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MINIREVIEW

Animal Models for Studying Female Genital Tract Infection with *Chlamydia trachomatis*

Evelien De Clercq, Isabelle Kalmar, Daisy Vanrompay

Department of Molecular Biotechnology, Faculty of Bioscience Engineering, Ghent University, Ghent, Belgium

***Chlamydia trachomatis* is a Gram-negative obligate intracellular bacterial pathogen. It is the leading cause of bacterial sexually transmitted disease in the world, with more than 100 million new cases of genital tract infections with *C. trachomatis* occurring each year. Animal models are indispensable for the study of *C. trachomatis* infections and the development and evaluation of candidate vaccines. In this paper, the most commonly used animal models to study female genital tract infections with *C. trachomatis* will be reviewed, namely, the mouse, guinea pig, and nonhuman primate models. Additionally, we will focus on the more recently developed pig model.**

Chlamydia trachomatis, a Gram-negative obligate intracellular bacterium, is the leading cause of bacterial sexually transmitted disease. World Health Organization values for 2008 estimated an annual increase of over 100 million genital tract infections with *C. trachomatis* worldwide (1). The incidence of cases is increasing in many countries (1, 2). Genital tract infections with *C. trachomatis* can cause cervicitis in women and urethritis in men. However, these infections remain largely subclinical in approximately 70% of women and 50% of men and consequently are often not detected (3). Untreated infections may lead to pelvic inflammatory disease, tubal scarring, ectopic pregnancy, infertility, and chronic pelvic pain in women, epididymitis in men, and infant pneumonia in children (4–7). Uncomplicated chlamydial infections can be treated easily with antibiotics, but once infection and pathology are established, treatment may be less effective. Asymptomatic individuals can be identified through screening programs, but this approach is likely to be too costly for developing countries. A vaccination program would be much cheaper and have a greater impact in controlling *C. trachomatis* infections worldwide. Computer modeling suggests that even a partially efficacious chlamydial vaccination program would rapidly reduce the prevalence of genital infection (8). Animal models are indispensable for the study of *C. trachomatis* infections and the development and evaluation of candidate vaccines. Various animal models have been developed, including mouse (9, 10), guinea pig (11, 12), nonhuman primate (13, 14), pig (15), rat (16), and rabbit (17) models. Here, the most commonly used animal models to study female genital tract infections with *C. trachomatis* will be reviewed, namely, the mouse, guinea pig, and nonhuman primate models. Additionally, we will focus on the more recently developed pig model.

MOUSE MODELS

Mice are the most commonly used animals to study genital chlamydial infections. The advantages of the mouse model are their small size, ease of handling, availability in sufficient amounts, and low cost. Moreover, there are many well-characterized inbred and knockout mouse strains available (18). The female mouse genital tract is susceptible to infection with both *Chlamydia muridarum* (9) and *C. trachomatis* (10), which has resulted in the establishment of two murine models: the *C. trachomatis* mouse model and the *C. muridarum* mouse model.

***C. muridarum* mouse model.** *Chlamydia muridarum*, previously known as *C. trachomatis* mouse pneumonitis biovar or MoPn, is a natural mouse pathogen that causes pneumonitis and was originally isolated from the lungs of mice (19). Intravaginal inoculation of *C. muridarum* in mice results in a genital tract infection that closely resembles acute genital *C. trachomatis* infections in women (9). The primary site of infection is the cervical epithelium. Subsequently, the infection ascends to the upper genital tract tissues (uterine horns and oviducts), which frequently leads to hydrosalpinx, fibrosis, and infertility, which are also common postinfection sequelae in women (20–22). Furthermore, a genital tract infection with *C. muridarum* early in gestation can result in premature termination of murine pregnancy (23).

Mice generally resolve a genital tract infection with *C. muridarum* without antimicrobial therapy in approximately 4 weeks and develop long-lived adaptive immunity that partially protects against reinfection (9, 24). Primary infection with *C. muridarum* not only yields partial protection against reinfection with the homologous *Chlamydia* strain but also, to a lesser degree, partially protects against heterotypic challenge with different *C. trachomatis* serovars. Mice that are reinfected have secondary infections of shorter duration and with less bacterial shedding than primary infection (25).

The initial inflammatory response to a genital tract infection with *C. muridarum* in mice is characterized by infiltration of myeloid cells in the genital tract tissues. Macrophages and lymphocytes, including B cells, $CD4^+$ T cells, and $CD8^+$ T cells, infiltrate as infection resolves. $CD4^+$ T cells predominate throughout the course of infection and form perivascular clusters that persist in the genital tract after resolution of infection (26). $CD4^+$ T cells are essential for protective immunity in the *C. muridarum* mouse model (27, 28). Gamma interferon (IFN-γ) and interleukin-12 (IL-12), both Th1-type cytokines, also contribute to protection against infection (29–31). However, the impact of IFN-γ on *C.*

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Address correspondence to Evelien De Clercq, eadclerc.declercq@ugent.be.

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muridarum is not as powerful as it is on *C. trachomatis* (32). $CD8^+$ T cells are not required for resolution of primary infection or immunity to reinfection, but they can contribute to protection via IFN-γ release (33). Nonetheless, it was recently demonstrated that $CD8^+$ T cell production of tumor necrosis factor alpha (TNF-α) promotes oviduct pathology following primary murine genital tract infection (34). Antibodies and B cells are also not necessary for eradication of primary infection (35, 36), but they play an important role in resistance to chlamydial reinfection (37). Moreover, Farris et al. (38) showed that both $CD4^+$ T cells and antibodies were required to induce an optimal protective immune response following major outer membrane protein (MOMP) vaccination.

In the *C. muridarum* mouse model, the course and outcome of infection can vary depending on the mouse strain studied, the inoculating dose, the age of the animal, and the hormone levels present. In general, C3H mouse strains show a more severe course of disease and a higher rate of infertility than other strains (20, 39, 40). Maxion et al. (41) showed that the infectious dose of *C. muridarum* affects the course of infection and the ascension of bacteria in the reproductive tract. Pal et al. (42) demonstrated that young mice are more susceptible to genital tract infections with *C. muridarum* than older animals. The estrous cycle appears to play a significant role in the pathogenesis of infection. In a study by Pal et al. (43), mice were less prone to develop an upper genital tract infection during the follicular phase than during the luteal phase.

Usually, mice are infected by intravaginal challenge with *C. muridarum*. An alternative, infrequently used approach is to challenge the mice directly in the upper genital tract, mostly the ovarian bursa, which increases the incidence of pathology of these tissues (44). The main concern with the latter approach is that it bypasses the natural route of infection (44, 45).

***C. trachomatis* mouse model.** As mentioned earlier, mice can also be genitally infected with human *C. trachomatis* serovars (10). Intravaginal inoculation with *C. trachomatis* typically produces a mild genital tract infection that resolves relatively quickly and is mostly unable to ascend to the upper genital tract. A higher number of infectious units is required to establish infection with *C. trachomatis* than with *C. muridarum*. Additionally, the peak bacterial load is approximately 2 log units lower, and there is less genital tract inflammation in mice inoculated with human serovars than in those infected with *C. muridarum* (40, 46, 47). In mice, experimental *C. trachomatis* infections cause postinfection sequelae, such as hydrosalpinx and infertility, only when high doses are inoculated directly into the uterus, uterine horns, or ovarian bursa (48–51), whereas infection by vaginal inoculation normally resolves without complications (40, 46, 47). However, Sturdevant et al. (52) demonstrated that frameshift mutations in a single genetic locus (CT135) significantly change the *in vivo* pathogenicity of a human *C. trachomatis* strain for the female mouse genital tract. Intravaginal inoculation with a mutant of their *C. trachomatis* strain in innate-immunity-deficient C3H/HeJ mice produced a naturally ascending infection which resulted in salpingitis. Their findings could contribute to the improvement of the *C. trachomatis* mouse model (52).

Studies examining the protective immune responses in the *C. trachomatis* mouse model have been contradictory. It has been demonstrated that strong adaptive immune responses are generated when mice are infected with *C. trachomatis* (53–55), but it has also been shown that these infections can resolve in the absence of adaptive immunity (56, 57), indicating that murine innate immune responses alone are able to eradicate the infection. Morrison et al. (58) evaluated infection in female mice in the presence and absence of $CD4^+$ T cells. In contrast to *C. muridarum* infection, *C. trachomatis* infection was unaltered in the absence of $CD4^+$ T cells. Mice infected with *C. trachomatis* developed protective immunity to rechallenge, but unlike *C. muridarum* infection, optimum resistance required multiple infectious challenges, despite the generation of adaptive serum and local chlamydia-specific immune responses (58). In contrast to intravaginal inoculation, intrauterine inoculation with *C. trachomatis* in mice results in a robust $CD4^+$ T cell response that is sufficient but necessary to clear the infection. Moreover, it provides for protection against reinfection (49). Ramsey et al. (25) demonstrated that primary infection of mice with *C. trachomatis* serovar E may lead to partial protective immunity against challenge with homotypic or heterotypic human strains, as shown by reduced chlamydial shedding and a shortened infection course. However, homotypic secondary challenge with serovar E may also result in a significant rate of infertility, while heterotypic challenge with human serovars does not aggravate the pathological outcome (46).

In the *C. trachomatis* mouse model, a number of infection characteristics appear to differ between *C. trachomatis* strains (47, 48). This may explain the serovar prevalence among human clinical isolates, in particular for the most prevalent (serovars D and E) and least prevalent (serovars H and I) serovars (47). Like *C. muridarum* infection, genital tract infection with *C. trachomatis* in mice is highly dependent on the mouse strain used, with C3H mice being more susceptible to infection than other strains (40, 46, 51, 59).

Comparison of the two mouse models. In both murine models, mice are generally pretreated with progesterone in order to induce prolonged diestrus. This enhances the initial infection rate of the genital epithelium, as it increases the number of target cells available for chlamydial infection (10). Yet, progesterone pretreatment alters the hormonal balance and the ensuing immunological state, making evaluation of any native hormonal contribution to the disease process impossible (60). However, the elimination of the variability of the estrous cycle and its potential effect on the infection is often desired in animal studies. Although progesterone pretreatment is frequently used in both models, it is not essential for infection of mice with *C. muridarum*, while the *C. trachomatis* mouse model is highly dependent on progesterone (10, 25).

There are remarkable differences in immunity and pathogenesis between the *C. muridarum* and *C. trachomatis* mouse models, but it is difficult to define which model best replicates chlamydial infection, pathogenesis, and immunity in women (58). First, a shortcoming of the *C. muridarum* model is that this *Chlamydia* species is not a naturally occurring human pathogen. Then again, the genomes of *C. muridarum* and *C. trachomatis* serovar D are remarkably similar in gene content and order, as well as in the presence of putative virulence factors (61–63). An important difference between both species is the presence of a tryptophan operon, which is present in the genome of *C. trachomatis* but not in *C. muridarum* (56, 64). Human genital *C. trachomatis* strains carry genes that encode a functional tryptophan synthase enzyme (*trpRBA*), which possibly uses exogenous indole supplied by cocolonizing microbes of the genital tract to evade IFN-γ-mediated indole 2,3-dideoxygenase (IDO) expression and thus tryptophan

starvation (64). However, IFN-γ does not induce IDO production in mice, it induces GTPases, which might sensitize *Chlamydia* to tryptophan starvation, possibly by GTP depletion (65). Thus, GTPases are important end line effectors of an IFN-γ response in mice. Nevertheless, *Chlamydiaceae* produce cytotoxins, which target GTPases and thus assist the bacterium in circumventing tryptophan starvation by GTP depletion (64, 65). Here, we can find another important difference between *C. trachomatis* and *C. muridarum*. *C. trachomatis* has a degraded cytotoxin, mostly nonfunctional, although differences in functionality at the serovar level have been reported (66). *C. muridarum* has three paralogous cytotoxin copies (67) and produces functional cytotoxins. Since *C. muridarum* and *C. trachomatis* show a difference in their responses to IFN-γ (32), a cytokine that plays an important role in the early clearance of *Chlamydia* from the genital tract (68), both species will probably also differ in their responses to other cytokines. Therefore, it is argued that investigating cytokine profiles in the *C. trachomatis* mouse model is potentially more clinically relevant than in the *C. muridarum* model (69). Second, *C. muridarum* is much more virulent in mice than *C. trachomatis* is. The developmental cycle of *C. muridarum* is more rapid, its duration being approximately half that of *C. trachomatis*, and *C. muridarum* is more prolific (69, 70). However, the pathology of the upper genital tract of *C. muridarum*-infected mice is comparable to that of women with post-chlamydial infection sequelae (20, 22). This similarity in pathogenesis and the strong adaptive immune response generated after infection make it a useful animal model for the study of *Chlamydia* pathogenesis and protective immunity (21), but the *C. muridarum* model mimics only acute phases of human *C. trachomatis* infections, not the chronic phases responsible for disease in humans (53). Therefore, the appropriateness of the *C. muridarum* mouse model for the study of genital tract infections with *C. trachomatis* in women has been questioned (69, 70). Lyons et al. (70) argued that infection of mice with *C. trachomatis* mimics in many ways both the course and outcome of infection in most women: an asymptomatic and self-limiting infection that only rarely results in severe upper genital tract sequelae. However, the *C. trachomatis* mouse model also does not allow development of the chronic infections observed in humans (71), and upper genital tract pathology can hardly be produced when mice are vaginally infected with *C. trachomatis* (40, 46, 47).

PRIMATE MODELS: PIG-TAILED MACAQUE

Several species of nonhuman primates, including the marmoset (72), grivet (73), baboon (74, 75), and pig-tailed macaque (13, 14), have been used as potential models to study genital *C. trachomatis* infections. The frequently used pig-tailed macaque model, developed by Patton et al. (13, 14), will be discussed here.

The pig-tailed macaque (*Macaca nemestrina*) is the preferred primate model for genital chlamydial infections for the following reasons. First, the anatomy and physiology of the female reproductive tract are similar to those in humans. As in women, they have a 28- to 30-day menstrual cycle, and their vaginal microflora also closely resembles that of women (76, 77). Second, pig-tailed macaques have a relatively quiet temperament and an ideal size, since they are large enough for most procedures but still manageable (77, 78). Third, this macaque species is naturally susceptible to genital tract infection with human biovars of *C. trachomatis*, and there is no need to pretreat the animals with, for instance, hormones to influence the infection (77).

Patton et al. (13, 14) developed two models in the pig-tailed macaque: an *in situ* model and a subcutaneous pocket model. In the *in situ* model, macaques are infected with *C. trachomatis* by cervical and/or intratubal inoculation to produce cervicitis and salpingitis (13, 79–81). The experimentally induced chlamydial disease in macaques is highly similar to that in humans. Repeated *C. trachomatis* salpingeal infections were shown to cause extensive tubal scarring, chronic salpingitis, and distal tubal obstruction, which are similar to the development of pelvic inflammatory disease (PID) in women (82). The *in situ* pig-tailed macaque model thus provides for an attractive animal model to study the pathogenesis and treatment of *Chlamydia*-induced PID (83, 84).

The subcutaneous pocket model is established by autotransplantation of salpingeal and/or endometrial tissues (14, 85). Briefly, segments of the oviducts (fimbria, ampulla, and isthmus) and/or endometrium are removed, cut into small pieces, and implanted subcutaneously into individual pockets made on the anterior abdominal wall of the macaque. The implants become vascularized and are surrounded by a connective tissue capsule. As many as 30 pockets, well established and separated from each other, can easily be made on the abdomen of each animal. The transplanted tissues have been shown to be susceptible to infection with *Chlamydia trachomatis* as indicated by reisolation of the organism. Inoculation of the bacteria into the pockets produces acute infection similar to acute salpingitis or endometritis in macaques infected in the intact genital tract.

In both the *in situ* model and the pocket model, systemic and local antibody responses develop after infection (13, 14, 79, 86). Van Voorhis et al. (87) showed that, in both models, Th1-like cytokines were induced by single and repeated chlamydial infection of salpingeal tissues. The models were also similar with respect to histopathology, with a predominantly mononuclear infiltration mainly composed of $CD8^+$ T cells and with lymphoid follicle formation. Both models showed evidence of progression to fibrosis. The similarity of their results validates the subcutaneous pocket model for the study of histopathology and immunopathology of *C. trachomatis*-induced salpingitis.

The advantage of the pocket model is that samples from a single macaque can be taken at multiple time points, which increases the yield of information from each macaque and conserves valuable animals (87). Moreover, sampling requires only minimal surgical intervention (78). Therefore, this model is ideal to study the kinetics of infection and the immune responses and to screen multiple antigens for vaccine development (85). However, the intact reproductive tract and thus the *in situ* model are still necessary to investigate pathogenesis of PID and infertility. Also, the natural progression of chlamydial infections cannot be monitored in the pocket model (88).

Although macaques are a very good model for human chlamydial disease, the use of this model is not without limitations. There are ethical considerations and practical disadvantages (high costs, adequate facilities, and expertise) inherent in primate models, which argue against the widespread use of this animal model (88, 89).

GUINEA PIG MODELS

Another model for chlamydial genital infections is the guinea pig infected with the *Chlamydia caviae* strain guinea pig inclusion conjunctivitis (GPIC). GPIC is a natural guinea pig pathogen that causes conjunctivitis (90). Experimental GPIC infection of the

guinea pig genital tract leads to an infection that closely resembles a genital tract infection with *C. trachomatis* both in male and female subjects (11, 12). GPIC mainly infects superficial epithelial cells of the cervix (91), but infection frequently ascends to the endometrium and oviducts, which can result in endometritis and/or salpingitis (92).

An important advantage of this model is that the genital tract infection can be transmitted sexually (12). The sexually transmitted infective dose of *Chlamydia* in guinea pigs has even been determined (93). Moreover, perinatal transmission is possible and, like human *C. trachomatis* infections, causes conjunctivitis in newborn guinea pigs (11).

Next, guinea pigs are a suitable animal model for the study of hormonal influences on genital tract chlamydial infection, since their female reproductive system closely resembles that of humans. Female guinea pigs have a 15- to 17-day estrus cycle, comparable to the 28-day menstrual cycle in humans. Also, female guinea pigs and humans both are spontaneous ovulators and have an actively secreting corpus luteum (94, 95). It was shown that estradiol, but not progesterone, makes guinea pigs more susceptible to chlamydial infections (96, 97). Human surveys show that estradiol has the same effect in women (98, 99).

In guinea pigs, both humoral and cell-mediated immunity are required for resolution of infection and immunity to reinfection (100–102). The immunity to reinfection that occurs in the animals is short lasting, which is also analogous to humans (103).

As already mentioned, the GPIC guinea pig model closely resembles disease following *C. trachomatis* infection in humans and is therefore suitable to evaluate potential vaccine candidates (104–106).

PIG MODEL

Vanrompay et al. (15) evaluated the pig as a large animal model for studying genital tract infections with *C. trachomatis*. There are several reasons for the selection of the pig as a model. First, pigs are physiologically and genetically closely related to humans (107, 108). Second, it was shown that the majority of genes expressed in the major porcine female reproductive tissues are ubiquitously expressed in human genital tissues (108). Dawson et al. (109) performed a comparative analysis of the porcine, murine, and human immune systems. They found that approximately 80% of the parameters examined were more similar between pigs and humans than between mice and humans. Third, pigs are naturally susceptible to infection with *Chlamydia abortus*, *Chlamydia pecorum*, *Chlamydia psittaci*, and *Chlamydia suis*. The latter species is phylogenetically highly related to *C. trachomatis*. Finally, multiple samples of one tissue can be obtained because of their larger dimensions, and pigs are practically and ethically more convenient for use as laboratory animals than nonhuman primates. However, using pigs as laboratory animals is more expensive and more complicated than using rodents, which limits the number of pigs per group. Therefore, the pig model is not appropriate for basic studies requiring large numbers of animals.

Vanrompay et al. (15) demonstrated that intravaginal inoculation of 16-week-old specific-pathogen-free (SPF) pigs with a 50% tissue culture infective dose (1×10^8 cells) of *C. trachomatis* serovar E strain Bour or strain 468 can lead to an ascending infection. Both strains replicated in the superficial epithelial cervical and uterine layers, which are the specific target sites for a genital tract infection with *C. trachomatis* in women. Inflammation and pathology occurred at the replication sites, and the bacteria could trigger a humoral immune response (15). There was no need to pretreat the pigs with hormones to enhance the infection. Pigs do not have a real anestrous phase like that of mice, but they have a period of ovarian quiescence from 13 weeks of age until 26 weeks of age which can be considered an anestrous condition. Therefore, their study demonstrated that pigs may be useful to study the pathology, pathogenesis, and immune response of genital tract infections with *C. trachomatis*.

Schautteet et al. (110) validated the pig model for screening vaccine candidates against genital chlamydial infections. Two recombinant protein vaccines based on PmpG or SctC were tested, representing a promising and less promising candidate vaccine antigen, respectively. As expected, protective immunity against an experimental genital *C. trachomatis* infection was higher in PmpG-immunized pigs than in SctC-immunized pigs.

The pig model was also successfully used to test a *C. trachomatis* DNA vaccine (111, 112). Mucosal *C. trachomatis* DNA vaccination induced significant protection against genital *C. trachomatis* challenge, although the infection could not be eradicated. Intradermal immunization was significantly less efficient in protecting experimentally infected pigs. Protection of the pigs against infection was correlated with efficient T cell priming and significantly higher serum IgA titers following vaccination.

Pigs experimentally infected with their natural pathogen *C. suis* are difficult to use as an animal model for human *C. trachomatis* infection because of the following. (i) *C. suis* induces reproductive failure in sows, characterized by discrete vulval discharge and a decrease in conception rate following artificial insemination, rather than tubal infertility and PID. (ii) We need more knowledge on the pathology and pathogenesis of genital *C. suis* infections in pigs.

CONCLUSION

None of the animal models used to study genital tract infections with *C. trachomatis* perfectly mimics the anatomy, histology, and endocrinology of the human reproductive system or the pathogenesis and immune responses occurring during a human genital *C. trachomatis* infection. Nonhuman primate models resemble the human disease most closely, but their use is complicated by ethical, financial, and practical issues. Working with mice is comparatively simple and inexpensive, making them the most commonly used animals to study genital chlamydial infections. However, results obtained in mouse studies cannot always simply be extrapolated to the human disease. Guinea pig models have several advantages over the mouse models, such as the higher similarity of their female reproductive system to that of humans. Pigs are physiologically and genetically more closely related to humans than rodents and are practically and ethically more convenient for use as laboratory animals than nonhuman primates. Therefore, the pig model could be an intermediate animal model between rodents and nonhuman primates or even a substitute for the nonhuman primate models.

As already mentioned, no single animal model for chlamydial genital infection can mimic exactly what occurs in humans, but each model reflects some aspects of human disease. Therefore, it is crucial to identify the most appropriate animal model for studying a specific aspect of genital tract infection with *C. trachomatis*. Figure 1 summarizes the advantages and disadvantages of the mouse, guinea pig, nonhuman primate, and pig models to study female

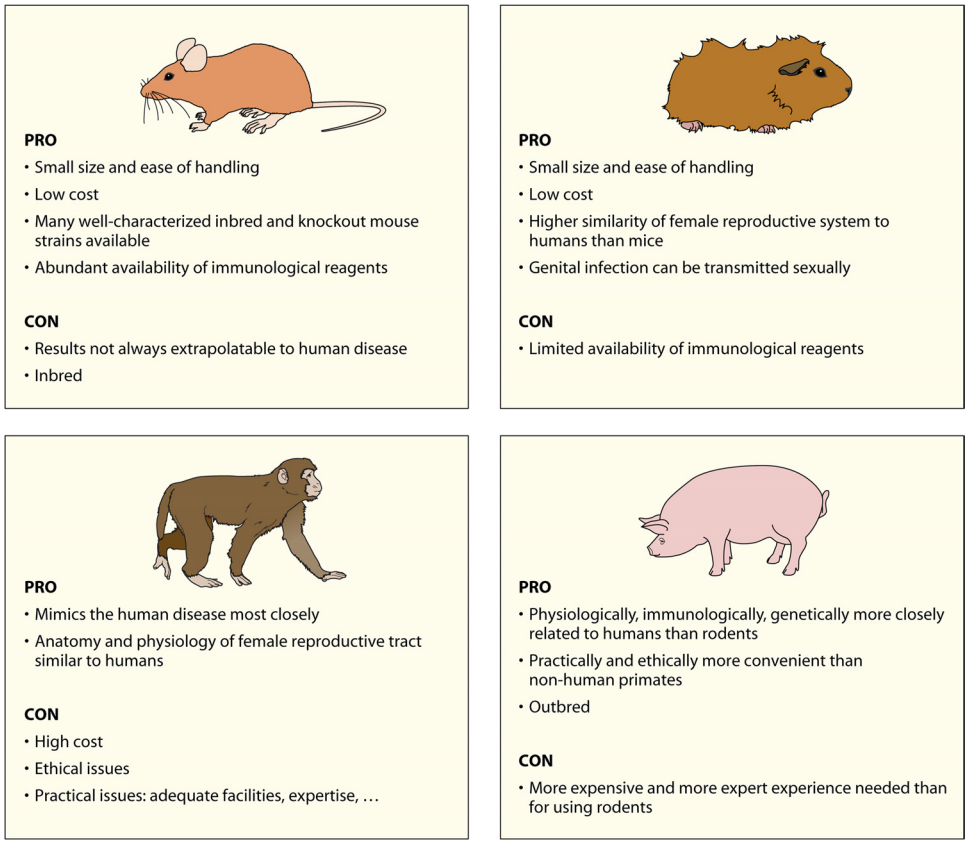

FIG 1 Advantages and disadvantages of the mouse, guinea pig, nonhuman primate, and pig models used to study *Chlamydia trachomatis* female genital tract infection.

genital tract infection with *C. trachomatis*. The mouse is the preferred model for immunological studies because of the abundant availability of immunological reagents and knockout mouse strains. The pig-tailed macaque is an ideal model to study the pathogenesis and treatment of *Chlamydia*-induced PID. In theory, the pig-tailed macaque model is also appropriate for studying pathology, hormonal influences on infection, and infection in the male genital tract. In practice, however, nonhuman primates are not suited for studies on the basic aspects of *C. trachomatis* infection. The guinea pig is an appropriate animal model to investigate pathogenesis, pathology, effects of reproductive hormones on infection, infection of males, and sexual transmission of infection. The pig model is also useful to study pathology and pathogenesis. Of course, the selection of the most appropriate animal model is mostly not straightforward, and a detailed discussion on this topic is not the aim of this minireview.

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