to new pertussis vaccines

Licensure of the DTaP-based combination vaccines and Tdap vaccines was supported by immunobridging to one of the DTaP vaccines (Daptacel or Infanrix) for which pertussis efficacy was demonstrated. However, this was only possible because each of these combination and Tdap vaccines contained the same pertussis antigens produced by the same manufacturer and using the same process as either Daptacel or Infanrix. Therefore, the overall anti-pertussis immune responses induced by the DTaP, DTaP-based combination, and Tdap vaccine formulations were considered comparable, not only in quantity, but also in quality, and were expected to provide protection via the same mechanism. Manufacturers are currently developing new pertussis vaccines to address the decreased durability of protection and reduced prevention of colonization observed following vaccination with licensed aP-containing vaccines relative to the wP-containing vaccines and following natural infection. However, these new pertussis vaccines use different manufacturing processes compared to the licensed products for which clinical efficacy data exist. Furthermore, without an established immunologic marker that predicts protection for pertussis, immunobridging to Daptacel or Infanrix cannot be used to demonstrate the effectiveness of new pertussis vaccines.

Section 5: New Pertussis Vaccine Development

The recognition that aP-containing vaccines fail to prevent colonization and transmission has increased interest in developing vaccines that combine the safety profile and protection against disease conferred by aP-containing vaccines with protection against colonization and enhanced duration of immunity. Several strategies have been proposed to generate vaccines that protect against colonization and disease. These include: 1) aP vaccines that use adjuvants that induce more optimal $T_H1/T_H2/T_H17$ responses and/or include additional antigens to target the bacterial cell on the mucosal surface; 2) wP vaccines engineered for reduced reactogenicity; 3) vaccines based on outer membrane vesicles or other novel platforms; and 4) live-attenuated vaccines.

Alternative vaccination routes, such as intranasal and cutaneous immunization, are also being explored. The restriction of *B. pertussis* to the airway mucosa suggests that vaccines that induce mucosal immunity may more effectively induce responses that prevent colonization, transmission, and disease.

Vaccines employing all these strategies are in various stages of development.

Section 6: Pertussis Controlled Human Infection Models

A significant challenge to the introduction of new pertussis vaccines lies in developing substantial evidence of effectiveness. The aP-containing vaccines currently in use were shown to protect against disease in prospective, clinical endpoint efficacy studies conducted in populations with high incidence of pertussis. Comparable studies would be difficult if not impossible to conduct today. Although the incidence of pertussis is increasing 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 in humans is compounded by the fact that pertussis incidence is cyclical, with peaks of disease alternating with troughs, and different regions experiencing peaks and troughs of pertussis incidence in different years. The baboon model of pertussis provides a useful tool for evaluating the ability of new antigens combined with new adjuvants to protect against colonization and disease before their study in human clinical trials. In addition, the baboon model can provide an important demonstration of the ability of new vaccines to induce responses that protect against severe disease.

Multiple alternative approaches will likely be required to provide substantial evidence of effectiveness of new vaccines. One component of such an approach may be the use of a pertussis controlled human infection model (CHIM). A regulatory precedent for this approach can be found in FDA's licensure in 2016 of Vaxchora for active immunization against disease caused by *Vibrio cholerae* serogroup O1 for persons 2 through 64 years of age traveling to cholera-affected areas. The primary evidence supporting the effectiveness of Vaxchora to prevent cholera in individuals traveling to cholera-affected areas was derived from human challenge studies.

There are significant challenges in developing a pertussis CHIM. Pertussis is transmitted by airborne respiratory droplets; therefore, appropriate containment facilities and/or study design may be required to prevent transmission to contacts within the clinical center, and effective antibiotic treatment may be required to ensure clearance of pertussis prior to discharge at the end of the study, to prevent accidental transmission to participants' 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. This "point of no return" with respect to rescue therapy and the potential for severe disease may limit a *B. pertussis* CHIM to the study of establishment of infection and evaluation of early, mild disease symptoms.

Robert Read and colleagues at Southampton University described the development of a pertussis CHIM using fully virulent *B. pertussis* (de Graaf et al., 2020). Healthy adult participants were inoculated intranasally with escalating doses of *B. pertussis* strain B1917, a clinical isolate representative of strains currently circulating in Europe. Following inoculation, participants were followed in an in-patient setting for disease symptoms, colonization, and shedding of *B. pertussis*. The authors demonstrated that human participants can be safely and asymptomatically colonized with *B. pertussis* and defined a challenge dose that resulted in colonization of 80% of participants. Non-specific symptoms were reported in a minority of participants. Azithromycin eradicated colonization within 48 hours in 88% of colonized individuals. The remaining 12% had cleared by the time of the

next sample collection seven days following azithromycin treatment. These results demonstrated that *B. pertussis* colonization can be deliberately induced in a controlled manner, leading to a systemic immune response without causing pertussis symptoms.

Scott Halperin and colleagues at Dalhousie University, using a dose escalation design, challenged healthy adults with *B. pertussis* strain D420, with the goal of identifying a dose that elicits mild catarrhal symptoms in 70–90% of participants. Half-log doses above and below were tested for confirmation. A dose of 10^7 colony-forming units (CFU) resulted in colonization of 86% of participants and mild symptoms in 73% of participants.

The results of these studies suggest that a symptomatic pertussis CHIM in adults may be reasonably safe and achievable.

CHIMs can be used safely and ethically for diseases that are self-limiting in healthy individuals or diseases for which a rescue therapy is available that can be used to quickly bring the participants back to good health (Merkel and Halperin, 2014). These models offer significant advantages over observational studies because they can be performed in a controlled setting involving subjects with known baseline immune status. The timing of the exposure is known, and the properties of the bacterial strain can be controlled. Because all subjects are exposed, results can be obtained with a smaller number of volunteers than studies that require the accumulation of cases as the result of natural exposure in the community. This is particularly true for pertussis, which occurs at a low frequency in the population, primarily in sporadic outbreaks that cannot be accurately predicted. Possible limitations of pertussis CHIMs include the reliability of modeling protection against infection by natural transmission using artificial inoculation with culture-grown bacteria and the use of early, non-specific symptoms as endpoints for evaluating severe disease.

Whether pertussis CHIMs in previously aP-vaccinated individuals accurately and robustly model pertussis colonization and disease following natural exposure and can be used to obtain human efficacy data to support the effectiveness of new pertussis vaccines will be discussed at this meeting of the Vaccines and Related Biological Products Advisory Committee. We ask the committee to discuss the proposed CHIM approach for evaluation of candidate pertussis vaccines.

Section 7: Discussion Questions for VRBPAC

1. Controlled human infection model – *Disease End point*

    a. Do *B. pertussis* controlled human infection models, in their current stage of development, produce signs and symptoms of disease that accurately and reliably reflect human disease caused by natural infection with *B. pertussis*?

    b. If yes, are *B. pertussis* controlled human infection models, in their current stage of development, sufficiently robust models of natural infection and disease to provide the primary human data to support effectiveness of new pertussis vaccines for booster vaccination of adults?

2. Colonization Model - *Colonization Endpoint*

    a. Can prevention of *B. pertussis* colonization be considered a surrogate endpoint that is reasonably likely to predict clinical benefit, specifically prevention of pertussis disease?

    b. If yes, do *B. pertussis* controlled human infection models of colonization, in their current stage of development, accurately and reliably reflect colonization following natural *B. pertussis* exposure?

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