Experimental Infection of Human Volunteers with
Haemophilus ducreyi: Fifteen Years of Clinical Data and Experience

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Haemophilus ducreyi causes chancroid, which facilitates transmission of human immunodeficiency virus type 1. To better understand the biology of H. ducreyi, we developed a human inoculation model. In the present article, we describe clinical outcomes for 267 volunteers who were infected with H. ducreyi. There was a relationship between papule formation and estimated delivered dose. The outcome (either pustule formation or resolution) of infected sites for a given subject was not independent; the most important determinants of pustule formation were sex and host effects. When 41 subjects were infected a second time, their outcomes segregated toward their initial outcome, confirming the host effect. Subjects with pustules developed local symptoms that required withdrawal from the study after a mean of 8.6 days. There were 191 volunteers who had tissue biopsy performed, 173 of whom were available for follow-up analysis; 28 (16.2%) of these developed hypertrophic scars, but the model was otherwise safe. Mutant-parent trials confirmed key features in H. ducreyi pathogenesis, and the model has provided an opportunity to study differential human susceptibility to a bacterial infection.

Haemophilus ducreyi causes chancroid, a sexually transmitted genital ulcer disease that is endemic in regions of Africa and Asia. Although the World Health Organization estimated the annual global prevalence of chancroid to be 4–6 million cases in the late 1990s, the epidemiology of the disease is not well characterized because of syndromic management and a lack of diagnostic testing [1, 2]. Chancroid facilitates the transmission and acquisition of human immunodeficiency virus (HIV) type 1 and is a public health concern [3].

H. ducreyi is a strict human pathogen that naturally infects genital and nongenital skin [4]. The bacteria presumably enter the skin through superficial abrasions that occur during intercourse [4]. Clinical disease is initially characterized by a painless papule that develops into a pustule at the site(s) of entry. Pustules erode into painful ulcers that prompt patients to seek medical attention 1–3 weeks after symptoms begin [2]. Purulent ulcers with ragged edges and suppurative lymphadenopathy typify the ulcerative stage [4].

During the 1980s and 1990s, chancroid outbreaks occurred in New York, New York, and New Orleans, Louisiana [5]. At the time of these outbreaks, data regarding the pathogenesis of H. ducreyi infection in humans were scarce [4, 5], and findings from in vitro and animal models could not be correlated with human disease. Given the initial clinical course of natural disease, we reasoned that experimental infection up to the pustular stage would pose minimal risk to volunteers. Thus, a model of experimental infection with H. ducreyi in humans was developed to better define the pathogenesis of and host responses to the organism [6, 7].

In this model, healthy adult volunteers were inoculated with H. ducreyi at multiple sites on the skin underlying the upper deltoid. On the basis of the delivery characteristics of the allergy testing device used for inoculation, the estimated delivered dose was calculated by dividing the colony-forming units loaded on the device by 1000 [8]. Papules developed within 24 h and either
spontaneously resolved or evolved into pustules over the next 2–5 days. Volunteers remained infected until they reached 1 of the following 3 clinical end points: (1) disease at all sites had resolved, (2) a pustule developed that was either painful or >4 mm in diameter, or (3) 14 days had passed after inoculation. After reaching an end point, all volunteers were treated with 1 oral dose of ciprofloxacin.

Within 24 h of inoculation, fibrin and collagen are deposited in the wounds. Polymorphonuclear neutrophils (PMNs) and macrophages traffic on the collagen and fibrin scaffolds, forming micropustules in the epidermis and dermis [9, 10]. By 48 h after inoculation, PMNs form an abscess that ulcerates through the epidermis [9, 10]. Below the abscess is a dermal infiltrate of myeloid dendritic cells, macrophages, memory and effector memory subsets of CD4 and CD8 T cells, and activated natural killer cells [11–15] (S.M.S., unpublished data). The dendritic cells likely phagocyte H. ducreyi [14], migrate to regional nodes, and sensitize naive T cells that eventually infiltrate the lesions, because H. ducreyi–specific T cell lines can be propagated from pustules [16].

The histologic character of experimentally induced pustules is nearly identical to that of natural ulcers [1]. In pustules, H. ducreyi are found in the abscess and dermis, where they associate with collagen, fibrin, PMNs, and macrophages, which fail to ingest the organism [10]. H. ducreyi also colocalizes with fibrin and PMNs in natural ulcers [17]. Thus, evasion of phagocytosis and the bactericidal activity of serum that transudates into lesions are the major mechanisms of bacterial survival in experimentally induced pustules and in natural disease. Here, we report our cumulative 15-year experience with the experimental human infection model of H. ducreyi. We describe clinical outcomes for the 267 volunteers who were infected with strain 35000 or its human-passaged derivative, 35000HP. We also describe the results obtained for 41 volunteers who were reinfected with 35000HP and the results of 20 mutant-parent comparison trials in the context of what is known about the pathogenesis of H. ducreyi infection.

SUBJECTS AND METHODS

Study population. Between 25 February 1993 and 31 December 2007, we infected 267 volunteers. Subjects included 162 women and 105 men; 212 subjects were white, 49 were black, and 6 were Asians. The mean (± standard deviation [SD]) age was 33.7 ± 10.3 years (range, 18–68 years). All volunteers were infected at least once with H. ducreyi. Safety data, such as information on hypertrophic scar formation, are reported for the entire cohort. All subjects provided written informed consent for participation and human immunodeficiency virus serological analysis, in accordance with the human experimentation guidelines of the United States Department of Health and Human Services and the institutional review boards of Indiana University and Purdue University Indianapolis.

For the analysis of initial infection, we included 220 subjects who were infected at 2 or 3 sites with the parent strain and who reached a clinical end point. If subjects participated in mutant-parent comparison trials, only the sites inoculated with the parent strain were included in the analyses. Subjects (n = 36) who participated in either dose-response trials [6], chemophylaxis trials [18], or other time course studies [7, 10, 12] were excluded because of a short duration of infection (1–4 days). Subjects (n = 11) who were HIV seropositive [15] were also excluded from the analysis.

Analysis of site independence. A total of 186 subjects who received identical doses of the parent strain at either 2 sites (n = 106) or 3 sites (n = 80) were included in the analysis of site independence. Cumulative data for 90 of the subjects inoculated at 2 sites were reported elsewhere [19]. The observed and expected outcomes were compared under the assumption of site independence by use of χ² tests.

Papule and pustule formation rates. We estimated the odds of papule and pustule formation on the basis of the estimated delivered dose of 35000 and/or 35000HP, sex, race, and age. For this analysis, we used logistic regression with generalized estimating equations to predict papule and pustule formation rates. The generalized estimating equations sandwich estimator for standard errors was used to calculate 95% confidence intervals (CIs) for these rates.

Second infections. Of 220 subjects included in the analyses of initial infections, 41 were infected a second time [19, 20] (S.M.S., unpublished data). For these 41 subjects, we estimated the odds of pustule formation on the basis of their previous outcome by use of logistic regression, as described above.

Mutant-parent comparison trials. To test the role of putative bacterial virulence factors in disease, we performed isogenic mutant-parent comparison trials [8, 21–28]. These trials were double-blind, multistage, dose-ranging studies with ≥2 stages. The primary end point was the pustule formation rate. The first group of volunteers was inoculated at 3 sites with a fixed dose (x) of strain 35000 or 35000HP on one arm and at 3 sites with varying doses (0.5x, x, 2x) of an isogenic mutant on the other arm [21, 22]. If the sites injected with the mutant and those injected with the parent formed pustules at similar rates, we inoculated a second group with similar doses. If pustules did not develop at sites inoculated with the mutant during the first iteration, the doses of the mutant were increased for each subsequent group until the estimated delivered dose of the mutant was ~10-fold greater than that of the parent. Mutants were categorized as attenuated (i.e., unable to cause pustule formation even at doses 10-fold greater than the parent dose that resulted in pustule formation), partially attenuated (i.e., able to cause pustule formation at doses 2- or 3-fold greater than the parent dose that resulted in pustule formation, but not at an equivalent dose) or
virulent (i.e., able to cause pustule formation at a dose equivalent to the parent dose that resulted in pustule formation).

RESULTS

Outcomes of initial challenges. A total of 220 subjects (88 men and 132 women) provided 538 sites (219 from men and 319 from women) for the analysis of papule formation. Of these 220 subjects, 192 (76 men and 116 women) provided 470 sites (192 from men and 278 from women) for the analysis of pustule formation.

Of 192 subjects, 186 were infected with identical doses of H. ducreyi strain 35000 or 35000HP at 2 or 3 sites, which were analyzed for independence. The number of people expected to have 0, 1, 2, or 3 pustules (figure 1) was calculated on the basis of the observed pustule formation rate and the assumption of independence. Among those inoculated at 2 sites, a greater than expected number of subjects developed pustules at 0 or 2 sites (P < .001) (table 1). Similarly, among those inoculated at 3 sites, a greater than expected number of subjects developed pustules at 0 or 3 sites (P < .001) (table 1). Thus, the outcome for infected sites in a subject inoculated with identical doses of the parent strain was not independent, which suggests a host effect on outcome, as reported previously [19].

We calculated the overall papule and pustule formation rates using logistic models and generalized estimating equations to account for the host effect on sites. Papules formed at 479 (89% [95% CI, 85.7%–91.9%]) of 538 sites (figure 2). There was a significant effect of dose on papule formation (P = .004); the odds of papule formation increased by 2% per unit increase in estimated delivered dose (figure 2). After adjusting for dose, we found no association between the likelihood of papule formation and either sex (figure 3) or race (data not shown).

A total of 470 sites were included in the calculation of pustule formation rates. The pustule formation rates for 85 sites inoculated with 35000 and 385 sites inoculated with 35000HP were not significantly different. Consequently, we analyzed results for the 2 strains together. Pustules formed at 256 of 470 sites, for an overall pustule formation rate of 54.5% (95% CI, 48.7%–60.1%) (figure 2). There was no statistically significant change in the odds of pustule formation as the dose increased. When the analysis was controlled for dose, men were significantly more likely than women to form pustules (odds ratio [OR], 1.94; [95% CI, 1.23–3.09]) (P = .005) (figure 3), a result that is consistent with previous reports [29]. There was no statistically significant association between pustule formation and either race or age (data not shown). Thus, the

Table 1. Observed number versus expected number of subjects who developed 0, 1, 2, or 3 pustules after being inoculated with Haemophilus ducreyi.

<table>
<thead>
<tr>
<th>No. of pustules</th>
<th>Subjects who developed pustules, no.</th>
<th>Inoculated at 2 sites</th>
<th>Inoculated at 3 sites</th>
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<td>Expected</td>
<td>Observed</td>
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<td>18</td>
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<td>Total</td>
<td>106</td>
<td>106</td>
<td>80</td>
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NOTE. Expected numbers were calculated on the basis of the observed overall pustule formation rate and the assumption of site independence. NA, not applicable.
most important determinants of pustule formation were host effects and sex.

Papules that progressed to pustules (n = 256) did so within a mean (± standard deviation [SD]) of 3.8 ± 2.2 days (range, 1–14 days). Papules that resolved (n = 156) did so within a mean (± SD) of 5.3 ± 2.6 days (range, 2–14 days). Only 7 pustules (2.7% [95% CI, 1.2%–6.2%]) reverted to papules and subsequently resolved without treatment. Thus, spontaneous resolution of papules was common in the model, whereas resolution of pustules was uncommon.

Of 140 subjects who formed ≥1 pustule, 122 (87.1% [95% CI, 81.6%–92.7%]) developed pain or pruritis at the pustule site. These subjects were treated for infection because of their symptoms after a mean (± SD) of 8.6 ± 2.7 days. Only 18 subjects who developed pustules did not develop local symptoms and thus remained infected for 14 days.

Of 192 volunteers, 139 (72.4% [95% CI, 66.1%–78.7%]) had ≥1 pustule when they reached a clinical end point and were defined as subjects who formed persistent pustules, whereas all sites of infection resolved for 51 subjects (26.6%...
(95% CI, 20.3%–32.8%)) who were thus defined as subjects whose initial infection resolved. Two subjects had papules at 14 days and were not included in either category.

**Outcomes of second challenges.** Of the subjects who were initially classified as either subjects who formed pustules or subjects whose infection resolved, 41 volunteered to be infected a second time [19, 20] (S.M.S., unpublished observations). Of 15 subjects whose initial infection resolved (13 women and 2 men) and who volunteered for a second challenge, 7 (46.7% [95% CI, 21.4%–71.9%]) experienced resolution of infection at all sites, 6 (40% [95% CI, 15.2%–64.8%]) formed ≥1 pustule, and 2 had papules at the end point. Of 26 subjects who formed persistent pustules during their initial infection (16 women and 10 men) and who volunteered for a second challenge, 23 (88.5% [95% CI, 76.2%–100%]) formed ≥1 pustule, 2 (7.7% [95% CI, 1.0%–25.1%]) experienced resolution of infection at all sites, and 1 had papules at the end point. When the analysis was adjusted for sex, a subject was more likely to experience resolution at all sites during the second infection if he or she had this same outcome during the first infection ($P = .010$). Similarly, a subject who formed persistent pustules was more likely to form ≥1 pustule during a second infection if he or she formed persistent pustules during the first infection ($P = .003$). For a subject who formed persistent pustules during the initial infection, the odds ratio of forming a pustule during the second infection was 3.8 (95% CI, 1.31–10.49) times that of a subject who experienced resolution of infection at all sites during the initial infection (figure 4). Thus, the subjects’ results segregated toward their initial outcome when they underwent a second challenge.

**Outcomes of sites inoculated with mutants.** In isogenic mutant-parent comparison trials, subjects served as their own controls for analysis of the host and sex effects. Two important themes emerge from the 20 trials published to date (table 2). First, the trials have validated the importance of the association between $H. ducreyi$ and fibrin, collagen, and the evasion of phagocytosis [9, 10]. Mutants that lack expression of outer membrane proteins involved in serum resistance (DsrA and DltA), adherence to collagen (NcaA), or fibrinogen binding (FgbA) and mutants lacking secreted proteins that are antiphagocytic (LspA1 and LspA2) are fully or partially attenuated in vivo [8, 22–24, 28]. In contrast, mutants whose gene products target host cells or compartments that do not have major roles in pathogenesis in vivo are not needed for virulence [8]. For example, mutants that do not make paragloboside-like lipooligosaccharide, hemolysin, and cytotoxic distending toxin, which primarily target adherence to and invasion of keratinocytes or killing of keratinocytes and fibroblasts, are virulent [32–37]. Similarly, a mutation in superoxide dismutase C, which promotes survival in phagolysosomes, a compartment that $H. ducreyi$ evades in vivo, is virulent [38]. Second, the trials have helped identify vaccine candidates. Although some gram-negative organisms contain as many as 40 TonB-dependent receptors, $H. ducreyi$ contains only the hemoglobin receptor (HgbA), the heme receptor (TdhA), and TdX, whose function is not known [26]. An HgbA mutant is attenuated for pustule formation in the model, whereas a TdhA and TdX mutant is virulent [26, 39]. Thus, HgbA is both necessary and sufficient for heme/iron acquisition by $H. ducreyi$ in humans. HgbA is conserved in $H. ducreyi$ strains and does not undergo phase or antigenic variation. Vaccination with purified HgbA elicits protective antibody–mediated immunity in the swine model [26, 40]. The results of these trials support the idea that HgbA may be an excellent vaccine candidate in humans.

**Figure 4.** Rate of pustule formation during second $Haemophilus ducreyi$ infection for volunteers who formed persistent pustules (+) or who experienced resolution of infection at all sites (×) during initial infection.
Risks and adverse events. We typically infect groups of subjects with a common inoculum. In 128 iterations, 2 groups (6 subjects) were infected with inocula that contained low levels of fungi or bacteria other than *H. ducreyi*. The subjects developed papules, were treated with ciprofloxacin once the contaminants were detected, and had no adverse outcomes. No subject developed fever or systemic symptoms due to experimental infection. Secondary transmission of *H. ducreyi* from a volunteer to another person has not occurred in 2123 subject-days of infection.

Although we excluded persons known to form keloids and hypertrophic scars, some subjects developed hypertrophic scars at sites of infection that were biopsied. Subjects did not form hypertrophic scars at infected sites that were not biopsied or at uninfected sites that were biopsied. Subjects were followed up for 6 months after inoculation. Of 191 volunteers who underwent biopsy, 18 were lost to follow-up. Of the 173 remaining subjects, 21 women and 7 men (16.2% [95% CI, 10.7%–21.7%]) developed hypertrophic scars. More women (21.7% [95% CI, 13.4%–29.8%]) than men (9.2% [95% CI, 2.7%–15.7%]) developed hypertrophic scars (*P* = .028). Of 31 African American subjects, 12 (38.7% [95% CI, 21.6%–55.9%]) developed scars, whereas 14 of 140 white subjects (10% [95% CI, 5%–15%]) developed scars (*P* < .001). Both of the Asian subjects who participated in the study developed hypertrophic scars. All subjects who developed hypertrophic scars received an intradermal injection of triamcinolone, and all scars became flat within 2 months.

### DISCUSSION

If performed under carefully regulated conditions, experimental infection of humans with *H. ducreyi* is safe and involves minimal

| Table 2. *Haemophilus ducreyi* mutants tested in the human challenge model. |
|---------------------------------|---------------------------------|-----------------|-----------------|-----------------|
| **Result, gene**               | **Definition**                  | **Function**    | **Subjects**    |                |
| Attenuated                      | **dsrA**                        | Ducreyi serum resistance A | OMP; major role in serum resistance | 6 [30]          |
|                                | **ncaA**                        | Necessary for collagen adherence | OMP; confers collagen binding | 10 [24]         |
|                                | **lspA1, lspA2**                | Double mutant, large superantigen proteins | Secreted proteins; prevent Fc-γ-mediated phagocytosis | 6 [22]          |
|                                | **pal**                         | Peptidoglycan associated lipoprotein | Lipoprotein; outer membrane stability | 9 [31]          |
|                                | **tadA**                        | Tight adherence protein A | Type IV secretion; secretion of Flp proteins | 15 [21]         |
|                                | **hgbA**                        | Hemoglobin-binding protein | Heme/iron acquisition and transport from hemoglobin | 9 [32]          |
| Partially attenuated            | **fgbA**                        | Putative fibrinogen binding OMP | OMP that binds to fibrinogen in ligand blot | 6 [28]          |
|                                | **dltA**                        | Ducreyi lectin A | OMP; partial serum resistance | 7 [23]          |
|                                | **wecA**                        | First enzyme in the ECA biosynthetic pathway | Initiates synthesis of putative ECA glycoconjugate | 5 [27]          |
| Virulent                        | **hhdB**                        | Secretion/activation of hemolysin | Lyses fibroblasts | 6 [33]          |
|                                | **losB**                        | D-glycerol-D-manno-heptosyltransferase | Extends LOS beyond KDO-triheptose-glucose | 5 [34]          |
|                                | **lst**                         | Lipooligosaccharide sialyltransferase | Adds sialic acid to major glycoform of LOS | 5 [34]          |
|                                | **glu**                         | Glucosyltransferase gene | Adds glucose to KDO-triheptose LOS core | 5 [35]          |
|                                | **cdtC**                        | Cytolethal distending toxin | Toxic for T cells, epithelial cells, and fibroblasts | 6 [36]          |
|                                | **cdtC, hhdB**                  | Double mutant, cytolethal distending toxin, hemolysin | Toxic for T cells, epithelial cells, and fibroblasts | 5 [36]          |
|                                | **sodC**                        | Superoxide dismutase C | Detoxifies reactive oxygen species for bacteria in phagolysosomes | 6 [37]          |
|                                | **momp**                        | Major OMP | OmpA homologue; minor role in fibronectin binding | 6 [38]          |
|                                | **ompP2A, ompP2B**              | Double mutant, porin proteins | Encode known classical trimeric porins | 8 [25]          |
|                                | **ftpA**                        | Major subunit of the fine tangled pilus | Unknown | 7 [39]          |
|                                | **tdX/tdhA**                    | Double mutant; TonB-dependent receptors | Heme uptake | 6 [26]          |

**NOTE.** Mutants were categorized as attenuated (i.e., unable to cause pustule formation even at doses 10-fold greater than the parent dose that resulted in pustule formation), partially attenuated (i.e., able to cause pustule formation at doses 2- or 3-fold greater than the parent dose that resulted in pustule formation, but not at an equivalent dose) or virulent (i.e., able to cause pustule formation at a dose equivalent to the parent dose that resulted in pustule formation). ECA, enterobacterial common antigen; KDO, 3-deoxy-D-manno-octulosonic acid; LOS, lipooligosaccharide; OMP, outer membrane protein.
risk. No subject developed fever, lymphadenopathy, or disseminated lesions. Most volunteers achieved a clinical end point prior to 14 days after inoculation because of local symptoms. Hypertrophic scars developed at biopsied infected sites in 28 (16.2%) of 173 subjects. Although we did not assess lesional levels of transforming growth factor–β in volunteers who formed hypertrophic scars, transforming growth factor–β transcripts are readily amplified from pustules (S.M.S., unpublished data), and expression of transforming growth factor–β may contribute to hypertrophic scar formation by enhancing localized production of collagen and fibronectin [41].

For the limited dose range employed in the model, the odds of forming a papule were dose dependent, whereas the odds of forming a pustule were not dose dependent. The latter result differs from those of analyses reported previously, in which site outcomes in a given subject were assumed to be independent [8, 29, 42]. However, the outcomes of multiple infected sites in a given subject were not independent, indicating a host effect [19]. When reinfected, the subjects had results that segregated toward their initial outcome (pustule formation or resolution of infection). The mechanism of disease resolution is unknown, but it is likely the result of enhanced phagocytic clearance in those subjects whose infections resolve. Some naturally infected patients experience spontaneous clearance of ulcers [2], although others experience multiple recurrences [43]. Taken together, the data suggest that some persons are prone to clearing infection, whereas others are prone to disease progression, and that protective immunity does not develop in those whose disease progresses to pustules or ulcers [19, 20].

The mechanisms that favor disease progression over resolution may be determined in part by the microenvironment at the infected site. Gene expression profiles of infected skin obtained from volunteers who were infected a third time after their first and second infections resolved are consistent with an effective immune response [44]. In contrast, profiles indicative of a hyperinflammatory, dysregulated immune response were present in samples obtained from persons who were infected a third time after developing persistent pustules twice [44]. Monocyte-derived myeloid dendritic cells obtained from the volunteers whose first and second infections resolved expressed transcripts that should promote T helper (Th)–1 and Th17 responses in response to H. ducreyi, whereas dendritic cells from the volunteers who formed persistent pustules twice expressed transcripts consistent with Th1 and regulatory T cell responses [44]. Th1 and Th17 responses may lead to a cytokine environment that promotes phagocytosis, whereas a combined Th1 and regulatory response may inhibit phagocytosis [44]. Alternatively, dendritic cells from the group whose infections resolved might direct natural killer cells to make an appropriate amount of interferon-γ during early stages of infection, which augments phagocytosis.

Men and women formed papules, or became infected, at equal rates; however, men were 2 times more likely to form pustules. The male-to-female ratio of naturally occurring chancroid in areas where the disease is endemic is 3:1, which in part reflects sex differences regarding susceptibility to disease progression [4]. In vitro, H. ducreyi dies at temperatures >35°C. We were unable to assess whether sex differences regarding susceptibility were associated with elevated body temperatures at the time of ovulation in women, because the menstrual cycles of female participants were not assessed in detail [29]. Alternatively, the sex effect may reflect the fact that women are more prone to proinflammatory rather than tolerizing responses, compared with men [45]. If women are less prone to tolerizing responses than men, and if a tolerizing response promotes phagocytic failure, women should be less susceptible to pustule formation than men.

H. ducreyi is more closely related to the animal pathogens Mannheimia haemolytica and Actinobacillus pleuropneumoniae than to human pathogens in the Pasteurellaceae family [46]. Rabbit, primate, swine, and murine models of chancroid have been developed; the infectious doses in these models range from 1 × 10^{4} to 1 × 10^{7} colony-forming units [2, 8]. Murine lesions result from the content of lipooligosaccharide in the inoculum, not viable bacteria. Bacteria are cleared over time in swine [38], and lesions in rabbits also clear spontaneously. In rabbits and swine, 1–2 weeks of infection evoke serum antibody responses and provide protection against repeated exposure; bactericidal activity develops in swine infected repeatedly [47, 48]. The animal models do not simulate human disease sufficiently for the study of pathogenesis or host responses, reflecting the fact that H. ducreyi diverged from other pathogens to occupy its unique niche in the human host [46].

In summary, experimental infection with H. ducreyi clinically and histologically mirrors natural infection and provides an excellent model for studying the pathogenesis of the infection. Since H. ducreyi naturally infects nongenital skin and causes a chronic limb ulceration syndrome [49, 50], the fact that the infection site was on the arm is not a major limitation of the model. Although our model is limited to the pustular stage of disease, the relationships between H. ducreyi and human cells in the model are maintained in natural ulcers [17], suggesting that the duration of infection is also a minor limitation. The model has significantly contributed to the understanding of H. ducreyi pathogenesis and has led to the discovery of immune mechanisms that may underlie differential human susceptibility to H. ducreyi infection.

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References


