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Union Minister of Health and Family Welfare

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hfm@gov.in

Subject: For Dr Harsh Vardhan, from PETA India: Request to cancel permission for the capture of wild monkeys for use in research by NIV

Dear Dr Harsh Vardhan Ji,

I am writing on behalf of People for the Ethical Treatment of Animals (PETA) India and our more than 2 million members and supporters to draw your attention to the Maharashtra government's recent decision to grant permission for the capture of rhesus monkeys for use by the National Institute of Virology (NIV) in the testing of a vaccine for the novel coronavirus (SARS-CoV-2).

This letter is co-signed by my colleague Dr Lisa Jones-Engel, a recognised authority on the role that free-ranging Asian primates play in the maintenance and transmission of infectious agents as well as their suitability as biomedical models of infectious diseases. Her decades of research and expertise have informed our response to NIV's misguided decision to capture wild rhesus macaques for use in SARS-CoV-2 studies.

Based on the scientific information presented below, we respectfully ask that you instruct NIV to halt this research and that you help the institute adopt superior, human-relevant, animal-free research methods instead.

Scientific Challenges and Zoonotic Risks

The recent decision by the Maharashtra government to grant permission for the capture of wild rhesus monkeys for use in SARS-CoV-2 vaccine testing by NIV is at odds with basic scientific principles. For decades, the international biomedical research community has acknowledged that rigorous scientific investigation requires a thorough understanding of any potentially confounding factors that may obscure scientists' knowledge of the immune function of their research subject.^{1,2,3} When the decision is made to use an animal model, the scientific community has consistently used well-characterised, specific-pathogen-free (SPF) animals capable of exhibiting a normal immune response to viral infection or vaccination.⁴ The use of SPF animals is also critical in protecting the health of laboratory workers and scientists who are exposed to them.

¹Morton WR, Agy MB, Capuano SV, Grant RF. Specific pathogen-free macaques: Definition, history, and current production. *ILAR J.* 2008;49(2):137-144. doi:10.1093/ilar.49.2.137

²Yee JL, Vanderford TH, Didier ES, et al. Specific pathogen free macaque colonies: A review of principles and recent advances for viral testing and colony management. *J Med Primatol.* 2016;45(2):55-78. doi:10.1111/jmp.12209

³Anderson DM. The Nonhuman Primate as a Model for Biomedical Research. *Sourcebook of Models for Biomedical Research.* 2008;251-258. doi:10.1007/978-1-59745-285-4_28

⁴Desrosiers RC. The value of specific pathogen-free rhesus monkey breeding colonies for AIDS research. *AIDS Res Hum Retrov.* 1997;13(1):5-6.

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Wild-caught rhesus macaques will not be well characterised and will most certainly not be SPF. More than 80% of rhesus macaques in India are in close proximity to human settlements.⁵ Infectious agents move with ease between human and non-human primate populations. It should be expected – and has been repeatedly shown – that pathogens such as *Mycobacterium tuberculosis* complex, picornaviruses, paramyxoviruses, influenza viruses, astroviruses, a broad range of enteric pathogens, and enzootic viruses are present in free-ranging rhesus macaque populations in Asia, and these pathogens can be shared among humans and monkeys.^{6,7,8,9,10,11,12} There is also a risk that zoonotic pathogens such as Kysanur forest disease virus would be spread to those who trap and handle free-ranging monkeys in Maharashtra.¹³

The presence of these and other infectious agents in recently captured macaques, as well as the act of trapping and transporting them, will compromise their immune function and distort the interpretation of the results of the vaccine studies at NIV. Finally, serologic tests for SARS-CoV-2 have been shown to perform poorly even in well-characterised SPF macaques.¹⁴

Animal models have consistently failed to replicate the pathology of disease observed in humans infected with severe acute respiratory syndrome coronavirus (SARS-CoV) or Middle East respiratory syndrome coronavirus (MERS-CoV). Please see the review by Greteback and Subbarao for a detailed

⁵Southwick CH, Siddiqi MR. Population trends of rhesus monkeys in villages and towns of Northern India, 1959–65. *J Anim Ecol.* 1968;37(1):199-204.

⁶Meyer HM Jr, Brooks BE, Douglas RD, Rogers NG. Ecology of measles in monkeys. *Am J Dis Child.* 1962;103:307-313. doi:10.1001/archpedi.1962.02080020319025

⁷Jones-Engel L, Steinkraus KA, Murray SM, et al. Sensitive assays for simian foamy viruses reveal a high prevalence of infection in commensal, free-ranging Asian monkeys. *J Virol.* 2007;81(14):7330-7337. doi:10.1128/JVI.00343-07

⁸Wilbur AK, Engel GA, Rompis A, et al. From the mouths of monkeys: Detection of *Mycobacterium tuberculosis* complex DNA from buccal swabs of synanthropic macaques. *Am J Primatol.* 2012;74(7):676-686. doi:10.1002/ajp.22022

⁹Karlsson EA, Engel GA, Feeroz MM, et al. Influenza virus infection in nonhuman primates. *Emerg Infect Dis.* 2012;18(10):1672-1675. doi:10.3201/eid1810.120214

¹⁰Oberste MS, Feeroz MM, Maher K, et al. Characterizing the picornavirus landscape among synanthropic nonhuman primates in Bangladesh, 2007 to 2008. *J Virol.* 2013;87(1):558-571. doi:10.1128/JVI.00837-12

¹¹Feeroz MM, Soliven K, Small CT, et al. Population dynamics of rhesus macaques and associated foamy virus in Bangladesh. *Emerg Microbes Infect.* 2013;2(5):e29. doi:10.1038/emi.2013.23

¹²Karlsson EA, Small CT, Freiden P, et al. Non-human primates harbor diverse mammalian and avian astroviruses including those associated with human infections. *PLoS Pathog.* 2015;11(11):e1005225. doi:10.1371/journal.ppat.1005225

¹³Sayed N. Maharashtra takes measures against spread of Kysanur forest disease. *Hindustan Times*, 23 January 2019. <https://www.hindustantimes.com/pune-news/maharashtra-takes-measures-against-spread-of-kyasanur-forest-disease/story-niFej2v3yFqR7K1ShIIR.html>

¹⁴Yee JL, Van Rompay KKA, Carpenter AB, et al. SARS-CoV-2 surveillance for a non-human primate breeding research facility [published online ahead of print, 2020 Jul 3]. *J Med Primatol.* 2020;10.1111/jmp.12483. doi:10.1111/jmp.12483

discussion of the limitations¹⁵ of all animal models, and also see an editorial by Leist and colleagues discussing novel animal-free test methods for the development of COVID-19 drugs and vaccines.¹⁶

Coronavirologist Professor Dave Matthews and colleagues recently published¹⁷ a study demonstrating that SARS-CoV-2 can mutate when undergoing replication in cell culture and/or during vaccine challenge studies in animals, including non-human primates. The authors state, "**This has clear implications for the use of Vero cells to propagate and grow large batches of the virus for research and especially virus batches grown for use in vaccine challenge studies. Moreover, it also raises the possibility that even virus stocks which have been carefully assayed for homogeneity could still spontaneously generate this deletion during animal challenge studies – particularly in non-human primates.**"¹⁸

This study and others demonstrate that it is reasonable to expect that some of the SARS-CoV-2 virus used to inoculate monkeys will mutate in order to more efficiently adapt to or infect this novel host. This, in turn, means scientists will have difficulty distinguishing the effects of the treatments or vaccines they're testing from the effect of the virus mutation.

NIV's critical research to develop treatments and/or vaccines to protect humans from COVID-19 can and should be conducted using cutting-edge research methods and tools. The use of wild, non-SPF monkeys will only delay and possibly derail these efforts.

Regulatory Agency Preference

The report of the first global regulatory workshop on COVID-19 vaccine development of the International Coalition of Medicines Regulatory Authorities advises researchers developing vaccines to draw on their experience of vaccine platforms and suggests that toxicology data and clinical data from other vaccines from the same platform can be used to support first-in-human (FIH) clinical trials. It also states that developers do not need to demonstrate vaccine efficacy in "animal challenge models" before proceeding to FIH clinical trials.¹⁹ The Central Drugs Standard Control Organisation has also reduced unnecessary

¹⁵Gretebeck LM, Subbarao K. Animal models for SARS and MERS coronaviruses. *Curr Opin Virol.* 2015;13:123-129. doi:10.1016/j.coviro.2015.06.009

¹⁶Busquet F, Hartung T, Pallocca G, Rovida C, Leist M. Harnessing the power of novel animal-free test methods for the development of COVID-19 drugs and vaccines. *Arch Toxicol.* 2020;94(6):2263-2272. doi:10.1007/s00204-020-02787-2

¹⁷Davidson AD, Williamson MK, Lewis S, *et al.* Characterisation of the transcriptome and proteome of SARS-CoV-2 using direct RNA sequencing and tandem mass spectrometry reveals evidence for a cell passage induced in-frame deletion in the spike glycoprotein that removes the furin-like cleavage site. *Genome Med.* 2020;12:68. <https://doi.org/10.1186/s13073-020-00763-0>
¹⁸*Ibid.*

¹⁹International Coalition of Medicines Regulatory Authorities. Global regulatory workshop on COVID-19 vaccine development: Summary report. 2020.
<http://www.icmra.info/drupal/sites/default/files/2020-03/First%20regulatory%20COVID-19%20workshop%20-%20meeting%20report%20March%202020.pdf>

requirements for animal toxicity tests in the development of therapies for COVID-19.²⁰

Experimenting on animals is not only unethical but also unjustifiable from a scientific perspective, since it repeatedly fails to produce results that address pressing human health issues.²¹

Regulations Require the Use of Available Non-Animal Methods

Section 17(2)(d) of The Prevention of Cruelty to Animals (PCA) Act, 1960, states that "experiments on animals [must be] avoided wherever it is possible to do so".²²

We humbly request that, in consideration of the fundamental scientific concerns surrounding the use of wild-caught, non-SPF monkeys, you instruct NIV to halt this research immediately. Additionally, we urge you to help NIV invest in and make the transition to non-animal research techniques in order to accelerate the development of vaccines and treatments for COVID-19.

We would be happy to arrange a teleconference to discuss this important issue. Dr Jones-Engel can be contacted via Skype at jones-engel or at LisaJE@peta.org, and I can be contacted on +91 8800897382 or at DiptiK@petaindia.org. We look forward to hearing from you.

Kind regards,



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²⁰Central Drugs Standards Control Organisation. Order listing the regulatory pathways for research and development for drugs and vaccines. 19 March 2020.
https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NTc2OQ

²¹National Center for Advancing Translational Sciences (NCATS). About NCATS.
<https://ncats.nih.gov/about>. Updated 4 February 2020. Accessed 3 July 2020.

²²The Prevention of Cruelty to Animals Act, 1960.
http://cpcsea.nic.in/WriteReadData/userfiles/file/No_59.pdf.