



Non-primate animal models for pertussis: back to the drawing board?

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Abstract

Despite considerable progress in the understanding of clinical pertussis, the contemporary emergence of antimicrobial resistance for *Bordetella pertussis* and an evolution of concerns with acellular component vaccination have both sparked a renewed interest. Although simian models of infection best correlate with the observed attributes of human infection, several animal models have been used for decades and have positively contributed in many ways to the related science. Nevertheless, there is yet the lack of a reliable small animal model system that mimics the combination of infection genesis, variable upper and lower respiratory infection, systemic effects, infection resolution, and vaccine responses. This narrative review examines the history and attributes of non-primate animal models for pertussis and places context with the current use and needs. Emerging from the latter is the necessity for further such study to better create the optimal model of infection and vaccination with use of current molecular tools and a broader range of animal systems.

Key points

- *Currently used and past non-primate animal models of B. pertussis infection often have unique and focused applications.*
- *A non-primate animal model that consistently mimics human pertussis for the majority of key infection characteristics is lacking.*
- *There remains ample opportunity for an improved non-primate animal model of pertussis with the use of current molecular biology tools and with further exploration of species not previously considered.*

Keywords *Bordetella pertussis* · Pathogenesis · Model · Infection · Colonization

Introduction

The impact of *Bordetella pertussis* for human infection continues to be substantial. As succinctly outlined by Cherry (2019) in his contemporary review, the impact of vaccines historically has been considerable, but there are yet many limitations and continuing issues that prevail. The limitations of current vaccines are compounded by the regional emergence of *Bordetella pertussis* resistance to the commonly used macrolides (Cimolai 2020a, 2020b). Considerable advances in the detection, treatment, and prevention of pertussis are laudable. The persistence of this infection worldwide and the current burden of continuing disease

invite reconsiderations, however, for how treatment and prevention may yet be improved. One key issue that has emerged is the selection of *B. pertussis* mutants with current acellular vaccines (Hegerle and Guiso 2014; Vodzak et al. 2017; Barkoff and He 2019; Ma et al. 2021). Bouchez et al. (2021) have followed such change longitudinally over two decades and have placed emphasis on the changes in pertactin. Genomic analyses of *B. pertussis* longitudinally illustrate an adaptive pattern of persistence (Bart et al. 2014).

Animal models have served various aspects of pertussis research for over a century (Elahi et al. 2007; van der Ark et al. 2012; WHO 2017). There is no doubt that non-human primate models come closest to reproducing the early and late phases of pertussis and prove worthy for analyses of both the basic immunology of infection and vaccination (Sauer and Hambrecht 1929; Shibley 1934; Culotta et al. 1935; Huang et al. 1962; Stanbridge and Preston 1974; Sato and Sato 1988; Warfel et al. 2012; Warfel and Merkel 2014; Pinto and Merkel 2017; Jiang et al. 2021). Regardless of the latter contributions and many thereafter, it is yet desirable to have an exemplary

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non-primate animal model that is capable of being used in larger groups and which obviates the complexity and other limitations of using non-human primates. Many such models have been utilized since the discovery of *Bordetella pertussis*, and several have led to major contributions in the understanding of pathogenesis, pathology, and vaccination (Belcher et al. 2021). Despite any such advances, all of the existing non-primate animal models have their unique potential benefits and weaknesses (Elahi et al. 2007; van der Ark et al. 2012; Melvin et al. 2014; Mills and Gerdtz 2014). As for animal model research with other microbial pathogens, various aspects of study may be better suited to different models for the same micro-organism (Herati and Wherry 2018).

In this narrative review, past non-primate animal models for pertussis are reviewed for their utility and limitations. The applications of the latter are placed in context of contemporary research but with due regard for the valuable historic research which has set the standard. It is proposed that improved or alternate laboratory models for pertussis are yet possible and deserve a renewed interest and investigation.

Attributes of a good model for pertussis

The clinical, microbiological, and pathological characteristics of human pertussis have been aptly characterized and generally accepted, but it is inevitable that there is more to learn (Cherry and Heininger 2019; Belcher et al. 2021). The essence of a good model for pertussis is to capture these features starting with the inaugural infectivity of the upper respiratory tract. Innate immunity or acquired mucosal immunity can both have some role in modifying the potential for the bacterium to initiate infection, and it would be expected that not all respiratory contacts with *B. pertussis* will necessarily lead to infection. For some aspects of consistency, it is useful to have a homogeneous model where, for example, all or most challenged animals have uniform progression and clinical manifestations of infection. Yet, the reality of human pertussis is that, although highly infectious among non-immune subjects, infection penetrance is over a spectrum from no infection to mainly upper and mid-respiratory infection to classical pertussis to advanced primary or secondary pneumonia (Craig et al. 2020). Some degree of this variability would make an ideal permissive animal model more similar to human disease although it could also increase the size of studies that may be required to achieve a desirable statistical power. Necessarily related to the latter is the ability to induce infection through simple intranasal inoculation or low-dose aerosol and with a low mortality rate. An ideal model should lend itself to the ability for infection to spread between animals. Long-term pertussis carriage has not appeared to be a confirmed feature of natural human infection, but recent reviews of asymptomatic transmission raise concern for both short-term and potentially long-term carriage (Althouse and

Scarpino 2015; Craig et al. 2020). Further understanding of the latter is warranted given how genetic amplification technology diagnostics determine that positive tests extinguish for an individual in the matter of 2–6 weeks. Our understanding of the latter is further complicated by the finding of avirulent *B. pertussis* during the course of infection and the relatively asymptomatic disease that may be found in studies of controlled human inoculations (Karataev et al. 2016; de Graaf et al. 2020). In vitro findings of persistence in human macrophages may give some impetus to further studies (Valdez et al. 2021).

The establishment of infection should not have to rely on co-administered non-*B. pertussis* materials or adjuvants. A complicating role of such co-administered materials, although at times being capable of assessment in controls, may detract from the natural course of infection that would otherwise be seen in humans.

Although severe human disease including death is most commonly associated with very young pediatric ages, pertussis clearly affects all age groups (Paddock et al. 2008; Sawal et al. 2009). Studying infection among both young and adult animals would therefore be desirable. Age-stratification study is of greater relevance now that acellular pertussis vaccines have generally shifted the age group for pertussis upwards. Early disease should be predominantly one of the upper and/or mid-respiratory tract analogous to the human catarrhal phase of infection. These regions of the respiratory tract should be amenable to sampling for both bacterium and immunological features. The model should be lend itself to study of attachment and ciliostasis, albeit the ciliated epithelium should remain relatively intact. Evidence of local immune stimulation and immune cell recruitment and the evolution of mucosal immunity would be desirable. An integrated and second phase of disease analogous to the human pertussis phase would be another goal. The latter could include progression to advanced lower respiratory tract infection (Table 1). The entire spectrum of the infection may or may not be complicated by secondary other bacterial infections from usual respiratory flora. The evolution of disease should ideally mimic other attributes of human pertussis including leukocytosis (including lymphocytosis) and various related physiological events (e.g., hyperinsulinemia, histamine sensitivity). Variability in the latter clinical presentations should be inherent. Live bacterium should be detectable during most of the early phases of infection and for some late phases of infection as well.

The animal model should be amenable to the study of acquired immunity, passive immunity, and vaccine-related immunity. The model should be open to the study of antimicrobial therapy whether for prevention or the treatment of active infection. Whether for the trachea or lung, a standardized pathology scoring system should be established to facilitate both the assessment of disease and its comparisons to quantification through bacterial

Table 1 Key findings in the human pathology of advanced pertussis

A	Ciliostasis
B	Descending respiratory involvement from upper to lowest airways
C	Airway secretions
D	Necrotizing bronchitis and bronchiolitis
E	Bronchopneumonia
F	Intra-alveolar hemorrhage
G	Alveolar epithelial necrosis and apoptosis
H	Fibrinous edema
I	Perivascular leucocyte aggregation
J	Perilymphatic leucocyte aggregation
K	Extracellular bacteria close to airway cilia
L	Intracellular bacteria in macrophages
M	Peripheral leukocytosis
N	Relative immune depletion of peripheral non-respiratory tissue, e.g., thymus, spleen, lymph nodes in severe disease
O	Pulmonary hypertension in prolonged disease
P	Possible co-infections—variable for viruses, bacteria, and fungi

counts analogous to other bacterial infection model systems (Cimolai et al. 1992, 1995, 1996a). To ensure routine infection, consistency often requires high inocula with the resultant increase in more severe lower respiratory infection than is seen in the spectrum of human infection.

Outside of human and primate infections, does any such ideal non-primate animal model exist? (Table 2).

Non-primate animal models of pertussis

Chick embryo

Chick embryo models of infection were initially suited to facilitate studies of virus infections given then the inability

to cultivate those pathogens during times of early discovery. The same model was then transposed into assessments for bacterial infections including pertussis. Early such modeling was able to induce chorioallantoic infections (Gallavan and Goodpasture 1937). Infection was better achieved through yolk sac inoculation rather than using the allantoic cavity (Shaffer and Shaffer 1946). A proportion of chick embryos had evidence of bronchopneumonic changes which were also associated with histopathological evidence of respiratory tract desquamation. The bacterium was shown to be associated with ciliated cells in the respiratory tracts. For studies where lethal doses would be utilized, e.g., antimicrobial studies, as little as a few viable bacteria could constitute an LD₅₀ (Jackson et al. 1950a, 1950b). Much higher doses (10³–10⁵), however, were utilized for day 7 embryonated eggs, and the latter would achieve at or near 100% mortality by 10 days.

This model was not thereafter widely used. Tuomanen et al. (1983) subsequently assessed the attachment of the bacterium to ciliated epithelial cells acquired from bronchial brushings. They found no attachment to ciliated cells from chickens versus variable attachment to ciliated cells acquired from several other animal species. Overall, the use of the chick embryo model would be very limited in scope compared to the desired attributes that would parallel human infection. Such limitation would not however rule out the potential for other avian species or birds of older age to act as models for future assessments. Parallels with avian and human psittacosis and some respiratory viral infections prompt an open door in this regard.

Leporine

Rabbit infection models were among the first assessed historically. In limited study, early investigators found that rabbits showed emaciation after exposure but no clinical

Table 2 Contemporary and past utility for non-primate animal models of pertussis. (NSD = not sufficiently detailed; Other illness = non-respiratory manifestations)

Model system	Contemporary use	Respiratory illness	Other illness	Respiratory pathology	Prolonged colonization	Transmission studies	Antimicrobial assessments	Vaccine potency	Immunological studies
<i>Chick embryo</i>	No	No	No	Variable	NSD	No	Yes	No	No
<i>Leporine</i>	No	Limited	NSD	Yes	Yes	No	No	No	No
<i>Guinea pig</i>	No	NSD	NSD	NSD	NSD	No	No	No	No
<i>Hamster</i>	No	NSD	NSD	NSD	NSD	No	No	No	No
<i>Ferret</i>	No	Yes	NSD	NSD	No	Yes	No	No	No
<i>Canine</i>	No	Yes	Yes	NSD	NSD	Yes, in puppies	No	No	No
<i>Porcine</i>	Yes	Yes	Yes	Yes	No	No	No	No	Yes
<i>Rat</i>	Yes	Yes	Yes	Yes	No	NSD	No	No	Yes
<i>Mouse</i>	Yes	Variable	Yes	Yes	Yes	Yes, in young	Yes	Yes	Yes

illness including cough (Mallory et al. 1913). Viable bacterium could be recultured. Soon after, other investigators claimed that young adult rabbits could be given the live bacterium intratracheally which would induce an interstitial mononuclear pneumonia (Sprunt et al. 1935). In that context, viable bacterium could only be recultured during the first 2 days post-infection. In fully adult rabbits, bacterium given intratracheally resulted in lymphocytosis and lung lesions (Sprunt et al. 1938). Heat-killed *B. pertussis* given in the same manner was associated with reduced pulmonary changes. Using New Zealand white rabbits, a 50% infectious dose of 10^4 CFU led to prolonged animal colonization for at least 2 months during which time *B. pertussis* could be recultured from the nares, tonsils, and lung (Ashworth et al. 1982). In the latter study, bacterial persistence inversely correlated with the development of nasal IgA that recognized the filamentous hemagglutinin. Preston et al. (1980) intranasally infected Dutch rabbits ranging in age from 3 months to a year with a large dose (5×10^{10}). Rabbits develop catarrh but no consistent cough. Nasal colonization could persist for up to 10 months. A serotype change in the bacterium could be seen for some prolonged colonizations, but previous exposure gave serotype-specific protection.

Weiss and Hewlett (1986) were led to conclude that rabbits did not show sufficient disease manifestations. Pittman (1984) also concurred with the latter and acknowledged that animals remain colonized with the bacterium commonly for an overly prolonged time period. Contemporary leporine studies have not been published. Of note, Tuomanen et al. (1983) showed some attachment of the bacterium to ciliated rabbit cells in vitro.

Intravenous injection of pertussis antigen in rabbits often leads to demise within a few days, and this effect is consistent with similar end-results in other animals inoculated with high doses of inactivated bacterium either intravenously or intraperitoneally (Hink and Johnson 1947). Historically, the latter effects have been largely attributed to endotoxin.

Guinea pig

Very limited published work on a guinea pig model is available (Culotta et al. 1938a, b). Large doses of bacterium, whether viable or not, given either subcutaneously or intraperitoneally led to animal death. Respiratory challenge and dose-titration studies are lacking. Given the potential active endotoxin (lipopolysaccharide, or lipooligosaccharide (LOS) as known for *B. pertussis*) in the bacterium's cell membrane, physiological effects including animal demise would be expected in a dose-dependent fashion, perhaps explaining the toxicity associated with large dosing. A revisitation of this animal model with intranasal or aerosol challenge would be welcome.

Although species distinct, hamsters are often comparable to guinea pigs for handling and experimental approaches. While live animal infection modeling is not detailed, several studies have examined the association of bacterium with hamster tracheal organ or tissue culture samples (Collier et al. 1977; Muse et al. 1977; Goldman et al. 1982; Tuomanen et al. 1983). Of note, phase I *B. pertussis* attaches to ciliated epithelial cells and also causes cell injury. Ciliated cells are lost from the epithelium in a time-dependent manner, but non-ciliated cells seemed structurally unaffected. Given the use of the hamster model for various viral and mycoplasma infections, and given the success in demonstrating pathology for hamster tracheal organ culture, intranasal or aerosol experiments are warranted.

Ferret

Very few studies have assessed infections among ferrets (Culotta et al. 1938a, 1938b). Large inocula were required to cause infection given either intranasal or intratracheal in a dose-dependent fashion. A clinical disease was said to include fever, tachypnea, weight loss, and polymorphonuclear or lymphocytic leukocytosis. Nasopharyngeal cultures were negative as early as day five, and post-vaccination immunity could not be achieved. Infection could not be transmitted from animal to animal. Pulmonary disease however was also caused by heat-killed bacterium.

Canine

Intratracheal infection of canines was one of the first animal models attempted (Mallory et al. 1913). Puppies were infected to mimic human infant infections. The animals died within 2–6 weeks, and *B. pertussis* could be recultured after initial challenge. Inaba and Inamori (1934) exposed puppies to an oral spray of live bacterium. It was found that puppies could transmit infection among themselves in a closed confine. The animals developed a cough and a leukocytosis/lymphocytosis. The canine model was not revisited thereafter it appears except for use in the study of some physiological parameters of pertussis (Nakamura et al. 1984). One of the major potential complicating issues could be the natural occurrence of *Bordetella bronchiseptica* as a cause of canine cough. It would be difficult to retrospectively gauge the relevance of the latter in the experiments of Mallory et al. (1913). It would therefore also be imperative to have *B. bronchiseptica*-free canine experimental colonies if this model were to be further assessed. The capability to have animals infect one another is not consistently seen in other non-primate animal models.

Porcine

Few have made use of a young porcine model for pertussis (Elahi et al. 2005, 2006a, 2006b; Foreman-Wykert and Miller 2005; Mills and Gerdtz 2014).

Pigs too can be infected with *B. bronchiseptica*, and the latter should be screened for prior to pertussis studies. Porcine tissue explants with human airway cells have been used to create a more simple model (Kessie et al. 2021).

Piglets are easily infected deep into the bronchial canal but with a high dose approximating 10^8 – 10^9 live bacteria. These experiments commonly used animals that were in the range of days 3–5 post-birth. Pigs which reach 4–5 weeks of age are resistant to infection. Infected piglets develop rhinorrhea, cough, and evidence of bronchopneumonia; manifestations are seen early. Other manifestations akin to human pertussis such as some physiological changes are also observed. The bacterium may be recultured from the lung and has an associated histopathology. In piglets that have been weaned and up to 25–30 days of age, an endotracheal delivery of bacterium-embedded beads (as for the rat lung model) can also induce pathology, although no such vehicle with bacterium causes disease among older pigs. Transfer of maternal antibody during lactation and feeding of piglets has allowed for some study of passive mucosal immunity. The use of a unique pig model to study pertussis vaccinology has been proposed (Vaure et al. 2021).

Murine

Rat

Several aspects of the rat model for pertussis proved valuable which led to a considerable study of pathogenesis and vaccination, but yet the mouse model seems to have both historically and contemporaneously dominated presumably due to the ease of use and the considerable knowledge of mouse immunology.

Early attempts to create a rat model are credited to Hornibrook and Ashburn (1939). With either albino Wistar or hooded rats, doses less than those used in the mouse models induced disease. Intranasal infection led to considerable and variably located lung disease. A cough was observed. Lethal doses were defined. *B. pertussis* could be recovered from the respiratory tract. There was an early peripheral polymorphonuclear response during the pneumonia and an accompanying lymphocytosis. The tracheal reaction was minimal. Despite the latter, Pittman (1984) later shared the experience that respiratory colonization was poorly reproducible. Csaba et al. (1969) had also used the Wistar rat for studies of histamine metabolism after intraperitoneal pertussis vaccine exposure. Others studied metabolic effects of carbohydrate metabolism after pertussis sensitization of rats (Gulbenkian

et al. 1968; Sumi and Ui 1975; Ainapure et al. 1977; Yajima et al. 1978).

A return to a similar model did not occur until the work of Woods et al. (1989). Using adult Sprague–Dawley rats, infection was accomplished with the intratracheal inoculation of infectious bacterium in the milieu of agar-mineral oil beads. Presence of viable bacterium was determined variably over 3 or more weeks. Bronchial disease and pneumonia progressed after several weeks which was accompanied by increased white cells and lymphocytosis. Physiological changes of hypoglycemia and cough were observed. While lacking several features of human disease, consistency for a disease that ultimately resulted in clinical resolution was seemingly made.

Variations on the above theme with adult Sprague–Dawley rats were soon achieved (Wardlaw et al. 1993; Hall et al. 1994; Parton et al. 1994; Hall et al. 1998, 1999). Emphasis was placed on the non-lethal nature of infection that was clinically accompanied by a measureable cough. Clinical illness was associated with a peripheral leukocytosis that maximized by approximately 10 days, and the latter coincided with the degree of lung pathology. Both intranasal and intratracheal (10^8 bacteria) infection could be achieved with live bacterium in agarose beads with or without added carrageenan. Viable *B. pertussis* could be recovered for nearly 2 weeks. Several very relevant observations on pathogenesis, immunology, and vaccinology of pertussis were made by this same research group. Of note, the investigators conceded that the use of a similar inoculum was overly toxic for young rats, thus not strictly reproducing the model of Hornibrook and Ashburn (1939). A resurgence of interest in the rat model has been recently published (Hall et al. 2021a, 2021b). Previous attributes have been repeated, and bacterial strain variability was shown.

Mouse

By far, mouse models for pertussis have been preferred albeit with considerable variation. For mouse strains so used in pertussis research, the designations have included Anglin/NIH, BALB/c, BALB/cAnNcR, BALB/cAnNCr1-Cmd, BALB/c By1, BALB/c J, BALB/c OlaHsd, C57BL/6, C57B16/J, CD1, CFI, CFW, DDY, C3H/HeJ, HAM/ISR, ICR, NIH, NiHiH (Sw), N:NIH, N:NIH/RIV, P7, SCID, SLC/ICR, Swiss, and white albino mice. Some of the latter may be common derivatives. In addition, various genetically engineered knockout mice have been utilized (Skerry et al. 2009; Dubois et al. 2021). Few studies have comparatively assessed these murine variants, and there is no single mouse strain which has been uniformly adopted (Andersen 1952; Bradford and Day 1945; Standfast 1951; Andersen and Bentzon 1958b; Pittman et al. 1980; Oda et al. 1983; Mills et al. 1993, 1998; Mahon et al. 1997; Leef et al. 2000; Banus et al.

2006, 2007b). Banus et al. (2005, 2007b) illustrate how variations among mouse breeds are more likely related to intrinsic variation of infection susceptibility loci that pre-exist infection rather than gene expression variation that occurs after the onset of infection. Just as important, however, is the potential for variability of these models to be dependent on the strain of bacterium that is utilized (Bradford and Day 1945; Kendrick et al. 1949; Standfast 1951; Andersen 1952; Andersen and Bentzon 1958b; Carter and Preston 1981). Whereas many studies have used murine models for infection per se, others have used variations on the theme to assess vaccine standardization or toxicity (Andersen 1952; Andersen and Bentzon 1958b; Wardlaw and Jakus 1968; Manclark et al. 1975; Cameron 1977; Bannatyne and Cheung 1981; Robinson et al. 1985; Morgeaux et al. 2020; Hoonakker 2021). Most contemporary vaccine studies have also used murine models (Solans et al. 2018; Debrie et al. 2019; Zurita et al. 2019).

For mouse infections, there are several aspects of dose-responsiveness in model systems. There is an incremental quantitative transition from sublethal to lethal dosing. With intracerebral inoculation, there is a dose-dependency for time to death and animal mortality rate (Hegarty et al. 1945; Andersen and Bentzon 1958a). For intranasal or aerosol exposure, there is a dose-related increase in the infection rate, and infection can vary depending on the volume of inoculum (Halperin et al. 1988). The death rate is dose related with aerosol challenge (Sato et al. 1980). Viable counts of bacteria in the animal lung are also higher in a dose-dependent fashion (Proom 1947; Fisher 1958; Sato and Sato 1988). The death rate among mice increases, and the time to death decreases also proportionate to the increasing inoculum (Hegarty et al. 1945; Proom 1947; Bradford and Day 1949; Standfast 1951, 1958; Fisher 1958; Gastal 1958). Furthermore, there is an age-dependent response (Burnet and Timmins 1937; Culotta et al. 1938a; Standfast 1951; Pittman et al. 1980; Sato et al. 1980; Standfast 1951). The latter phenomenon would in part potentially mimic the age-dependent susceptibility in humans. Pertussis as a cause of death is very uncommon in the contemporary era despite the worldwide prevalence of disease and despite a predilection for younger age groups. Most studies have used mice of ages 2–6 weeks. Neonatal murine studies are uncommon.

Intravenous inoculation of live bacterium did not give consistent results and was uncommonly used (Brownlee and Bushby 1948; Andersen 1952; Morse and Riester 1967). High doses of bacterium given intravenously are cleared very quickly from the bloodstream and may not be detected within a few days. Such administration could nevertheless induce a leukocytosis. Given intraperitoneally, high doses ($\geq 10^9$) led to animal demise (Proom 1947; Brownlee and Bushby 1948; Kendrick et al. 1949; Andersen 1952; Geller and Pittman 1973; Institute of Medicine Committee 1991).

The latter was ascribed to endotoxin effects. Lower doses were inconsistent for producing infection. Intraperitoneal inoculation could result in bacteremia immediately after, but such a finding was not thought to imply bacterial replication. The quantitation of bacteremia was directly correlated with the peritoneal dose, and bacteremia was short-lived if animals survived akin to the rapid clearance of bacterium with intravenous injection. Toxic effects for either intravenous or peritoneal administration of either live bacterium or early whole cell vaccines must be weighed in the context of pre-existing bacterial lipopolysaccharide toxicity (Geurtsen et al. 2007).

The intracerebral model of infection historically had its merits but evidently had little to do with respiratory infection. One key feature linking the two routes was the presence of ciliated cells in both the central nervous system and the respiratory tract (Berenbaum et al. 1960; Hopewell et al. 1972). The intracerebral model was used for assessing vaccine potency (Kendrick et al. 1947, 1949; Andersen 1952; Cooper 1952; Masry 1952; Andersen and Bentzon 1958a; Fisher 1958; Wardlaw and Jakus 1968; Oda et al. 1984; Robinson et al. 1985; Cameron 1988; Sato and Sato 1988). Infection in this model is confined to the cerebrospinal fluid and contiguous membranes without the direct invasion of other brain tissue (Kendrick et al. 1947; Berenbaum et al. 1960). The disease and mortality onset occurred after an incubation period and with a progressive disease course. The bacterial strain chosen for such studies is crucial as Preston and Evans (1963) contended that even fresh isolates from human infection did not often function well in the intracerebral model. Kendrick et al. (1947), Andersen (1952), and Andersen and Bentzon (1958a) had also found the same. Typically the *B. pertussis* strain 18,323 (variably designated 18–323; NCTC 10,739 or ATCC 9797) was used, but it is unclear how passages and variations of that strain may have compared to contemporary isolates; some similarity to *B. bronchiseptica* has been suggested, and the nature of the bacterium gives the belief that it is an outlier in *B. pertussis* taxonomy. The model nevertheless lent itself to various observations on sero-specificity. Intracerebral doses of 100 colony-forming units or less usually allowed for mouse survival, whereas doses higher and up to 10^5 bacteria were associated with mortality (Kendrick et al. 1947, 1949). Bannatyne and Cheung (1981) estimated an LD_{50} of approximately 10^3 bacteria with strain 18,353 (presumably 18,323—NCTC 10,739; ATCC 9797). The LD_{50} is very much dependent on the strain used (Andersen and Bentzon 1958a). Passage of live bacteria from the brain of one mouse to another was not uncommonly associated with phase shifts according to bacterial colony morphology on solid recovery growth media. Such change, however, was not the same as that seen with agglutigen shifts among human isolates (Carter and Preston 1981). For the purpose of assessing

acellular vaccines, the intracerebral challenge route has been of limited value. The protective effects of passive immunity were assessed in this model (Holt 1972). It had also been used briefly and successfully to assess antimicrobial therapy for pertussis (Hegarty et al. 1945; Brownlee and Bushby 1948; Bell et al. 1949).

Most studies have utilized the intranasal challenge model, but there has nevertheless been considerable variability in several regards. These models used sublethal or lethal per-nasal dosing. For sublethal challenge, viable bacterial counts of 10^3 – 10^6 were applied usually in a single administration. For example, the use of 5×10^3 – 5×10^5 inocula in one study led to an approximately 3–5% subsequent frequency of animal death (Fisher 1958). Other studies recorded no animal deaths with inocula slightly above or below the latter. In contrast, lethal dose ranges usually varied 5×10^7 – 5×10^8 . For example, some investigators have found 70% mortality after a dose of 1.5×10^8 colony-forming units (Carter and Preston 1981). Similar doses have established 80–100% mortality in other studies (Winter 1953). Similar doses may have lethal effect in neonatal mice versus sublethal effects in older mice (Scanlon et al. 2017). Whereas some models may be mildly resistant to nasal colonization, an antibiotic pretreatment to eradicate some usual nasopharyngeal can facilitate the latter and allow for the use of smaller inocula (Soumana et al. 2021). Pre-immunization may also affect the dose required (Hegerle et al. 2014; Kang et al. 2021; Prygiel et al. 2021). Apart from variation with bacterial strains, the volume of application with nasal inocula led to variation regardless of bacterial load (Halperin et al. 1988). Bacterium can be recovered from nasal washes within the first several days (Willems et al. 1998). Peak lung counts of bacterium occur by days 7–21 after infection (Proom 1947; Andersen and Bentzon 1958a; Gray and Cheers 1967; Holubová et al. 2020). A higher inoculum achieves greater lung counts (Proom 1947; Andersen and Bentzon 1958a; Fisher 1958; Soumana et al. 2021). The distribution of bacteria in lung infection, the lung counts, and the number of mice infected can vary widely (Halperin et al. 1988). Whereas the latter may be seen as markers of inconsistency for a model, such variation does mimic the variability of clinical disease potentially seen in humans. It is less likely however that humans consistently develop pneumonia versus other respiratory foci for infection. Among primary mouse infections, viable bacterium in lung may persist for up to 1–2 months which would be quite unusual for human infection since clinical improvement occurs much earlier and nasopharyngeal viability of *B. pertussis* is relatively short especially as assessed by culture in contrast to amplification technologies (Andersen 1953; Gray and Cheers 1967; Khelef et al. 1994; Cimolai et al. 1996b). Soumana et al. (2021) found that smaller intranasal doses led to longer nasopharyngeal colonization up to 60 days or more. Scanlon et al. (2017) showed

that neonatal mice infected by the intranasal route can pass infection on to other neonatal mice, but transmission has not been evident among older mice. Re-infections usually are associated with lung clearance within 4–8 days. Acellular vaccine was found to promote nasal carriage in some studies (Hegerle et al. 2014; Holubová et al. 2020). The intranasal model has been used to assess pathogenesis, passive immunity, and vaccination in many studies (Masry 1952; Winter 1953; Komatsu et al. 2010; Higgs et al. 2012; Solans et al. 2018; Zurita et al. 2019; Aispuro et al. 2020; Blackwood et al. 2020; Rouleau et al. 2020; Dubois et al. 2021; Prygiel et al. 2021). Winter (1953) also used this model to begin critical studies that would define the specific nature of protective immune responses. This model was further used to assess antimicrobial efficacy (Bradford and Wold 1939; Hornibrook 1942; Bradford et al. 1944; Bradford and Day 1945, 1949; Day and Bradford 1952; Gastal 1958).

The challenges with model variability thereafter led several to attempt a more stable and consistent model of infection. Aerosolization of inoculum served to address several such limitations. Standardization of such a model is often referred back to the work of Sato et al. (1980). These investigators exposed mice to a 30-min aerosol duration with up to 10^9 – 10^{10} bacteria/mL. Mortality among mice was both age dependent and dose dependent (Halperin et al. 1988; Halperin et al. 1991). Thereafter, concentrations of bacteria per volume and duration of exposure have varied somewhat among studies (Oda et al. 1983; Halperin et al. 1991; Redhead et al. 1993; Barbic et al. 1997; Mills et al. 1999; Xing et al. 1999). Some research has found that much lower doses can be lethal, and standardization within experiments would need to be performed for given strains of both bacterium and mouse especially when neonatal or very young (8–10 day) mice are used (Oda et al. 1984; Halperin et al. 1988; Ross et al. 2013; Scanlon et al. 2017). The actual viability of bacteria from a calculated cell suspension may be lower than anticipated (Oda et al. 1983). The aerosol challenge was found to create more consistent lung infection counts, lead to more consistent bilateral lobe pathology, and to be associated with a diffuse lung disease. With challenges using initial bacterial concentrations in the proximity of 10^9 bacteria/mL during aerosol, lung tissue quantitations of 10^4 bacteria were found within 1 h. Guiso et al. (1999) proposed that the aerosol model could not evaluate protection afforded by component vaccines in contrast to the intranasal model. The latter was in contrast however to the modification of the model used by Xing et al. (1999). Otherwise, despite any proposed limitations, the aerosol challenge model has been used to make considerable progress in the understanding of many immunological features of infection not limited to but including role of passive immunity, efficacy of vaccines including acellular vaccines, importance to generate multi-antigen exposures, contributions from effector functions of

the Fc portion of immunoglobulins, importance of interferons in disease, role of B cells and T cells and their subsets, role of natural killer cells specifically, and quality of Th1 and Th2 vaccine responses (Imaizumi et al. 1985; Halperin et al. 1991; Mills et al. 1993, 1998; Redhead et al. 1993; Shahin et al. 1994; Barbic et al. 1997; Mahon et al. 1997, 2000; Leef et al. 2000; Byrne et al. 2004; Skerry et al. 2009; Higgs et al. 2012; Ross et al. 2013; Wilk et al. 2017; Zurita et al. 2019; Borkner et al. 2021; Sanchez-Alvarez et al. 2021). Notable among the latter is the very long persistence of infection and colonization among mice with B or T cell deficiencies and the ability to facilitate disseminated infection when interferon-gamma functionality is abrogated (Mills et al. 1993; Mahon et al. 1997). The finding of different predominant immune responses to either whole cell or acellular vaccines would be of value to more carefully mimic observations from human immunology. It is also not clear if antibody effector functions will differ between animal models and humans whether post-disease or post-immunization.

In general, the mouse model whether via nasal infection or aerosolization has some useful attributes akin to human infection. Infection of mice with high quantitations of bacterium will inherently shorten the incubation period after exposure. Infections through either route do not apparently cause a perceivable cough in animals (Locht 2021). It is not evident whether sophisticated methods of cough detection will change the latter perception (Chen et al. 2013; Zhang et al. 2017; Chen et al. 2020). There are variable mimics of age-dependent infection and complications, mucosal and pulmonary disease, and accompanying physiological changes. Costs of mouse maintenance, the availability of murine-based reagents, and the widespread availability of knockout mice of varying design all favor use of such a model. Applications to the study of maternal passive immunity or mucosal immunity or mucosal immunity generally have been detailed (Oda et al. 1983; Debrue et al. 2019; Solans and Locht 2019; Aispuro et al. 2020; Blackwood et al. 2020; Borkner et al. 2021; Dubois et al. 2021; Solans et al. 2021). The latter are yet to be intensively compared to pertussis immunity in the human maternal-newborn unit (Lichty et al. 1938). Application to the study of a novel and contemporary live-attenuated vaccine has also been feasible (Solans et al. 2018). Regardless, it would remain to be determined whether determinants of immunity in these model systems at all resemble those in humans. Mice and humans nevertheless differ in their responses to the potentially toxic effects of vaccination, e.g., adverse central nervous system manifestations.

Physiological parameters of infection

The human variability of clinical pertussis is established (Cherry and Heinger 2019). That there are specific and non-specific clinical and laboratory test responses

pre-programmed in animal model systems is already acknowledged (Banus et al. 2007a). Indeed, the latter investigators were able to define *B. pertussis* susceptibility loci in a mouse model. Such inherent variability in either human or model disease is consistent with the anticipated variability analogous to most if not all infections. On this theme, various physiological effects of pertussis infection or bacterium exposure have been discussed (Morse 1976).

Apart from direct clinical manifestations of respiratory tract infection which can be either variable or none-at-all in the model systems, the occurrence of leukocytosis in peripheral blood has been reproduced (Morse 1976; Pittman et al. 1980; Sato et al. 1981; Pittman 1984; Nogimori et al. 1984; Oda et al. 1984; Shahin et al. 1990; Halperin et al. 1991; Hoonakker 2021). A particular variation for humans is a prominent lymphocytosis. Nevertheless, in addition to the latter, blood counts are considerably variable ranging from apparently normal to polymorphonuclear leukocytosis to mixed leucocytoses with increase in both lymphocytes and neutrophils. The pattern of leukocytosis is complicated by the potential for secondary bacterial infections from usual respiratory flora which are more commonly associated with polymorphonuclear leukocytosis. Several studies in animal models do not differentiate the white blood cell profile in the context of reporting leukocytosis. Some research has attributed these in vivo effects to lymphocytosis-promoting factor that is synonymous with the key pertussis toxin and which is variable among bacterial isolates (de Wildt et al. 1983; Scanlon et al. 2019). It would be of some value for an animal model to be susceptible to such variability as seen in humans. Nogimori et al. (1984) were able to implicate a specific domain in the pertussis toxin that stimulated lymphocytosis in a rat model. A more complex hypothesis of leukocytosis is proposed by Eby et al. (2015).

Elements of weight gain or loss have been used as a metabolic marker in many studies (Sato et al. 1980; Pittman 1984; Halperin et al. 1988; Shahin et al. 1990; Banus et al. 2006; Hoonakker 2021). Weight loss coincides with infection or with exposure to vaccine. Thus, the latter clinical phenomenon has also been used to assess vaccine toxicity in various but especially murine models (Cameron 1977). For human infection, weight loss can occur as a consequence of increased metabolism, circulating lymphokines, emesis, and inanition during illness. Given other more tangible parameters, this physiological attribute attracts less importance in the desirable animal model of pertussis.

There are many studies which have focused on pertussis-related glucose and insulin physiology (Belcher et al. 2021; Hoonakker 2021). It is not entirely clear how commonly relevant this topic may be directly to human infection. In both primates and mice, hypoglycemia can be found during experimental infection with sublethal inocula (Sidey et al.

1987; Kubrava et al. 2013). Young children with hypoglycemia during pertussis complications have been reported, but the risks for such hypoglycemia can be multifactorial (Congeni et al. 1978). In a series of patients with whooping cough, no hypoglycemia was found although mild hyperinsulinism could be shown (Furman et al. 1988). In another series, the hyperglycemic responses to epinephrine were blunted during infection of children, but again, no significant hypoglycemia could be discerned (Badr-El-Din et al. 1976). Similar phenomena were also observed post-vaccination among children (Sen et al. 1974). There is yet the prospect that only some patients might be at particular risk for impact on glucose metabolism, the extreme results of which might lead to neuropathology such as seizures that have been seen uncommonly both after infection or vaccination (Pittman 1986; Wilson et al. 2010). Hennesen and Quast (1979) proposed nevertheless that most post-vaccination severe side effects could be attributed to patient hypoglycemia. Kreeftenberg et al. (1984) had found mild hypoglycemia in mouse models after vaccination, hence speculating on the relevance to post-vaccination complications in humans. Furman and colleagues (1981) could demonstrate pertussis infection- or vaccination-induced hyperinsulinemia and hypoglycemia but duly qualified on the potential for other factors to affect the same in a model system. Attribution of hypoglycemia to purely pertussis toxin was also published (Morse and Morse 1976; Sidey et al. 1987). Hyperinsulinism is concomitant to the aforementioned hypoglycemic events (Gulbenkian et al. 1968). There is a generic effect on insulin secretagogues (Yajima et al. 1978). In addition, pertussis sensitization in animal models predisposes to alternations in how adrenaline interacts with glucose metabolism (Szentivanyi et al. 1963; Gulbenkian et al. 1968; Sumi and Ui 1975).

Histamine sensitization has been observed in several model systems. Such sensitization in a murine model appeared to be temporary and measured over 7–10 days (Parfentjev et al. 1947; Maitland et al. 1955; Bergman and Munoz 1977; Ortez 1977; Halperin et al. 1991; Hoonakker 2021). A similar effect and timing was also found among vaccinated children (Sen et al. 1974). Bergman et al. (1977) ascribed histamine sensitization in mice to pertussis endotoxin but with similar effects caused by other bacterial endotoxins. There was variability among animal models for any such effect (Parfentjev et al. 1947; Stronk and Pittman 1955). The role of pertussis endotoxin in this effect had been previously suggested (Malkiel and Hargis 1964). Maitland et al. (1955) found that animals could be immunized with the histamine-sensitizing factor. Yet others more recently ascribed similar effects to pertussis toxin and its ADP-ribosylating enzyme activity; such association is more commonly held (Morse and Morse 1976; Gomez et al. 2007). Serotonin sensitivity may also be a concomitant finding (Morse 1976).

Other metabolic changes can be measured such as post-vaccine or infection modulations in autonomic responsiveness. These may be exemplified by blood pressure variation and vasodilatation (Morse 1976; de Wildt et al. 1983). Such findings resembled post-vaccination changes among vaccinated children when isoproterenol-induced variation in heart rate was assessed (Sen et al. 1974). Pulmonary hypertension can be found post-infection, but it is not clear if this has anything to do with vascular responsiveness or lung infection proper albeit there is a possible link with pertussis toxin (Scanlon et al. 2019, 2021).

Cutaneous administration of bacterial antigen can induce edema in mice, thus having initiated concepts of localized physiological responses to vaccine administration (Hink and Johnson 1947). Others have found that cerebral vascular permeability may be altered shortly after intravenous administration of heat-killed *B. pertussis* in a murine model (Arniel 1976). It is not clear if the latter effect is due to endotoxin or a collection of factors. Nevertheless, Malkiel and Hargis (1964) proposed that anaphylactic reactions in mice could be induced by pertussis endotoxin. A murine model for acute autoimmune encephalomyelitis was created with adjuvanticity from *B. pertussis* (Linthicum 1982; Linthicum and Frelinger 1982). Encephalomyelitis was in part ascribed to changes in vascular permeability (Linthicum et al. 1982). The concept of *B. pertussis* adjuvant effects in animal models was more broadly proposed (Morse 1976). Pertussis toxin particularly acts as a co-adjuvant in experimental autoimmune encephalomyelitis (Maria et al. 2021).

Future prospects

Over three decades ago, Noel Preston and colleagues then proposed limitations of available animal models and their correlation with human disease for various reasons and indications (Carter and Preston 1981; Preston 1988). Undoubtedly, the currently available models for infection and, variations of, have considerable potential to continue adding value to the understanding of pertussis infection and vaccination. What has changed?

Purely in vitro analyses, including tissue culture or tracheal organ culture, will have had their value for various aspects of pertussis research and will continue to do so (Holt 1972). As realized in the context of the current SARS-CoV-2 pandemic, tissue explants can be manipulated for study with the spectrum of molecular tools now available.

It is yet unlikely that all potentially viable animal models have been assessed, and especially since experimental failures were often unlikely to be published. Regardless, there are a number of animal species, including among small mammals, that are either underrepresented or not

mentioned at all in infection model assessments. Likewise, whereas the past models have been considerably helpful, there is plenty of room for greater sophistication.

One aspect of any such modeling that is relatively lacking is application to concepts of mucosal protection. That mucosal immunization could work was proposed very early from murine models of intranasal infection where intranasal vaccination proved more effective than intraperitoneal immunization (Dow 1940; North and Anderson 1942; Andersen 1953). A useful model should ideally have the attributes to facilitate further understanding of initial infection, upper respiratory tract disease, and local immunity. Such study that is integrated with systemic vaccine responses is particularly needed to further any improvements with current component vaccines or other related studies (Melvin et al. 2014; Warfel and Edwards 2015; Solans et al. 2018, 2021; Debrie et al. 2019; Solans and Loch 2019; Dubois and Loch 2021; Dubois et al. 2021; Sanchez-Alvarez et al. 2021; Saso et al. 2021). Local mucosal immunization also attracts considerable interest (Hall et al. 2021a). Inevitably, animal model systems are focused on short-term analyses, but yet human exposure, disease, and protection are long-term issues. That mucosal protection is applicable to human prevention has been supported by the lower frequency of pertussis among offspring of pregnancies that have received antepartum vaccination (Zumstein et al. 2021). Recent studies in primates also support a potential approach for direct mucosal immunization (Naninck et al. 2021). Given that the majority of manifest disease is related to the airways, consideration may also be made for co-infections (Sawal et al. 2009).

Progress in molecular biology has the potential to advance various aspects of animal models. With the study of either new models or models modified with current molecular tools, there is promise that the next generation of infection models will become available to better explore experimental and clinical pertussis.

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