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How well do you know your monkeys?

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We read with interest the letter to the editor titled "How well do you know your monkey model" (1), written in response to our review article "The nonhuman primate model of tuberculosis" (J Med Primatol 41: 191–201) (2). This letter, by Engels and colleagues, raises an important issue about the use of the tuberculin skin test (TST) to detect *Mycobacterium tuberculosis* (*Mtb*) infection in nonhuman primates (NHPs). While we tend to agree with their general philosophy that improved detection of tuberculosis (TB), in particular latent TB, requires the development of more robust technologies, their understanding of our model is inherently flawed.

The authors take for granted that all NHPs used in biomedical research are imported from nondomestic source countries. This is just not the case. The source of all Indian origin rhesus macaques in the US since the late 1970s has been from domestic breeding colonies. This was necessitated by a global ban on the export of Indian rhesus macaques by the government of India at that time. Since then, all Indian origin rhesus macaques at the NPRCs have been domestically bred and the animals are extremely well characterized with respect to infectious diseases such as tuberculosis (TB). As the authors state, rigorous preventive medicine programs have focused on maintaining negative TB status in domestic NHP colonies for many years.

The authors are correct that the highest risk of TB infection in NHP occurs in animals imported from nondomestic sources. As a result, a best practice with respect to such animals is to keep them completely segregated from domestically bred NHPs. NHP originating from areas where TB is prevalent in the human population are extensively screened prior to inclusion at these NPRCs, or not used for TB research studies. Well-characterized domestic sources of NHP or NHP imported from areas without endemic TB are considered for these particular studies. It is the result of these strategies, that no TB outbreak has been detected at the TNPRC amongst domestically bred macaques, for more than two decades now.

The author's contention that "TST commonly fails to detect infection" is an overstatement, at least with respect to rhesus macaques. In an outbreak at the TNPRC close to 10 years ago in imported Chinese origin rhesus monkeys, the TST was diagnostic and was the screening method used to effectively identify cases and contain infection to a single room. Admittedly, adding other testing modalities increased our ability to confirm the diagnosis in this

particular group of animals. The relatively low incidence of spontaneous TB cases in the literature compared to the number of domestic NHP used in research is a testament to the effectiveness of the TST used as a screening tool. If the TST "commonly" failed to detect cases of TB in domestic breeding colonies these colonies would have a much greater prevalence of disease than is currently noted.

This contention is also supported by experimental data. In almost 125 Indian rhesus macaques experimentally infected since 2005, with *Mtb* CDC1551, H37Rv, Erdman or defined mutants of *Mtb* (3–8, unpublished results), here at the TNPRC, TST was able to detect *Mtb* infection. In many of these studies, which involved a vaccination component (6–8), TST always detected vaccination with BCG as well. In fact, we found no difference in the ability of TST and PRIMAGAM® (an interferon-gamma release assay comparable to QUANTIFERON-GOLD®) to detect experimental *Mtb* infection in domestically bred Indian rhesus at identical time-points.

There is no argument that better TB diagnostic assays need to be developed and that the TST is far from a perfect screening tool. This is the driving force behind the development of nucleic acid based diagnostic tests for detecting human infections. However, the enthusiasm for such tests is dampened by the requirement for technology and infrastructure in resource-limited settings.

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