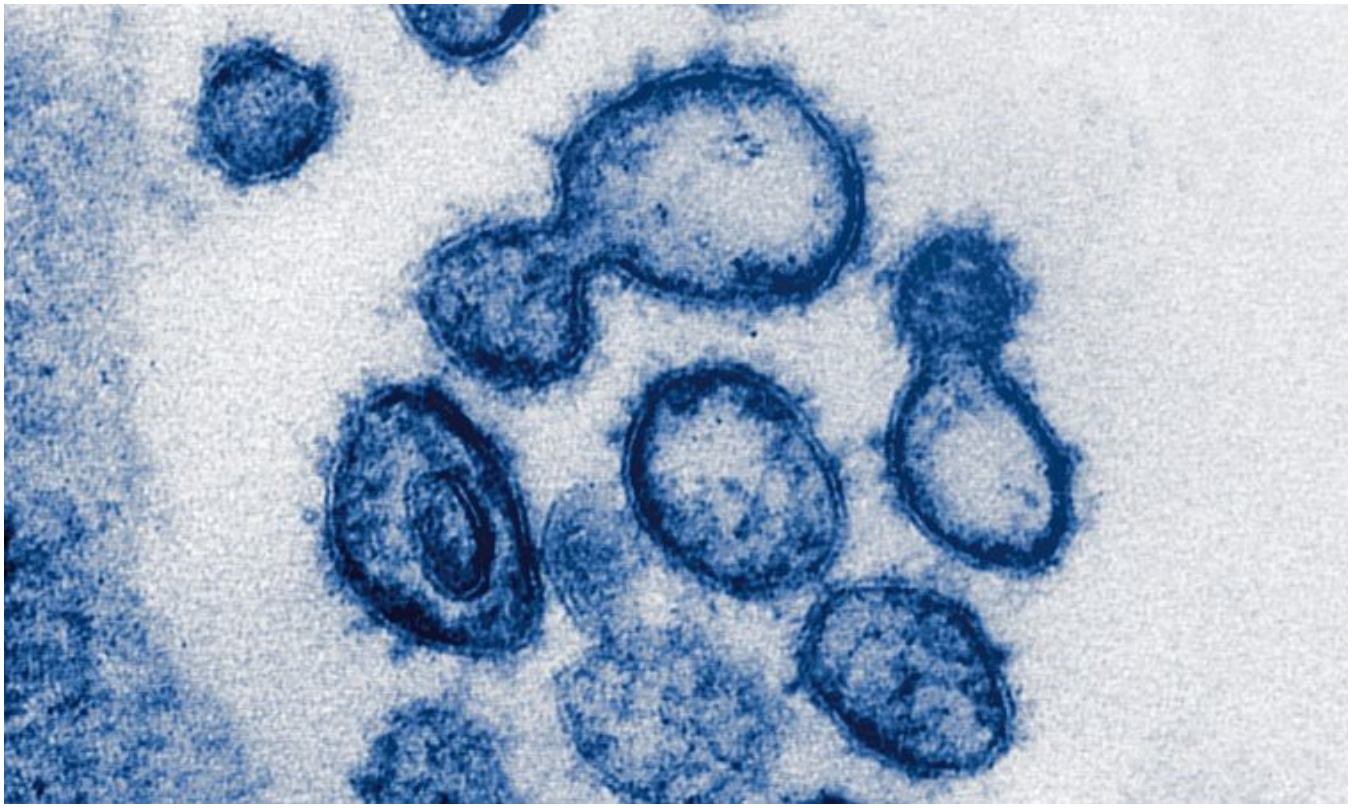
NEWS Q&A · 26 MARCH 2020

Should scientists infect healthy people with the coronavirus to test vaccines?

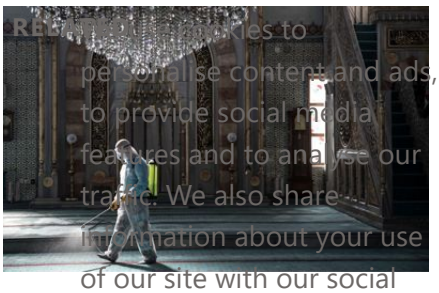
Radical proposal to conduct 'human challenge' studies could dramatically speed up vaccine research.

Ewen Callaway



The SARS-CoV-2 virus imaged by an electron microscope. Credit: NATIONAL INSTITUTES OF HEALTH-RML/SPL

As hundreds of millions of people, maybe billions, avoid social contact to spare themselves and their communities from coronavirus, researchers are discussing a dramatic approach to research that could help end the pandemic: infecting a handful of healthy volunteers with the virus to rapidly test a vaccine.



The coronavirus pandemic in five powerful charts

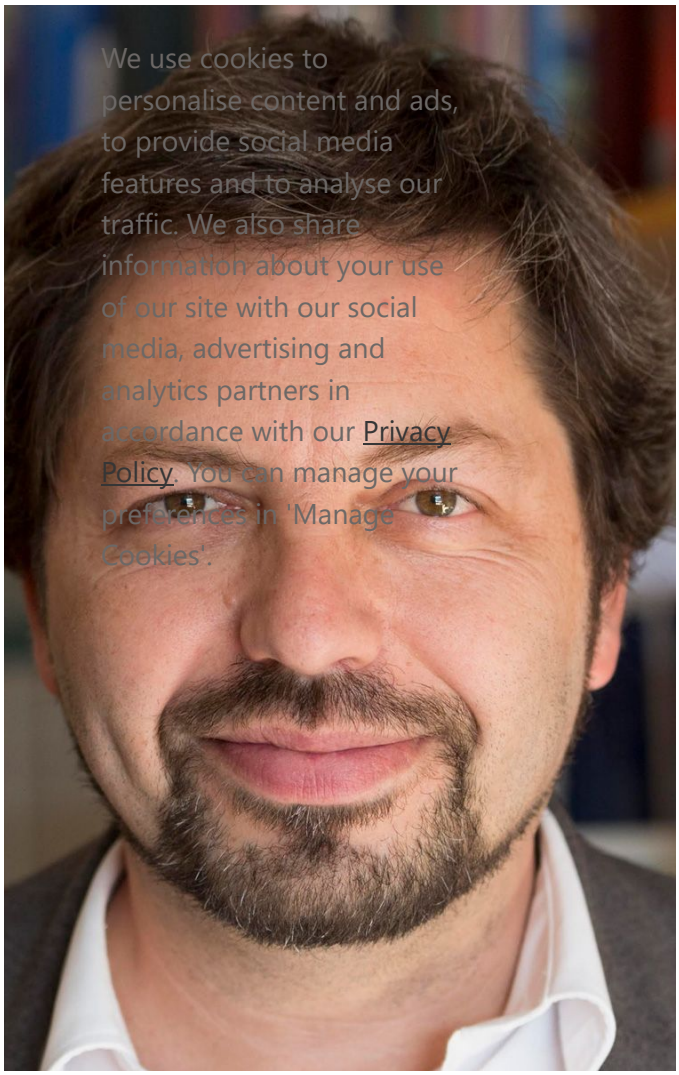
Many scientists see a vaccine as the only solution to the pandemic. Clinical safety trials began this month for one candidate vaccine, and others will soon follow. But one of the biggest hurdles will be showing that a vaccine works. Typically, this is done through large phase III studies, in which thousands to tens of thousands of people receive either a vaccine or a placebo, and researchers track who becomes infected in the course of their daily lives.

A quicker option would be to conduct a 'human challenge' study, argue scientists in a provocative preprint published this week[1] . This would involve exposing perhaps 100 healthy young people to the virus and seeing whether those who get the vaccine escape infection.

Nir Eyal, the director of the Center for Population-Level Bioethics at Rutgers University in New Brunswick, New Jersey, and lead author of the preprint, tells *Nature* how the study could be done safely and ethically. Participants, he argues, might even be better off for it.

Why should we consider human-challenge studies of experimental coronavirus vaccines?

The main attraction is that they could greatly accelerate the time to approval and potential use. The thing that takes the longest time in testing vaccines is phase III efficacy testing. That's done on many, many people, some of whom get the vaccine and some of whom get placebos or competing vaccine



Bioethicist Nir Eyal.

candidates. Researchers then look for differences between these two groups in infection rates.

However, many people will try to be careful in this outbreak — self-isolate, say — and it will take a very long time until interpretable results emerge. If, instead, one exposes all study participants to the pathogen, one can not only rely on far fewer volunteers but, more importantly, take a much shorter period to get results.

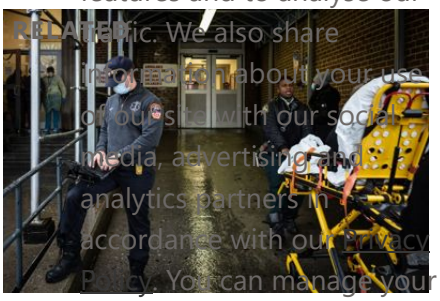
Are there any precedents for infecting healthy people with a pathogen?

We do human-challenge studies for less deadly diseases quite frequently. For example, for influenza, typhoid, cholera and malaria. There are some historical precedents for exposure to very deadly viruses. The thing that demarcates the design that we propose from some of these historical instances is that we feel there is a way to make these trials surprisingly safe.

How could you conduct such a study?

You would start only after some preliminary testing to ensure that a vaccine candidate is safe and that it accomplishes an immune response in humans. You then gather a group of people at low risk from any exposure — young and relatively healthy individuals — and ensure that they are not already infected. You give them either the vaccine candidate or a

placebo and wait for enough time for an immune response. And then you expose them to the virus.



How blood from coronavirus survivors might keep hospitals afloat

You then follow all the participants very closely to catch any signs of infection as early as possible. You are trying to check if the group that received the vaccine is doing better than the one that received the placebo. That might be in terms of viral levels, the time until symptoms emerge or whether they're infected or not.

What's the risk to participants?

The risk of harm can be reduced very significantly by selecting people who are relatively young — we envisage between the ages of 20 and 45 — and otherwise healthy. You would also select people who are already likely to be exposed to COVID-19 — either during the trial or sometime later. Unfortunately, there will be many of us who fit this description because we live in high-transmission areas.

You would also protect study participants by examining them daily or more frequently for infection and by providing them with excellent treatment immediately upon detecting infection. That's not trivial. I've advised critical-care doctors preparing for surges of coronavirus. And we strongly expect — based on the experience in Italy and more — that there will be acute shortages of critical-care resources. By the time vaccine candidates are tried, there may be some treatments that are proven to work. And surely, the brave volunteers we recruit should be assured ready access to those.

The dramatic-sounding exposure of healthy volunteers to the virus is therefore adding less net risk than you might think. It might even be curiously safer for some to join the study than to await probable infection and then try to rely on the general health-care system.

Is this ethical?

It might seem as though anybody volunteering to participate in such a study lacks capacity for rational decision-making or must have misunderstood the informed-consent form. However, human beings do many important things out of altruism. And, as I said, although the study introduces risks, it also removes risks. And the net risks, while unclear, are not clearly extremely high. So, it is actually potentially rational — even from a selfish point of view — to participate in such a study.

We also let humans volunteer to do risky things all the time. We let people, for example, volunteer to be emergency medical services during this period. That significantly elevates their risk of getting infected. But it's also very important. In clinical trials in general, we don't focus only on reducing risks to participants; we focus on achieving a reasonable balance between the added risks that they take and the importance for the community. In this case, vaccines could be our soceities' only way out of the bind between economic stagnation and widespread mortality.

Should participants be paid?

I happen to be a bioethicist who doesn't have huge objections to attracting study participants by offering financial incentives. But I think in this study, ensuring a high level of public trust is important, and I would advise researchers not to attract volunteers through high payments. This would have the advantage of making sure that the study doesn't prey on the poor.

Do you worry that countries with authoritarian governments could conduct such studies on vulnerable groups, such as prisoners or members of persecuted minorities?

We would only recommend conducting the studies in an ethical fashion, with fully informed consent. Vaccine makers want to sell their product to other countries. They want to publish their scientific articles in prestigious journals and there would be many obstacles if their trial doesn't adhere to widely accepted standards.

US government funders considered a challenge trial for a vaccine against the Zika virus a few years ago, but decided against it. Do you think funders will come to a different conclusion with the coronavirus?

I believe that this case is quite different from that of Zika vaccine. In the Zika vaccine-challenge study, the decision against it was in part because there were risks to non-participants — primarily sexual partners of participants, and any fetuses they might be carrying. By isolating study participants for a limited period, we can completely extinguish the risk to non-participants. Do I believe that countries will jump on board? Judging from the response we are getting from various stakeholders since publishing the preprint, I believe that many will.

doi: 10.1038/d41586-020-00927-3

This interview has been edited for length and clarity.

References

1. Eyal, N., Lipsitch, M. & Smith, P. G. Preprint at DASH http://nrs.harvard.edu/urn-3:HUL.InstRepos:42639016 (2020).

Nature ISSN 1476-4687 (online)