# Animal tests and Covid-19

Introduction

Researchers around the world are racing to test a potential vaccine against the novel coronavirus or Covid-19, which has so far infected 7.2 million people worldwide and killed over 408,000.

Sadly, this process will inevitably involve a significant amount of animal tests being conducted on a range of species including mice, rats, hamsters, cats, guinea pigs, ferrets and monkeys. And as researchers and countries compete to get a vaccine or treatment, the same or similar animal tests could be repeated, leading to even more suffering.

There is a real risk that, rather than helping us these animal tests will instead mislead researchers – good vaccines or treatments could be disregarded as ineffective and potentially harmful vaccines could be progressed to human trials on the back of unreliable animal tests.

Now, perhaps more than ever, it is vital that we consider the quality and humaneness of our science and continue our work to advance the development of progressive, non-animal methods.

We want to see a safe and speedy vaccine for Covid-19 using non-animal scientific methods which relate directly to the disease in humans and which have the potential to deliver safer, more effective vaccines and treatments to the market more quickly. To do this, we need global, regional and national coordination and much more funding and support for these methods.
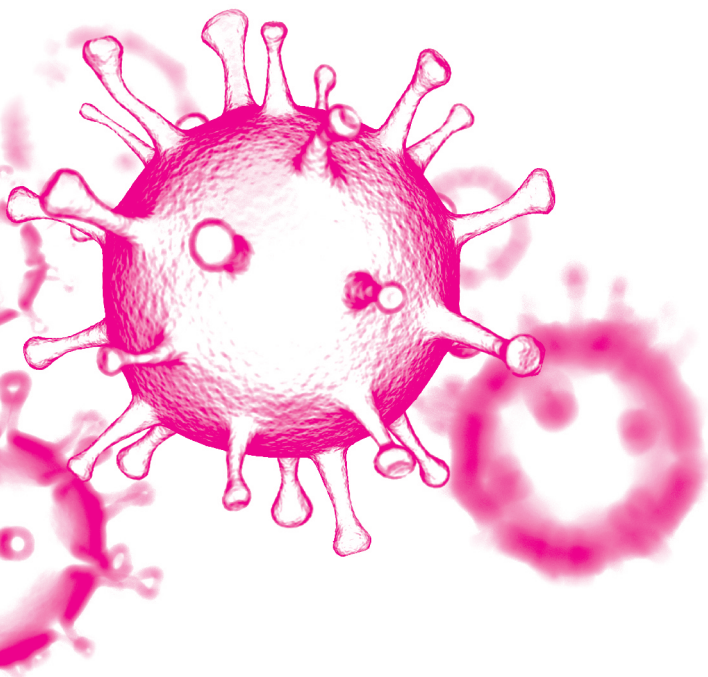
What is the current situation with a COVID vaccine?

The genetic sequence of SARS-COV-2, the novel coronavirus that causes Covid-19 was first published on 11 January 2020[2]. There are now more than 130 potential Covid-19 vaccines being developed around the world[3]. Most of these vaccines are in the early stages of testing, which typically involves animals.

To date, ten of these vaccines are currently being tested in humans, five made in China, three in the US, one in the UK and one in Germany, with other countries soon to follow.

Some of the most promising vaccines have been developed using new technology that has never been used in an approved vaccine before.

For example, one of the frontrunners is US-based company Moderna whose vaccine was apparently able to skip some of the typical animal tests and move quickly into human trials because of the novel way it was produced. Instead of the traditional method of injecting people with an inactivated or weakened version of a virus, Moderna's scientists have figured out a way to engineer and inject the molecular instructions needed to make the protein found on the surface of the virus directly into the human body[4]. This triggers an immune response in a similar way to traditional vaccines, potentially safer and also avoiding the lengthy and expensive production process. Moderna's mRNA-1273 vaccine was the first to begin phase 1 human trials on 16 March 2020 apparently after just one test in mice who were given an experimental vaccine for MERS (a related coronavirus) that was produced in the same way[5].

Oxford University's vaccine, originally named ChAdOx-1-S, is also a frontrunner after showing 'promising' results in monkey tests (see below). The vaccine is made from a weakened version of another virus (adenovirus) that causes cold and flu-like symptoms in chimpanzees[6]. It has received £90 million in funding from the government and is now undergoing phase 1 clinical trials . AstraZeneca recently announced a $1.2 billion deal with the US government to produce 400 million doses of the vaccine, now renamed AZD1222, if it proves effective[7].

Other top contenders include two vaccines from Chinese companies CanSino Biological and SinoVac, both of which are undergoing human testing after 'promising' results in a phase 1 human study and a monkey study, respectively (see below)[8].

Many experts have claimed that a vaccine will take about 12-18 months to develop and therefore could be expected to be available sometime in 2021[9]. However, history tells us that this is unlikely. Typically, it takes an average of 10-15 years for a vaccine to go from an idea to an approved product[10]. The fastest vaccine ever developed was for mumps, which took four years[11]. Even with accelerated development programs (like what we are seeing now), a vaccine for Ebola has only just been approved by the US Food and Drug Administration (FDA) in December 2019 – five years after the 2014 outbreak[11].

Unfortunately, there is no guarantee that we will ever get a vaccine for Covid-19. The Dengue fever virus was identified in 1943, but the first vaccine was only approved in 2019[12]. And, despite decades of testing we still have no HIV vaccine and there is also no approved vaccine for other recent outbreaks like MERS and SARS (both of which are also coronaviruses) and Zika.

Only about 6% of potential vaccines make it through to market[13]. Failures are typically due to safety concerns or simply because the vaccine did not work in humans. For example, a SARS vaccine was found to make people even more susceptible to the disease in a human trial[14].

There is also the worry that with the number of Covid-19 cases dropping, there will not be enough people on which to test the vaccine[15]. For example, despite lots of effort and funding to develop vaccines for MERS and SARS early on in their epidemics, momentum was lost as the outbreaks subsided and the vaccine trials were eventually abandoned[16].

What animal tests are being done?

We, like many are shocked by the number of animal tests being reported from all around the world, in the US, China, Canada, Australia and across Europe, using monkeys, hamsters, ferrets, mice and cats.

It is impossible to give figures for the numbers of animals being tested on because these are not published regularly and certainly not in relation to Covid-19. Research by Cruelty Free International however has just shown that nearly 200 million animals are used in all testing per year around the world, including 207,724 tests using dogs and 158,780 tests using monkeys.[17]

Animals are being used in regulatory tests to see if new vaccines for Covid-19 are safe. In these tests, animals will be injected with – or forced to inhale – the vaccine, often at higher doses than humans would ever be and watched to see if they become ill typically over 28 or 90 days before they are killed and their organs examined for signs of damage.

Tests are also being conducted to see if the vaccine works i.e. can prevent or reduce infection. In these tests, the animals are vaccinated and then infected with the Covid-19 virus. **For example:**

Oxford (UK) vaccine study:[18]

Six rhesus monkeys were injected with the vaccine before being exposed to the Covid-19 virus. A control group of three non-vaccinated monkeys were also exposed to the virus. All the monkeys were monitored for 7 days for signs of infection before being killed and dissected.

At the end of the study, all nine monkeys tested positive for the virus, which means that the vaccine was unable to prevent vaccinated animals from becoming infected and would therefore not likely be able to stop spread to others. Three of the vaccinated monkeys and all the control monkeys suffered from rapid breathing because of the infection.

However, since the vaccinated monkeys were found to develop less severe symptoms overall (e.g. no signs of pneumonia), the vaccine was progressed to human trials.

Sinovac Biotech (China) vaccine study:[19]

Ten rhesus monkeys were injected with two different doses of the vaccine three times over a two-week period. The Covid-19 virus was then injected directly into their lungs through a tube down their windpipes. A control group of five non-vaccinated monkeys were also infected with the virus.

Seven days later, the monkeys were killed and dissected. All the unvaccinated monkeys developed severe pneumonia before they were killed. While no virus was detected in the organs of the monkeys given the higher dose of the vaccine, monkeys vaccinated with the lower dose did show some signs of infection.

However, the researchers referred to this as a 'viral blip' and the vaccine has moved into human trials.

As well as vaccine development, animals are also being used in experiments to test potential treatments for people that get infected with Covid-19 such as antibody and antiviral treatments and in basic research projects aimed at finding the most susceptible species (that can be used in future research and/or regulatory tests) or trying to understand how the virus causes infection.

Existing drugs are also being studied to see whether they can be re-purposed to treat Covid-19 patients. While many of these, including the recently hyped malaria drug chloroquine, will have already been tested for safety in previous animal tests, additional tests may be conducted to try to show that they are fit for their new intended purpose.[20]

Scientists in China conducted a series of experiments in dogs, cats, ferrets, ducks, pigs and chickens to determine which species could be infected with Covid-19.[21]

Most of the experiments involved injecting the virus up the animals' noses and keeping them isolated in cages so that nose and rectal swabs could be taken before they were killed and dissected. They concluded that ferrets and cats are the most susceptible to Covid-19 – although they still don't develop the same symptoms as humans do, while dogs, pigs, ducks and chickens are not easily infected with the virus.

Another group of Chinese researchers infected hamsters with Covid-19 and reported that they developed signs of the disease, including weight loss and rapid breathing.[22]

A US-based company called Emergent BioSolutions is using horses to produce an antibody-based drug for Covid-19.[23] Because of their size, horses are often used as factories of plasma and antibodies and are regularly bled for this purpose.
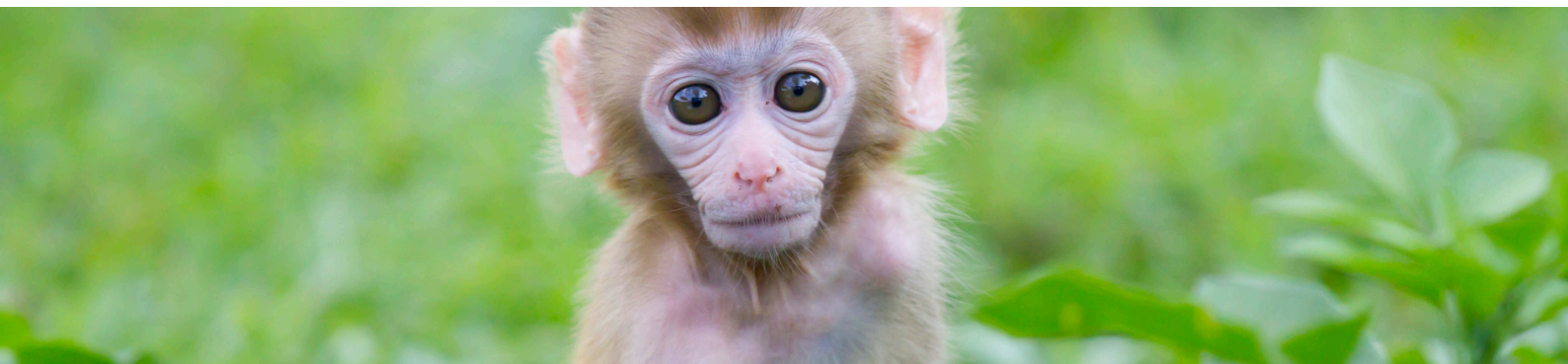
What are the scientific problems with using animals for COVID-19 research?

History has shown us that tests in animals are not predictive of what will happen in humans. Animals are not mini-humans – they often do not suffer from the same disease as us and they respond differently to drugs.

Over 90% of new drugs that appear to be safe and effective in animals go on to fail in human clinical trials.[24] There is specific evidence for vaccines too. An HIV/AIDS vaccine has been sought for more than three decades, with no success, despite hundreds of clinical trials on dozens of vaccine types showing promise in tests on monkeys.

Researchers around the world are scrambling around to find the perfect animal model of Covid-19 but have no found one yet. Typical 'laboratory animals' such as mice, rats and dogs are not as susceptible to it as humans are. Even monkeys – considered the most similar species to us – do not develop the most severe symptoms that Covid-19 causes in humans.[25] And yet animals continue to be used even though they are not able to provide clear-cut answers.

The initial promise of genetically modified (GM) mice as the solution has not transpired so far. When non-GM mice were infected with Covid-19, nothing much happened (they were hard to infect successfully), so some scientists went back to an old GM mouse from years ago that was produced during the SARS outbreak, bred it to greater numbers, and were hopeful that they would be useful after some more genetic tweaking.[26] However, Covid-19 only induced mild diseases in those mice.

It should be noted that none of the 'frontrunners' in the Covid-19 vaccine race have passed the early testing stages with flying colours. As mentioned above, the Oxford vaccine was not able to prevent infection in monkeys, although it did reduce the development of severe symptoms, and the Sinovac vaccine provided only partial protection in monkeys after also being tested in mice and rats. Even the Moderna vaccine led to negative side effects in human volunteers in phase 1 trials, including nausea and high fever while CanSino's vaccine caused severe fever in 8% of their trial participants.

This raises the question of whether animals are truly useful to inform vaccine (and other drug) development, especially in situations where they are progressed into human trials despite disappointing and/or ambiguous results in animal tests. In our view, researchers seem to pick and choose which data they want to focus on and which they want to ignore, depending on the situation. In fact, a recent workshop on Covid-19, held by the International Coalition of Medicines Regulatory Authorities (ICMRA), concluded that efficacy tests in 'animal challenge models' (where animals are infected with the virus after being vaccinated to find out whether the vaccine works) are not actually needed to progress into human trials.[27] And yet, they are still being conducted!

What are the alternatives to using animals?

Replacing animal tests does not mean putting human patients at risk. It also does not mean halting medical progress. Instead, replacing animal testing will improve the quality as well as the humaneness of our science.

Thankfully, the development of alternative methods is growing. Due to innovations in science, animal tests are being replaced in areas such as toxicity testing and drug development. But much more needs to be done.

The reasons why animal testing persists are often not scientific. Instead it can be due to conservatism within the scientific establishment – it is easier and more comfortable to simply do what has always been done. Test results on animals can be easily compared to earlier tests on animals to give confidence to scientists. Regulators can adopt a 'tick box' approach, divorced from the needs of the real world.

Organoids (tiny mini organs)[28] and microphysiological systems[29], i.e. 'body/organ-on-a-chip' technologies are both human-relevant methods, which provide a more realistic way to test new therapies. Both methods are now being used with immune cells added to them, which is particularly appropriate for vaccine development and can also be exposed to antibodies, or to the serum of infected or vaccinated people to test efficacy.

A Spanish team has already shown that SARS-CoV-2 can infect engineered human blood vessel and kidney organoids and that a human based enzyme can inhibit this, providing promise for a potential treatment.[30]

3D-cultured artificial human lymph nodes[31] have been created to model both innate and adaptive immunity and have been used in the evaluation of flu vaccines. A 3D human airway cell model[32] has also been developed that can be used for evaluating the effect of potential drugs on the human respiratory system.

Studies in healthy and infected human volunteers are also key. For example, human studies have shown that antibody responses to Covid-19 infection are often weak, and/or wane relatively quickly, allowing reinfection of a previously infected individual[33]. Human studies also showed that some of the antibodies to SARS prevented infection, and some of these cross-react to Covid-19, which is promising.[34] Lung fluid cultures and biopsy samples from patients can also be used to study the virus genome and investigate lung tissue damage. 'Passive' vaccines are also being investigated, whereby antibodies to the virus are injected into patients – either from Covid-19 'survivors', or from in vitro (cell-based) production.[35]

Advanced techniques include mathematical modelling of transmission and infection rates, which have proved vital to our understanding and control of the pandemic[36]. Computer programs are also being used to screen for potential vaccine and drug candidates based on their chemical and structural properties and/or similarity to existing therapies[37].
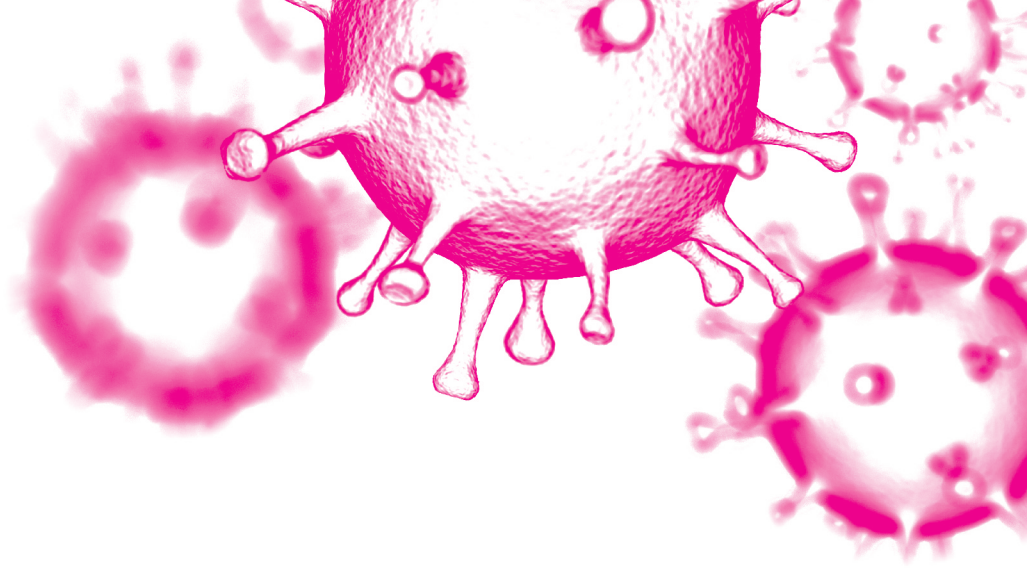
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