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Editorial

Ending Monkey Research for Microbiology and Infectious Disease: A Shift towards Rigorous *In Silico* Analysis and Other Methodologies

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Received: 30 July 2026; Accepted: 24 August 2026; Published: 8 September 2026

How To Cite: Lau, S.K.P.; Woo, P.C.Y. Ending Monkey Research for Microbiology and Infectious Disease: A Shift towards Rigorous *In Silico* Analysis and Other Methodologies. *eMicrobe* **2026**, *2*(3), 15. https://doi.org/10.53941/emicrobe.2026.100015

In November 2025, "Scientists at the Centers for Disease Control and Prevention of the United States of America have been told to phase out all of their monkey research" [1]. This represented a landmark change for research in microbiology and infectious disease.

There are a number of reasons for using non-human primates (NHPs) in microbiology and infectious disease research. The first and foremost one is their high genetic, anatomical, and physiological similarity to humans. Many NHP species share a large proportion of their genome with humans, resulting in comparable cellular receptors, immune signaling pathways, and metabolic processes. This similarity allows human pathogens to infect NHPs via natural routes and cause disease manifestations that closely resemble those observed in humans. In contrast, rodents and other commonly used laboratory animals often require genetic modification or artificial infection routes to model these diseases. Second, NHPs are important for studying immune system function. The innate and adaptive immune responses of these animals closely mirror those of humans, including antibody production, T-cell responses, cytokine signaling, and immune memory. This makes NHPs good animal models for evaluating vaccine efficacy, immunogenicity, and safety prior to human clinical trials. Third, NHPs are extremely valuable for studying long-term infections and latency, which are difficult to model accurately in short-lived animal species. Fourth, NHPs have enabled the study of complex organ systems and behaviors that influence infectious disease outcomes. For example, similarities in brain structure make them important for investigating neurotropic infections, while comparable reproductive physiology allows the study of congenital infections. Furthermore, their social behavior can also provide insight into transmission dynamics and host factors influencing susceptibility.

Among the NHPs, several species are particularly important for microbiology and infectious disease research. Macaques, especially rhesus macaques (*Macaca mulatta*) and cynomolgus macaques (*Macaca fascicularis*), are the most widely used. For example, after we have discovered hepatitis E virus genotype 7 (HEV7) in dromedary camels and HEV8 in Bactrian camels, we successfully used an HEV8-positive Bactrian camel fecal sample to inoculate two cynomolgus macaques and induced chronic and systemic infections, demonstrating the zoonotic potential of HEV8 [2–4]. Other species include African green monkeys (*Chlorocebus sabaeus*), common marmosets (*Callithrix jacchus*), and baboons (*Papio* species), each selected based on the specific research question. For example, marmosets are sometimes used due to their small size and susceptibility to certain viruses. In our study on the Middle East Respiratory Syndrome coronavirus (MERS-CoV), the marmoset model was used for the study of renal complications and their underlying pathogenetic mechanisms [5]. One of the most important reasons for using marmosets in this study is that these animals express dipeptidyl peptidase-4, the functional cellular receptor for MERS-CoV, with a structure and tissue distribution similar to that in humans.

NHP research has been central to understanding the pathogenesis of many serious infectious diseases. One of the most prominent examples is human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) research. Simian immunodeficiency virus (SIV) infection in rhesus macaques and cynomolgus macaques closely mirrors many key aspects of HIV infections in humans, including $CD4^+$ T-cell depletion, chronic immune activation, and progression to AIDS-like disease. This has allowed researchers to study early viral transmission, viral reservoirs, immune responses, and mechanisms of immune dysfunction in ways not possible in humans. Furthermore, NHP models have also been indispensable in the development of antiretroviral therapy, including evaluation of drug efficacy, pharmacokinetics, resistance, and toxicity, as well as prevention strategies such as pre-exposure prophylaxis [6,7]. In addition to HIV, examples of other viruses studied using NHPs include Ebola virus, Zika virus, Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), MERS-CoV, and SARS-CoV-2 [5,8,9]. During outbreaks due to these emerging viruses, NHPs are often used to rapidly evaluate disease mechanisms and test vaccines or antiviral drugs when no other suitable models exist. Apart from viruses, NHPs have also been instrumental in research on tuberculosis. Macaques infected with *Mycobacterium tuberculosis* develop disease that closely resembles human tuberculosis, with a full range of tuberculosis states, including latent infection, subclinical disease, reactivation, and active pulmonary or extrapulmonary tuberculosis [10,11]. Importantly, NHP models have been particularly important in studying the immunopathogenesis of tuberculosis. They have helped clarify the roles of $CD4^+$ and $CD8^+$ T cells, innate immune responses, cytokine signaling, and immune regulation in controlling or exacerbating disease. More specifically, primate studies have demonstrated that disease outcome is determined not only by bacterial burden but also by the balance between protective immune and immune-mediated pathology. This has helped researchers understand how tuberculosis persists in the body and how immune responses control or fail to control the infection.

Despite all the advantages of using NHPs in microbiology and infectious disease research, significant concerns have been raised due to their high cognitive abilities, social complexity, and capacity to experience distress. As a result, NHP research is subject to strict regulations in many countries. Typically, NHP studies require extensive ethical review and justification, demonstrating that the research addresses an important scientific or medical question and that no suitable alternative exists. As a principle, the best option is to use computational analysis and modeling as well as other methods that do not require the use of whole animals, such as cell culture and organoid [12–14]. If the use of animal models is necessary, less sentient animal species, such as BALB/c mouse and its variants (e.g., severe combined immunodeficiency mouse, humanized mouse, transgenic mouse), are preferred [15]. Lastly, if the use of NHPs is considered essential, the number of animals used should be minimal, and housing, care, and experimental techniques should be optimized so that pain and distress can be reduced. The phasing out of all NHP research in the Centers for Disease Control and Prevention of the United States of America should make us reflect whether the use of NHPs in our own research laboratories is really irreplaceable, and whether we can shift towards rigorous *in silico* analysis and other methodologies.

Funding

This work was partly supported by the Feature Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE-115-S-0023-A) in Taiwan.

Conflicts of Interest

Given the role as Editor-in-Chief, Patrick C.Y. Woo had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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