Vaccine Development and Ethical Sidetracking: Nonhuman primates in COVID-19 Biomedical Research

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Abstract

The current ethical paradigm condones the use of nonhuman animals for biomedical research experiments. Such use of animals has been acknowledged as a practice that comes with a considerable moral burden, and thus certain regulations have been established to control it. The singularity of nonhuman primates (NHPs), in terms of their cognitive and emotional complexity, grants them virtual personhood status, which is reflected in a stricter legislation, that nonetheless allows their use in certain cases. The pandemic brought about by SARS-CoV-2 has accelerated the classical drug development design model, and NHPs have been among the species used to test novel therapies. In this study, a search on the characteristics of NHPs and experimental techniques performed for COVID-19 vaccine development purposes will be used to weigh the costs and benefits of these practices. Taking a critical viewpoint, the results of these studies will be analyzed beyond their quantitative dimensions, considering the harm entailed for humans and NHPs, as well as the extension of potential benefits.

Keywords
COVID-19, vaccine development, animal experimentation, nonhuman primates

Resumen

El paradigma ético actual avala el uso de animales no humanos para experimentos en investigación biomédica y, al reconocerse como una práctica con una considerable carga moral, se han establecido ciertas regulaciones. La singularidad de los primates no humanos (PNH) en cuanto a su complejidad cognitiva y emocional conlleva su consideración como personas en ciertos aspectos, que se refleja en una legislación más estricta, pero que igualmente permite su uso en ciertos casos. La pandemia causada por el SARS-CoV-2 ha precipitado la investigación hacia su diseño más clásico, y los PNH se han usado para poner a prueba nuevas terapias. En este estudio, la búsqueda de las características de los PNH y de los procedimientos experimentales para el desarrollo de la vacuna de la COVID-19 se usará para ponderar los costes y beneficios de estas prácticas. Bajo una mirada crítica, los resultados de estos estudios serán analizados más allá de los números, considerando los daños sufridos por humanos y PNH, además de la extensión de los beneficios.

Palabras clave
COVID-19, desarrollo de vacunas, experimentación animal, primates no humanos

Introduction

COVID-19 emergency

The emergence and uncontrolled spread of infectious diseases calls for an international effort to reverse their harmful effects on humans. From the scientific field, biomedical research is the keystone to explore novel and inventive solutions that are ultimately aimed at developing pharmacological therapy. The use of well-established technical knowledge and considerable funding are required to design and, in due time, distribute a treatment with guarantees of safety.

However, the rapid propagation of SARS-CoV-2 (the coronavirus disease 2019 or COVID-19) and its effect on humans has disrupted classic drug development tempos. In this scenario, there has been an urgent need to acquire knowledge on the virus, infection mechanisms and the pathophysiology of the disease before an effective vaccine could be launched to market. For this purpose, nonhuman animals have been used in laboratories as infection, treatment and drug safety models prior to human trials.

Animal experimentation

Animal experimentation is a regular practice in science, used in basic and clinical research, product testing, toxicity assays and in educational institutions. The most recent data reports that around 10 million animals have been annually used in the EU, and approximately 700,000 in the USA, for scientific purposes (European Commission, 2018; US Department of Agriculture, 2019). However, this is an underestimate, as many other animals are killed to provide experimental tissues, maintain specific strains or because they are a surplus to the required number (Knight, 2011). The final estimate totals approximately 115.3 million animals used yearly, a more than ten-fold increase over the officially-reported figure (Taylor *et al*., 2008). The most frequently used species in the EU are mice (52%), fishes (26%) and rats (9%). On the other extreme, experimental-use cats and nonhuman primates (NHPs) form a minority (0.3%). Animals are used for basic research (46%), applied research (27%), toxicity and safety testing (18%), animal-derived product production (5%) and other purposes (4%), a category that includes education and preservation of species (US Department of Agriculture, 2019).

A number of public authorities have stated that the use of nonhuman animals for scientific reasons should be brought to an end, and replaced in time with other techniques. The legislation restricts the use of certain species and practices. Every project is mandatorily reviewed and approved by ethical committees that guarantee

that nonhuman animals will be treated prioritizing their wellbeing and avoiding unnecessary distress, pursuant to the current standards. Before the approval of any protocol, the 3R principle (replacement, reduction and refinement) must be considered: alternative methods must replace the use of nonhuman animals. If this is not possible, the number of individuals must be minimized and the procedures refined to cause as little pain as possible.

Ethical paradigms

The use of nonhuman animals for scientific purposes has historically been a subject of debate raised from different ethical perspectives, including the religious viewpoint, under which all animals are considered worthy of mercy. The establishment of the first animal laboratory, in Oxford in 1885, was quickly contested in and outside academic spheres, with figures such as Charles L. Dodgson (better known as Lewis Carrol) decrying "*the cost of torturing God's creatures*". The protests advocated a moral consideration of the animals, and firmly opposed "vivisection" (what we now know as animal experimentation), cruelty and torture.

After almost 140 years, animal experimentation is still a subject of debate and paradoxically common in biomedical research. Yet, the results from the studies of consciousness, intelligence and sentience in nonhuman animals openly question the institutionalization of this practice. The scientific understanding of sentience proves that many species are capable of processing subjective life experiences, including feelings such as pain and emotions. With the scientific understanding of sentience, animal experimentation is but one example of the practices that must be urgently redesigned. The moral agency of all sentient animals raises ethical questions, similar to the ones raised in the past on human experimentation (Johnson, 2020), and requires a thorough revision.

Considering the scientific conclusions in the field of sentience, only a systematic disregard of the life and wellbeing of sentient nonhuman animals would justify their experimental use in biomedical research. Positions that defend animal experimentation are increasingly unpopular, as in recent decades social awareness has been raised, and has ultimately crystallized in so-called animal welfare policies. In this sense, this *utilitarianism* – the current ethical paradigm – occupies an intermediate position: the use of animal models is considered legitimate as long as the benefits outweigh the costs. Therefore, a significant gain of knowledge would justify the sacrifice of animals. On the other extreme are *abolitionists* who consider believe in the moral agency of sentient animals – individuals with a life that has an intrinsic value regardless of their relationship with or use for humans – and advocate the

defense of their rights and interests. Under the abolitionist perspective, no amount of suffering for human benefit is justifiable, as all human and sentient nonhuman animals have the same right to live, thrive and avoid undesirable experiences.

The NHP singularity

Among all nonhuman animals, NHPs are the group most similar to humans. Our close relationship in shared genetic components makes NHPs a good model for the study of human disease. But, the general acknowledgement of their capacity for consciousness, intelligence, culture and language, as well as their behavioral traits, raises unprecedented empathy towards them that subsequently challenges the current utilitarianism (Johnson, 2020). European legislation on animal experimentation states that "*Animals have an intrinsic value which must be respected*". The laws recognize nonhuman animals' right to be treated as sentient creatures and stress the importance of the 3Rs. Within this directive, the singularity of NHPs is recognized and treated as a special case because it "*is of the greatest concern to the public*". That is why their use in research requires scientific justification of the impossibility to use an alternative method or species. NHP research for the protection of the natural environment, forensic inquires and education is banned. It is nonetheless allowed to experiment with NHPs for applied research and drug testing, and for basic research and species preservation, only in case of debilitating or life-threatening conditions in humans. According to the European commission, NHPs are the best suited species to test biopharmaceuticals and drugs that affect the eyes, coagulation, the central nervous system, female genitals, fertility and that cause vomiting or birth defects. They also recommend the use of young primates for safety testing of pediatric drugs (European Commission, 2017).

Aims and development of the study

For the purposes of this article, exhaustive bibliographical research has been conducted to report on the role of NHPs for COVID-19 vaccine research. The main aim of this study is to collect information from public sources to analyze the experimental procedures and their transparency as well as the consequences. Subsequently, we propose a critical analysis considering practical, legal and ethical implications to engage in debate on the cross-talk of science and ethics, and the changes of scientific design in the advent of alternative methods.

Methods

A bibliographic search in PubMed using the terms "((COVID) OR (SARS)) AND (VACCINE)" filtering the species as "Other animals" was done for the period of March 2020 - March 2021. Of the 691 results, 65 comprised the terms "primate", "monkey", "macaque", "baboon", and/or "marmoset" in either their title, abstract or authors' affiliation. Finally, a more detailed search was performed to select the studies directly using any species of NHP and discarding reviews and non-research manuscripts. Forty studies remained for further exploration (**Table 1**). The selected articles were thoroughly analyzed. The items of interest were the species, number of individuals, origin and procedures directly affecting the NHP while still alive and for their killing.

Table 1. Studies using NHP for COVID-19 research from Marc 2020 to March 2021

Title	DOI	Journal	Date
Comparison of rhesus and cynomolgus macaques as an infection model for COVID-19.	10.1038/s41467-021-21389-9	Nat Commun	2021 Feb
Exhaled aerosol increases with COVID-19 infection, age, and obesity.	10.1073/pnas.2021830118	Proc Natl Acad Sci U S A	2021 Feb
SARS-CoV-2 induces robust germinal center CD4 T follicular helper cell responses in rhesus macaques.	10.1038/s41467-020-20642-x	Nat Commun	2021 Jan
SARS-CoV-2 spike glycoprotein vaccine candidate NVX-CoV2373 immunogenicity in baboons and protection in mice.	10.1038/s41467-020-20653-8	Nat Commun	2021 Jan
A therapeutic neutralizing antibody targeting receptor binding domain of SARS-CoV-2 spike protein.	10.1038/s41467-020-20602-5	Nat Commun	2021 Jan
Neutralizing antibody-dependent and -independent immune responses against SARS-CoV-2 in cynomolgus macaques.	10.1016/j.virol.2020.12.013	Virology	2021 Feb
Responses to acute infection with SARS-CoV-2 in the lungs of rhesus macaques, baboons and marmosets.	10.1038/s41564-020-00841-4	Nat Microbiol	2021 Jan
D614G Spike Mutation Increases SARS CoV-2 Susceptibility to Neutralization.	10.1016/j.chom.2020.11.012	Cell Host Microbe	2021 Jan
Baricitinib treatment resolves lower-airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques.	10.1016/j.cell.2020.11.007	Cell	2021 Jan
Correlates of protection against SARS-CoV-2 in rhesus macaques.	10.1038/s41586-020-03041-6	Nature	2021 Feb
Nanoparticle Vaccines Based on the Receptor Binding Domain (RBD) and Heptad Repeat (HR) of SARS-CoV-2 Elicit Robust Protective Immune Responses.	10.1016/j.immni.2020.11.015	Immunity	2020 Dec
Dalbavancin binds ACE2 to block its interaction with SARS-CoV-2 spike protein and is effective in inhibiting SARS-CoV-2 infection in animal models.	10.1038/s41422-020-00450-0	Cell Res	2021 Jan
A single-dose live-attenuated YF17D-vectored SARS-CoV-2 vaccine candidate.	10.1038/s41586-020-3035-9	Nature	2021 Feb
Cellular events of acute, resolving or progressive COVID-19 in SARS-CoV-2 infected non-human primates.	10.1038/s41467-020-19967-4	Nat Commun	2020 Nov
Establishment of an African green monkey model for COVID-19 and protection against re-infection.	10.1038/s41590-020-00835-8	Nat Immunol	2021 Jan

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Title	DOI	Journal	Date
Virulence and pathogenesis of SARS-CoV-2 infection in rhesus macaques: A nonhuman primate model of COVID-19 progression.	10.1371/journal.ppat.1008949	PLoS Pathog	2020 Nov
Elicitation of Potent Neutralizing Antibody Responses by Designed Protein Nanoparticle Vaccines for SARS-CoV-2.	10.1016/j.cell.2020.10.043	Cell	2020 Nov
NVX-CoV2373 vaccine protects cynomolgus macaque upper and lower airways against SARS-CoV-2 challenge.	10.1016/j.vaccine.2020.10.064	Vaccine	2020 Nov
Hydroxychloroquine prophylaxis and treatment is ineffective in macaque and hamster SARS-CoV-2 disease models.	10.1172/jci.insight.143174	JCI Insight	2020 Dec
Vascular Disease and Thrombosis in SARS-CoV-2-Infected Rhesus Macaques.	10.1016/j.cell.2020.10.005	Cell	2020 Nov
SARS-CoV-2 infection of African green monkeys results in mild respiratory disease discernible by PET/CT imaging and shedding of infectious virus from both respiratory and gastrointestinal tracts.	10.1371/journal.ppat.1008903	PLoS Pathog	2020 Sep
An Antioxidant Enzyme Therapeutic for COVID-19.	10.1002/adma.2020049011	Adv Mater	2020 Oct
SARS-CoV-2 spike produced in insect cells elicits high neutralization titres in non-human primates.	0.1080/22221751.2020.1821583	Emerg Microbes Infect	2020 Dec
SARS-CoV-2 Assays To Detect Functional Antibody Responses That Block ACE2 Recognition in Vaccinated Animals and Infected Patients.	10.1128/JCM.01533-20	J Clin Microbiol	2020 Oct
An adenovirus-vectored COVID-19 vaccine confers protection from SARS-COV-2 challenge in rhesus macaques.	10.1038/s41467-020-18077-5	Nat Commun	2020 Aug
A Thermostable mRNA Vaccine against COVID-19.	10.1016/j.cell.2020.07.024	Cell	2020 Sep
Development of an Inactivated Vaccine Candidate, BBIBP-CorV, with Potent Protection against SARS-CoV-2.	10.1016/j.cell.2020.06.008	Cell	2020 Aug
ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques.	10.1038/s41586-020-2608-	Nature	2020 Oct
Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques.	10.1038/s41586-020-2607-z	Nature	2020 Oct
A vaccine targeting the RBD of the S protein of SARS-CoV-2 induces protectiveimmunity	10.1038/s41586-020-2599-8	Nature	2020 Oct
Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates.	10.1056/NEJMoa2024671	N Engl J Med	2020 Oct
Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates.	10.1038/s41586-020-2558-4	Nature	2020 Sep
An Alphavirus-derived replicon RNA vaccine induces SARS-CoV-2 neutralizing antibody and T cell responses in mice and nonhuman primates.	10.1126/scitranslmed.abc9396	Sci Transl Med	2020 Aug
Potently neutralizing and protective human antibodies against SARS-CoV-2.	10.1038/s41586-020-2548-6	Nature	2020 Aug
Recombinant SARS-CoV-2 spike S1-Fc fusion protein induced high levels of neutralizing responses in nonhuman primates	10.1016/j.vaccine.2020.06.066	Vaccine	2020 Jul
Infection with novel coronavirus (SARS-CoV-2) causes pneumonia in Rhesus macaques	10.1038/s41422-020-0364-z	Cell Res	2020 Aug
SARS-CoV-2 infection protects against rechallenge in rhesus macaques.	10.1126/science.abc4776	Science	2020 Aug
DNA vaccine protection against SARS-CoV-2 in rhesus macaques.	10.1126/science.abc6284	Science	2020 Aug
SARS-CoV-2 Receptor ACE2 Is an Interferon-Stimulated Gene in Human Airway Epithelial Cells and Is	10.1016/j.cell.2020.04.035	Cell	2020 May

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Title	DOI	Journal	Date
Detected in Specific Cell Subsets across Tissues. Development of an inactivated vaccine candidate for SARS-CoV-2.	10.1126/science.abc1932	Science	2020 Jul

Results

Main results

A total of 581 NHPs were used for COVID-19 vaccine research from March 2020 to March 2021 (with an average of 12 per study, ranging from 2-52 individuals). The most frequent species was *Macaca mulatta* (rhesus macaque) by far, followed by *Macaca fascicularis* (crab-eating macaque or cynomolgus monkey) *Chlorocebus aethiops* (grivet), Macaca nemestrina (southern pig-tailed macaque), *Callithrix jacchus* (common marmoset) and *Papio hamadryas* (hamadryas baboon). One study failed to mention the species, referring to the subjects as "macaques" (Ren *et al.*, 2020). Two different species were used in five studies and species were used in one study. The majority of studies did not clearly state the origin of the subjects (wild or purpose-bred), the use of anesthesia and/or analgesics or the killing procedure (**Table 2**).

Table 2. Details of NHP studies selected

Number of individuals		**581**
Species	Macaca mulatta	70,0%
	Macaca fascicularis	22,5%
	Chlorocebus aethiops	10,0%
	Macaca nemestrina	5,0%
	Callithrix jacchus	2,5%
	Papio hamadryas	2,5%
	Unreported species	2,5%
Origin	Wild	2,50%
	Purpose-Breeding	35,0%
	Unreported	65,0%
Use of anesthesia/analgesics	Yes	45,0%
	No	0,0%
	Unreported	55,0%
Killing procedure	Reported	77,5%
	Unreported	22,5%

Experimental procedures

As the majority of the studies were vaccine trials, virus inoculation was widely reported. Numerous techniques were used for this procedure: oral, intravenous, intramuscular, subcutaneous, intranasal, intratracheal, intraperitoneal, conjunctival and aerosol exposure. For the extraction of biological samples from live NHPs, blood was obtained by venipuncture, and mucosal tissues via nasopharyngeal, oral, conjunctival and rectal cotton swabs. Other procedures such as bronchoscopy and bronchoalveolar lavage (to collect a sample from the lungs) were reported in some studies.

Veterinary care was provided in some studies, including physical, clinical and behavioral monitoring. Biological constants were obtained by different means, including rectal body temperature measurements and data collection by surgery-implanted telemetric devices. Imaging by X-ray and computed tomography were used to study lung morphology. Respiration was assessed by respirometry and plethysmography. Intranasal and intratracheal gavage were some of the other techniques used with NHPs.

The most extensively used anesthetic was ketamine, but xylazine, tiletamine, zolazepam, atropine and medetomidine were also used. After the experiments, NHPs were killed – an act reported as *euthanasia* – with an overdose of opioids and barbiturates, in some cases following the administration of analgesics. None of the studies mentioned any later planning for the NHPs, such as animal repurposing or relocation in specialized centers or sanctuaries. It is likely that all NHPs, regardless of whether they belonged to a control or non-control group, were killed after their respective studies.

Evaluation of costs

These experimental procedures entail different degrees of distress and pain for the NHPs. Yet, events that can be potentially damaging can occur long before their entry into a study. The capture of wild NHPs is highly stressful and physical injuries often occur. NHP isolation from their social network has considerable psychological consequences. Intermediary holding centers are often located in the country of origin, and frequently have suboptimal conditions that do not guarantee NHP welfare. Transportation to distant countries and continents takes a long time and the individual is exposed to stressful stimuli (visual, thermic, auditory inputs, shaking, etc.). Beyond physical and psychological harm, this process can trigger deficits in the immune response that increase the risk of disease (Knight, 2011). Only the study by Fahlberg and colleagues explicitly states that four *Chlorocebus aethiops* were wild-caught (Fahlberg et al., 2020), and 65% of the studies do not report the origin of their NHPs.

NHPs involved in biomedical research are held in cages. According to the legislation, the minimum cage dimensions for 1-2 individuals is species-dependent and is set to 0.5 m2 x 1.5 m for marmosets, 2.0 m2 x 1.8 m for macaques, squirrel monkeys and verbets and 7.0 m2 x 1.8 m for adult baboons. For highly-sensitive individuals such as these, being deprived of the liberty to roam and engage in social networking at will can trigger psychological consequences. The dissimilarities between animal housing and their natural environment can result in behavioral anomalies that include stereotypy, aggressiveness, neglect or killing of young and self-harm. Environmental enrichment is an acknowledged resource to minimize boredom and other consequences that can compromise the individual's well-being. Holistic enrichment in laboratories involves sensorial, physical and social stimulation, the introduction of puzzles and novel elements in the cage as well as the lack of routine in food variety and frequency. The selected studies do not mention the features of caging and environmental enrichment, since most of the individuals come from specialized facilities (Buchanan-Smith, 2011).

As stated, all the procedures planned for a study involving nonhuman animals require the approval of the relevant ethics committees. There are rating categories determined by "*the degree of pain, suffering, distress or lasting harm expected to be experienced by an individual*". The severity ranges from mild, in which the individual suffers short-term mild pain, suffering or distress, but there is no significant impairment of well-being, to severe, in which pain is either grievous or long-lasting, or the result greatly impairs normal functioning. The experimental procedures of the selected studies can be categorized as follows:

– *Mild*: use of anesthesia, administration of substances by subcutaneous, intramuscular and intraperitoneal routes, gavage and intravenously via superficial blood vessels, short-term deprivation of social partners and non-invasive imaging with appropriate sedation or anesthesia (although the use of anesthesia is unreported in most studies).
– *Moderate*: frequent application of test substances that produce moderate clinical effects, surgery under general anesthesia and appropriate analgesia for the implantation of biomedical devices.
– Severe: vaccine potency testing characterized by persistent impairment of the animal's condition, associated with long-lasting moderate pain, distress or suffering.

Most nonhuman animals, even untreated nonanimals used in control groups, are killed after the experiment. There are diverse legal methods for killing nonhuman animals: physical (cervical dislocation, decapitation, concussion, shooting, captive bolt), suffocation (with carbon dioxide or inert gases), electrical stunning or

anesthetic overdose. Some procedures, especially the most potentially harmful, are only permitted in certain species. Possibly because of their singularity, the only legal method to kill NHPs is by an anesthetic overdose. In the selected studies, the substances chosen to kill the subjects were opioids and barbiturates, such as embutramide or pentobarbitone.

Evaluation of benefits

The benefits of NHP biomedical research in COVID-19 vaccine development must be thoroughly evaluated. The applicability of the results, whether positive or negative, will be measured with their translation to clinical studies. For this, the selected studies will be examined taking into account the number of citations, the goals of the studies that cite them and the replication/confirmation of previous results. Subsequent studies that follow the lead in NHP experimentation are not foreseen in the immediate future. Therefore, a refractory time between publications should be considered.

Like any model in biomedical science, NHP research has a number of limitations that can limit or bias results. Therefore, an evaluation of the quality standards will be performed, including the quality of NHPs for COVID-19 infection models, randomization of groups, bias due to non-blinded researchers or the statistical power calculations to ensure the optimal sample size. Moreover, an exploration of currently available alternative methods may prompt the partial or total replacement of invasive animal experimentation in the near future. Techniques such as cell culture, computational biology, *organ-in-chip*, etc. will be compared to the current techniques used in NHPs.

Conclusions

Limitations

The methodology used for this study has several shortcomings that must be considered. Published results obtained in any scientific study are not immediately assimilated by the scientific community. Therefore, studies in development might be following the lead of previous literature and therefore validating their usefulness. Moreover, relying only on publicly available studies will lead to conclusions that do not exactly reflect reality. Numerous other experiments – using many other NHPs – have been conducted by research institutions and private companies, the results of which will remain unpublished. Therefore, the real magnitude of this phenomenon is considerably underestimated and will most probably remain undisclosed.

Final disclosure

Old and new ethical concerns about animal experimentation have emerged in the context of the current pandemic. Urgency is an unexpected factor in the old debate about the moral agency of nonhuman animals, particularly in the confrontation between the mechanistic view – in which animals are mere machines responding to external stimuli – and the abolitionist position that purports the personhood of sentient animals.

Philosophy is critical to establish a social consensus based on shared values that will ultimately mark ethical boundaries and official regulations. The gap between science and ethics is perpetuated by the lack of interdisciplinarity and the failure of effective cross-talk (Webb, Woodford and Huchard, 2019). Ethical sensibility is considered unscientific, while ethical skepticism prevails over scientific achievements. Therefore new interdisciplinary approaches are required to overcome this unsuccessful dialogue.

Thus, in the current emergency, the lack of a road map has inevitably driven the development of the COVID-19 vaccine into the classical design. This design is not only in need of a profound revision but is also controversial: although certain principles are well-established, the moral position of nonhuman animals falls in an equivocal grayscale that is clearly unsatisfactory for researchers and animal right activists. An in-depth evaluation of the scientific response to the pandemic is needed to assess the costs and benefits to all sentient animals and to devise inventive solutions in accordance with our shared scale of values.

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