Is *Brucella* an enteric pathogen?

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Below, we comment on the article by Renée M. Tsois, Glenn M. Young, Jay V. Solnick and Andreas J. Bäumlér (Exit strategies of intracellular pathogens. *Nature Rev. Microbiol.* **6**, 883–892 (2008))¹.

As suggested previously², the authors propose that the stealthy strategy and cognate reduction in pathogen-associated molecular patterns (PAMPs) of envelope molecules are crucial to *Brucella* pathogenicity. Although we agree with this view, we feel that the article overemphasizes the parallels with *Salmonella enterica* subsp. *enterica* serovar Typhi. Both pathogens invade the lymphatic system and proliferate within regional lymph nodes, but *Brucella* cannot be grouped with enteric pathogens. It is doubtful that primary invasion after *Brucella* ingestion occurs through the intestine. Indeed, dairy products are a source of contagion but solid epidemiological evidence and studies in volunteers have shown that ingestion is inefficient compared with other routes (for example, skin abrasions and aerosols)³. Moreover, although *Brucella* is markedly sensitive to gastric juice, no relationship between achlorhydria and brucellosis has been observed³, indicating that mucosae are not regularly penetrated beyond the oropharynx. Importantly, brucellae can be isolated from tonsils, there is regional lymphadenitis and constipation is far more common than diarrhoea^{3,4}. In cattle, colonization of the lymph nodes that drain the face area is about as frequent in natural infection as in artificial conjunctival infections⁵.

All these observations indicate that the upper mucosae are the normal site of entry, which is consistent with the formidable ecophysiological challenge that the rumen and the intestine pose to brucellae. Whereas *Salmonella* envelopes are

effective barriers that allow growth in the presence of bile salts, *Brucella* envelopes are permeable to hydrophobic compounds. This is not a coincidence, because the reduction of *Brucella* lipopolysaccharide PAMPs^{2,6} (which is essential in the stealthy strategy) is connected to loss of the barrier⁷. It is true that when ligated ileal loops of calves are experimentally injected with large amounts of *Brucella*, the bacteria penetrate through lymphoepithelial M-like cells⁸. However, this probably reflects the use of this model and of large amounts of brucellae, rather than the outcome of an oral infection. Clinically, there is no intestinal damage in brucellosis, whereas necrosis of Peyer's patches is common in untreated typhoid fever.

That *Brucella* is not an enteric pathogen is also supported by phylogenetic and cellular studies. The brucellae belong to the Alphaproteobacteria⁹, together with *Bartonella*, *Anaplasma*, *Ehrlichia* and *Rickettsia*, all of which are intracellular pathogens and share common themes of pathobiology¹⁰. For example, fever is not manifested in concordance with proinflammatory acute responses triggered by PAMP-bearing molecules^{2,6,11}, as occurs in typhoid fever, but rather as a consequence of adaptive immunity and, in some cases, hypersensitivity. In addition, *Salmonella* spp. use at least two type III secretion systems that are encoded in pathogenicity islands (1 and 2)¹² whereas, consistent with its phylogeny, brucellae rely on a type IV secretion system (VirB) for intracellular survival and replication¹³. Recently, one of our laboratories has reported that *Brucella* Btp1 interferes with the Toll-like receptor 2 signalling pathway, suggesting that *Brucella*

and *Salmonella* share some mechanisms of immune evasion¹⁴. However, the marked structural, physiological and phylogenetic differences between these two bacteria are fundamental features that set a clear distinction in their pathobiology.

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