HHS Public Access

Author manuscript

J Med Primatol. Author manuscript; available in PMC 2015 May 29.

Published in final edited form as:

J Med Primatol. 2013 February ; 42(1): 46–47. doi:10.1111/jmp.12030.

How well do you know your monkey TB model?

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We read with interest the recent review article by Kaushal et al. [1] describing advances and promoting the use of non-human primates (NHP) as models to study tuberculosis (TB). Here, we raise some caveats that must be addressed to better understand the NHP model of TB and its limitations.

Laboratory NHPs are imported from 'source countries', where TB is highly prevalent among humans and where NHP–human contact is abundant [2]. For decades, TB has been recognized as a significant infectious threat to NHPs used in biomedical research. Epizootics of *Mycobacterium tuberculosis* complex (MTBC) infection in NHP colonies were linked to high mortality in these settings, driving the development of 'specific pathogen- free' (SPF) colonies, where rigorous screening protocols were designed to assure that animals are not infected with MTBC and a specified group of viruses. Mycobacterial infection is particularly troublesome to detect, as it can remain latent for long periods, reactivating unpredictably to produce active, transmissible infection. Primate laboratories have relied upon the tuberculin skin test (TST) to screen for mycobacterial infection in animals. Rigorous protocols, requiring regular TST, typically at 6-month intervals, combined with strict quarantines for newly imported animals, have been widely implemented to prevent transmission among NHP as well as transmission from NHP to laboratory personnel. In spite of these efforts, outbreaks of TB among SPF laboratory NHPs continue to occur [3], suggesting that MTBC continues to circulate in these populations and/or may be periodically reintroduced with newly imported animals.

We recently published a case series describing MTBC infection in several laboratory pigtailed macaques [4]. Prior to experimental infection with a chimeric immunodeficiency virus, these SPF macaques had been screened at 6-month intervals with the TST, following standard protocol and repeatedly tested negative. MTBC DNA was detected in tissues from the index animal as well as six close contacts. These cases of SHIV/MTBC coinfection were overlooked at necropsy because they did not fit the expected presentation of MTBC infection. Pathologists excluded the possibility of MTBC infection based on the negative pre-experiment TSTs and the SPF status of the colony. This recent cluster, added to numerous prior documented epizootics of TB in NHP colonies, further questions the utility of TST as a screening and diagnostic tool.

How could an SPF animal evade the stringent procedures designed to detect the MTBC bacteria? One problem may be that mycobacterial disease in NHP may manifest in patterns beyond those that are familiar to clinicians [5]. For decades, mycobacterial infection in NHPs was thought most often to cause fulminant disease associated with granulomatous lesions. We are now beginning to understand that the pathology of experimental TB infection is much more complex, and there is great variation in host response within and among NHP species [6]. Additionally, we now know that variation in the strain of MTBC to which a host is exposed influences that host's response to infection; some strains are much less likely to produce a detectable host immune response [7–12]. Thus, it is in fact possible, and even probable, that after decades of importation of hundreds of thousands of NHPs from high-incidence countries, MTBC infections undetectable by our present protocols are present in our colonies [2, 13].

The problematic use of immune-based tests for TB in high-incidence human populations has already been recognized and addressed by the WHO, which took the extraordinary step of recommending that immune-based tests no longer be used in these populations [14, 15] and instead recommend the use of nucleic acid amplification tests. According to researcher David Dowdy, 'Both the scientific community and WHO have spoken—existing serological tests have no role in the diagnosis of active tuberculosis' [16].

If, indeed, TST commonly fails to detect infection, how widespread is MTBC infection in populations of NHP used in research? Data obtained using animals of questionable infection status may confound results of experimental trials. These concerns are particularly germane to research on MTBC transmission, where knowing the infection status of an animal is critically important. Is it possible that, instead of observing the course of experimental infection, we are actually observing concurrent natural infection or reactivation of previously acquired natural infections that have continued to evade detection by TST? Our recently published results [2, 4] suggest that tests based on the detection of MTBC DNA may improve our ability to detect tuberculosis infection in NHP populations and hold promise for maintaining tuberculosis-free NHP colonies. It is time to reexamine infection control protocols at NHP facilities, using data, not dogma, as our guide to producing a scientifically honest NHP biomedical model.

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