# Sarah Caddy

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Q1

## What initially sparked your interest in viral immunology and vaccines?

I initially trained as a veterinary surgeon, and spent several years vaccinating animals and treating animals suffering from viral diseases. However, I realised that I was only making a difference to a small number of animals by working in clinics. It became clear I could potentially make a much bigger impact by contributing to our understanding of the fascinating world of viruses through research. At the molecular level there is little to differentiate viruses of animals and humans, so my work now bridges virology and immunology relevant to all species.

Q2

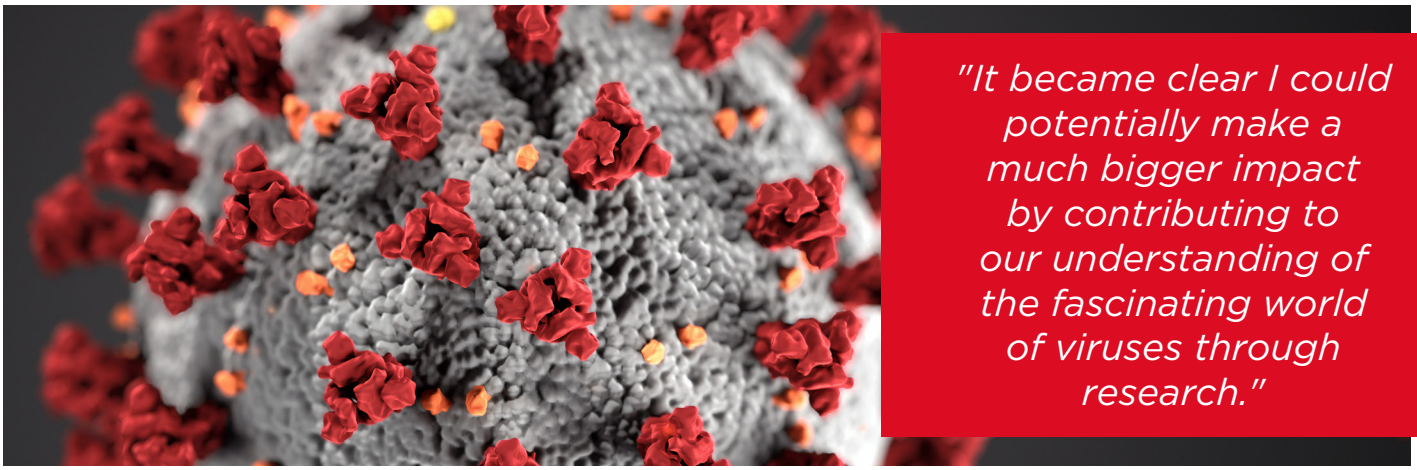
## How did your previous work on studying norovirus and Ebolavirus help you transition to studying severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)?

My PhD focussed on zoonotic aspects of noroviruses, and for part of this I conducted a large quantitative polymerase chain reaction-based screen for several norovirus strains. The end of my PhD coincided with the recent Ebola outbreak in West Africa, so I was then able to volunteer my molecular skills in a diagnostic and research lab in Sierra Leone, testing patient samples for Ebola by quantitative polymerase chain reaction and performing virus sequencing. When the SARS-CoV-2 pandemic reached the UK, this meant that I immediately wanted to offer my expertise in a similar capacity. I never expected the skillset gained in Sierra Leone would one day be valuable in Cambridge.

Q3

## As a volunteer with the COVID-19 Genomics UK (COG-UK) Consortium, could you tell us how genomic data is being used to aid control of COVID-19?

At the start of the first lockdown in March 2020 I joined the Cambridge arm of the COG-UK consortium for 2 months. This involved performing full genome sequencing for all of the SARS-CoV-2 positive samples within the region. When these results were analysed alongside detailed epidemiological data, it was possible to identify a number of hospital-acquired cases of the virus. As we were able to generate sequencing data within days of a positive sample, this led to implementation of more effective infection control measures.



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Since this time, COG-UK has been able to identify and monitor any changes in virus sequence across the country, which has proven to be of significant importance as new virus variants emerge.

Q4

**There are now several known variants of SARS-CoV-2. Is there ways of preventing the virus mutating, and is there a way of predicting such mutations?**

Viruses with an RNA genome inevitably mutate due to inaccuracies in genome replication. This is advantageous to the virus as, although the majority of mutations will have no effect on virus survival, a few will enable the virus to evade immune responses. Unfortunately, this means that there is no way to stop viruses mutating, although the impact will be less if there are fewer infections. Predicting mutations is possible though, and has been done via a number of ways. One method is through computational analysis and comparison to similar viruses. The other way is to grow virus in the lab and repeatedly use it to infect new cells in the presence of antibodies. This immune pressure can often induce the emergence of virus variants that can replicate despite the presence of inhibitory antibodies.

Q5

**You recently co-authored a paper titled: 'Viral nucleoprotein antibodies activate TRIM21 and induce T cell immunity.' Could you summarise the key take-home messages of this article?**

My current main research focus is understanding how antibodies protect us from viruses. In particular I have been interested in revealing the role of 'non-neutralising' antibodies. These are antibodies targeting internal viral antigens that don't block virus infection *in vitro*, but we know they are protective *in vivo*. Our work has shown that non-neutralising antibodies can actually enhance antigen presentation via the intracellular antibody receptor TRIM21. This therefore leads to enhanced activation of T cells, shown to be critical for survival from infection in our mouse models. Overall, this means that testing for neutralising antibodies alone may miss important correlates of protection. It also suggests that inclusion of internal viral proteins in vaccines may be valuable.

Q6

**At the Cambridge Institute for Therapeutic Immunology and Infectious Diseases (CITIID), you have previously developed a project for COVID-19 testing in animals. What evidence is there on COVID-19 pet transmission?**

There is good evidence that experimentally infected cats are susceptible to SARS-CoV-2, and there are a number of case reports of pet cats and a few pet dogs testing positive for the virus. However, there is no evidence that pets can transmit the virus back to humans. The story is very different for mink as there is now solid evidence based on sequencing data that mink can transmit the virus to people. But for cat and dogs, although transmission to humans remains a theoretical risk, this is deemed to be extremely low.

Q7

**One of your research interests is understanding how viral vaccines work in infants and how they can be improved. What new developments in this field are on the horizon in 2021?**

Vaccine efficacy in very young infants is often reduced due to the presence of maternal antibodies. This is a phenomenon that has been recognised for decades across multiple species, but the mechanisms of inhibition are still not clear. One solution to this problem is to focus on vaccinating mothers, and then relying on maternal antibodies to protect infants. This is likely to be the strategy that will be employed in 2021 for the SARS-CoV-2 vaccines. But we know maternal antibodies wane at different rates in infants, which means some infants will be unprotected whilst still very young. New vaccines for infants that can somehow overcome inhibition by maternal antibodies are a long sought-after goal.