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Editorial Response: Are all *Bartonella henselae* Strains Created Equal?

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Of the five Bartonella species associated with disease in humans, B. henselae causes the widest spectrum of pathology, including disease with granulomatous features (cat-scratch disease), vascular proliferative features (bacillary angiomatosis-peliosis, BA-BP), and a predominantly intravascular focus (bacteremia-endocarditis). In the wake of the initial detection of B. henselae and its laboratory propagation in 1990 [1, 2], investigators have learned that B. henselae is distributed worldwide; that cats are reservoirs for the organism; that fleas are vectors for transmission among cats [3, 4]; and that B. henselae, like other Bartonella species, establishes an intimate and persistent relationship within the bloodstream of its hosts. Yet, we understand little about the diversity and population structure of B. henselae and the genetic basis for its pathogenicity. In this regard, the key questions are whether a small number of clonal types account for a disproportionate amount of disease, whether some clonal types are more likely than others to cause a particular type of pathology, whether there is a restricted geographic distribution of specific clonal types, and what is the possible genetic basis of type-specific differences in virulence.

PFGE chromosomal profiles distinguished between these two strains and B. henselae ATCC 49793, originally isolated from the blood of a febrile patient with AIDS in Oklahoma [2], as well as a German feline strain; however, other B. henselae strains were not examined in parallel. In fact, PFGE patterns have been determined for only a small number of B. henselae strains [8]. Thus, it is difficult to compare Berlin-1 with other isolates from around the world. Recently, Sander and colleagues [9] isolated 13 B. henselae strains from 100 domestic cats in Freiburg, Germany [9]; it would be interesting to include these strains in this analysis.

Two other genotypic methods have been proposed for B. henselae strain discrimination: restriction fragment length polymorphism (RFLP) analysis of the intergenic transcribed spacer (ITS) region within the rRNA operon [10], and repetitive element PCR [11]. Each method has revealed moderate strain diversity among the small numbers examined so far [12, 13], in contrast with even more limited diversity among Bartonella quintana strains.

As B. henselae strain typing databases expand and become more standardized, investigators will be able to compare the diversity of strains within cat reservoirs with the diversity of strains that cause various human clinical syndromes. Early studies have revealed a greater number of ITS RFLP strain types in the blood of HIV-infected bacteremic patients than in the cat-scratch-disease lesions of immunocompetent individuals [10, 12], but the role of confounding variables has not been adequately assessed. The possibility that particular B. henselae clones or strains are associated with specific clinical syndromes still cannot be excluded. The work of Arvand and colleagues and other groups will eventually provide data with which human-associated and cat-associated isolates can be compared [9, 14, 15]. It is expected that greater strain diversity will be found within the natural reservoir (cats) than within incidental hosts (humans). In most instances, the strains associated with human disease will also be found in the cats with which these patients had direct contact [13].

The geographic distribution of strains remains unclear. Incomplete data indicate that B. henselae is endemic in the United States, Europe (France, Germany, Holland, and Denmark), Africa (Zimbabwe and South Africa), Australia, and Japan. These diverse sites provide a rich potential source of B. henselae. In general, such methods should provide quantifiable measures of evolutionary distance between any two
strains, relying on genetically stable markers of genomic ancestry. Primary sequence is a useful, quantifiable character. Although rDNA is a phylogenetically reliable marker, it often fails to provide sufficient resolving power at the strain level. Other genetic loci such as the rRNA operon ITS will need to be evaluated further.

Second, many of the most important virulence-associated genes in microbial pathogens are promiscuous and evolutionarily "unstable:" they are shared among strains by means of plasmids, transposable elements, and phages. These genes need to be targeted separately. However, few virulence-associated genes of B. henselae have been identified. It would be expected that the products of such genes subvert host defenses mediated by skin dendritic cells and soluble bloodborne factors, facilitate penetration of tissue stroma and attachment to erythrocytes, elicit angiogenic host cytokines and growth factors, and recognize environmental signals within humans, cats, and fleas. Powerful strategies to identify these genes take advantage of their selective expression within a relevant host environment [16].

In addition, it is now known that many of these genes in general are physically clustered on a plasmid or within a chromosomal "pathogenicity island" and are acquired in "quantum evolutionary leaps" [17, 18]. Might the distribution and composition of pathogenicity islands among extant B. henselae clonal populations explain differing associated disease manifestations? Although there is no evidence to support this speculation, the methods that have been used to identify B. henselae strains are insensitive to pathogenicity island or virulence gene polymorphisms. With continued efforts to identify disease-associated genes by means of genetic and genomic approaches, the population and genomic structure of B. henselae will become more clear. With full genome sequencing for B. henselae under way, it may not be long before B. henselae isolates and the corresponding host responses are both characterized and compared by using comprehensive DNA microarrays in a semi-automated format.

References