# COVID-19: WHAT ARE THE BIG QUESTIONS AND WHAT HAVE WE LEARNED?

*Image from https://www.niaid.nih.gov/news-events/novel-coronavirus-sarscov2-images*

Here's a round of up of all the questions we've been asked during the pandemic. We've pulled together the science behind each question and our aim is to provide insight and information grounded in scientific evidence. It's just as important to highlight what we don't yet understand and the burning questions that we need to address to tackle the pandemic. Here we explain some of the words and concepts relating to the virus that are being used in the media, as well as answering practical questions such as is it safe to send things in the post without spreading infection? Engaging with what is happening and understanding the virus will give us all the best chance to navigate the complicated and often conflicting news, and to protect ourselves, our families, communities and work places.

The research in some of these areas is very fast moving so this is up to date as of 21st May 2020. Answering some of these questions may have been useful earlier in the pandemic, but as we seem to be entering a new phase it is a good time to repeat and reflect on all of these. We've focussed on the evidence, but it of course relies on our analysis and interpretation.

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# HERE ARE THE QUESTIONS WE TACKLE…

**What exactly is SARS-CoV-2 and how does it infect you?**

**How does SARS-CoV-2 spread and why do we have to stay 2m apart?**

**How long is SARS-CoV-2 stable and infectious on surfaces and do I still need to wash my shopping?**

**Will wearing masks and gloves protect me from infection?**

**Where did SARS-CoV-2 come from: bats, pangolins or a lab?**

**How does the virus cause disease and why do some people get severe disease but others have no symptoms?**

**How does understanding the disease drivers help us to develop treatments?**

**Why are people of black Asian and minority ethnic (BAME) backgrounds and men more affected in the UK?**

**How has computer modelling of the outbreak been used and what can it tell us?**

**What is the 'R number' or 'reproduction rate' and why does the government care so much about it?**

**What are the different tests and what do they tell us?**

**Is SARS-CoV-2 mutating to become more deadly?**

**Will temperature scanners at airports prevent SARS-CoV-2 spread?**

**What is herd immunity?**

**What is the route to a vaccine and how and when will we know if it works?**

**Will there be a second wave and how do we emerge from lockdown without a vaccine?**

## First things first: what do we actually call it?

The names for the virus and disease have been used interchangeably in the news, which has led to some confusion.

- The **VIRUS** is called **SARS-CoV-2.**
- The **DISEASE** caused by the virus is called **Covid-19** (**Co**rona**vi**rus **d**isease-20**19**).

SARS-CoV-2 is a different to the virus that caused an outbreak of a **s**evere **a**cute **r**espiratory **s**yndrome (SARS) in 2002-2003, this is known as SARS-CoV-1.

## What exactly is SARS-CoV-2 and how does it infect you?

Viruses are too small to see with the naked eye and can only be visualised with extremely high-powered microscopes (electron microscopes). To give you an idea of the scale, SARS-CoV-2 is ~10,000x smaller than your average grain of table salt. This image of SARS-CoV-2 is taken with an electron microscope, the colour is added afterwards so you will see similar virus images of all different colours in the media.

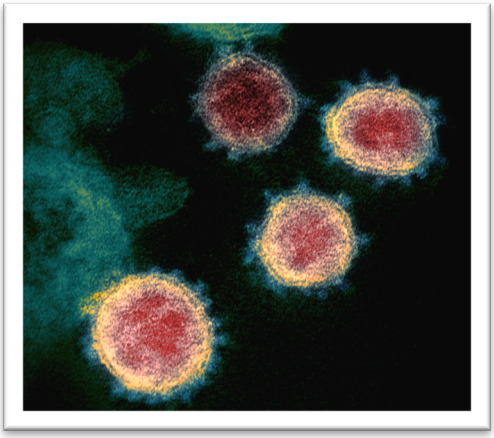


*Image from https://www.niaid.nih.gov/news-events/novel-coronavirus-sarscov2-images*

Coronaviruses got their name from the appearance of the viruses, which have spikes around the outside that look like a crown, corona meaning crown-like (takes a bit of imagination and squinting). We now know a lot more about the coronaviruses, and their key components are shown in this cartoon:

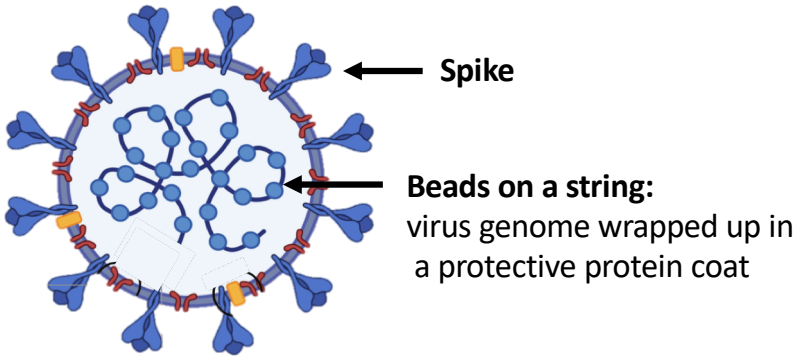



*Image modified from study reference 1.*

The outer layer of the virus is studded with spikes. The spike protein is the one of the main parts of the virus that is recognised by your immune system to mount a response against. The spike plays an important role in infection, as it enables the virus to stick to molecules on the cell surface, opening a pathway into the cell. Once inside the cell, the virus releases its inner contents, which are shown in the cartoon as beads on a string. The 'string' is the virus' genetic material, or **GENOME,** which just means the complete set of its genes. The SARS-CoV-2 genome is made of a molecule called **RNA**, which is slightly different to the DNA that makes up our genes. The genome is wrapped up in a protective protein coat (the 'beads'), which stop it being destroyed by the cell's defences.

The genome contains the instructions for making new viruses, starting with making the new virus proteins. SARS-CoV-2 has about 25 proteins, which although not the smallest virus is still relatively few. To put it in context our cells make about 25,000 proteins! Yet these 25 virus proteins are able to hijack the cell's machinery and turn it into a virus-producing factory. They also switch off many of the cell's in-built defences against infection, so that **REPLICATION** (the process of making new viruses) can proceed at high rates. The virus proteins make new copies of the genome, which are packaged up as new viruses ready for release. Release happens as the infected cell bursts and dies, and the new viruses go on to infect neighbouring cells. In this way, the virus spreads through tissues, or is released into the nose or airways, ready to be coughed out . Then it can be breathed in by another person or hitch a ride on your hand/tissue when you wipe your nose, get transferred to a surface (such as a door handle/phone/pen, to name a few) and passed on to the next person. We describe below the types of cells the virus can infect and where in your body it does this to cause disease.

## How does SARS-CoV-2 spread and why do we have to stay 2m apart?

By now we all know the most common routes of spread (**TRANSMISSION**): the virus can be released in droplets produced when someone coughs. As well as being breathed in directly if you are close enough, these droplets can travel through the air and land on surfaces up to approximately 2m away. Infectious viruses can be picked up from these surfaces, and transferred to other surfaces or your nose/mouth if you touch your face, which is why hand washing and not touching your face are so important.

What is less clear is whether you can spread it by just breathing and talking which can create aerosols or smaller droplets that are thought to stay in the air for longer and travel further, and have been suggested as a way that asymptomatic people may spread disease. The virus can be detected in saliva samples. However, at the moment there is no good evidence to support aerosol transmission of SARS-CoV-2, or whether the aerosolised droplets carry enough virus to infect someone. However it cannot be ruled out. There are also reports that some people get diarrhoea with Covid-19 (see below for more detail on disease), and that virus can be detected in poo samples. It's not yet clear if the virus remains infectious in poo, and if this represents another route of transmission- faecal-oral via contaminated hands. Either way and if in doubt, hand washing with hot soapy water is your best bet.

***The most common routes of spread or transmission of SARS-CoV-2: coughing or sneezing and picking up the virus on your hands and touching your face.***

## How long is SARS-CoV-2 stable and infectious on surfaces and do I still need to wash my shopping?

At the start of the outbreak a lot of information came out about this without it being properly tested. Just detecting a virus on a surface does not mean it is infectious. The only way to confirm this is to isolate virus from different surfaces over time/in different conditions and confirm whether the virus can still infect cells in the lab. These studies have only recently been done. They found that the type of surface determines how long SARS-CoV-2 is stable and infectious, and that temperature and humidity can affect it too (study reference 2).

**These are therefore only guidelines:**

- **Paper**: 3 hours
- **Cardboard**: 24h
- **Plastic and stainless steel**: 72h, although it becomes steadily less infectious over the 3 days.

✓**Top tip:** *if you're worried about your post/newspapers being contaminated, we suggest waiting for >3h before handling, if you touch them before this just be sure to wash your hands without touching your face. You don't need to worry that you personally will pass anything on via the post, as by the time it reaches the recipient any virus you may have put on it will no longer be infectious. The person receiving it just has to follow the 3h rule in case someone has touched it more recently. The same goes for deliveries in cardboard boxes but you would need to leave these > 1 day before touching. Hand washing is key. Washing deliveries in plastic bags or boxes with hot soapy water will inactivate any virus and the same goes for shopping, otherwise hand washing and not-face touching rules apply. They didn't check material like clothes, so if you have been out and are worried about exposure or contact, these are best going straight into a hot wash or being left in a washing bin for several days first.*

## Will wearing masks and gloves protect me from infection?

### Masks…

Wearing a mask has been suggested to protect us when in public or especially when in close contact with people. It is thought to reduce virus spread by capturing droplets produced by an infected person coughing. It's important to know that there is no good evidence to say that masks will fully protect you, especially if they are not fitted properly, however there aren't really good enough scientific studies on this to say either way. So wearing a mask, or face covering of any sort, has been advised, particularly when in close contact. So it is important that even if you are wearing a mask, you must still take other preventative measures such as social distancing, and not touching your face to rearrange your mask for example. Only handle it by the ear straps and do not touch the part in contact with your nose/mouth as you can spread it from there.

## Gloves…

As the virus cannot directly infect your hands, gloves will not directly protect you, but can of course stop you coming into direct contact with the virus when you're out. **However they only work if you use them properly. The** best way to think about this is to imagine them as a second skin, so you should still take care not to touch your face even with gloves on. You should also not touch items that you will later use without gloves, a key culprit is your phone. The virus can transfer from your gloves to your phone, and if you later touch your phone without gloves at home and touch your face (more likely when you're more relaxed at home), then it's still possible to infect yourself this way. You also have to remove gloves properly, making sure you don't touch the outside of the gloves which you should consider is contaminated. The best way is to pinch it at the top by your wrist and peel off inside out for the first glove (as in the picture), then for the second hold the inside of the glove at the wrist and peel off inside out. Here's a video if it helps: https://www.youtube.com/watch?v=ATU383IIfT8

✓**Top tip:** *We suggest good hand hygiene and awareness may be more effective than gloves. Use hand sanitiser when you're out, and for example before you touch your phone when in public places. Hand sanitisers need to have 70-80% alcohol content to kill the virus, and you must let it dry before touching anything, as this dehydrates the virus to kill it. Do not touch your face whilst out and wash your hands as soon as you get in or often as you can.*

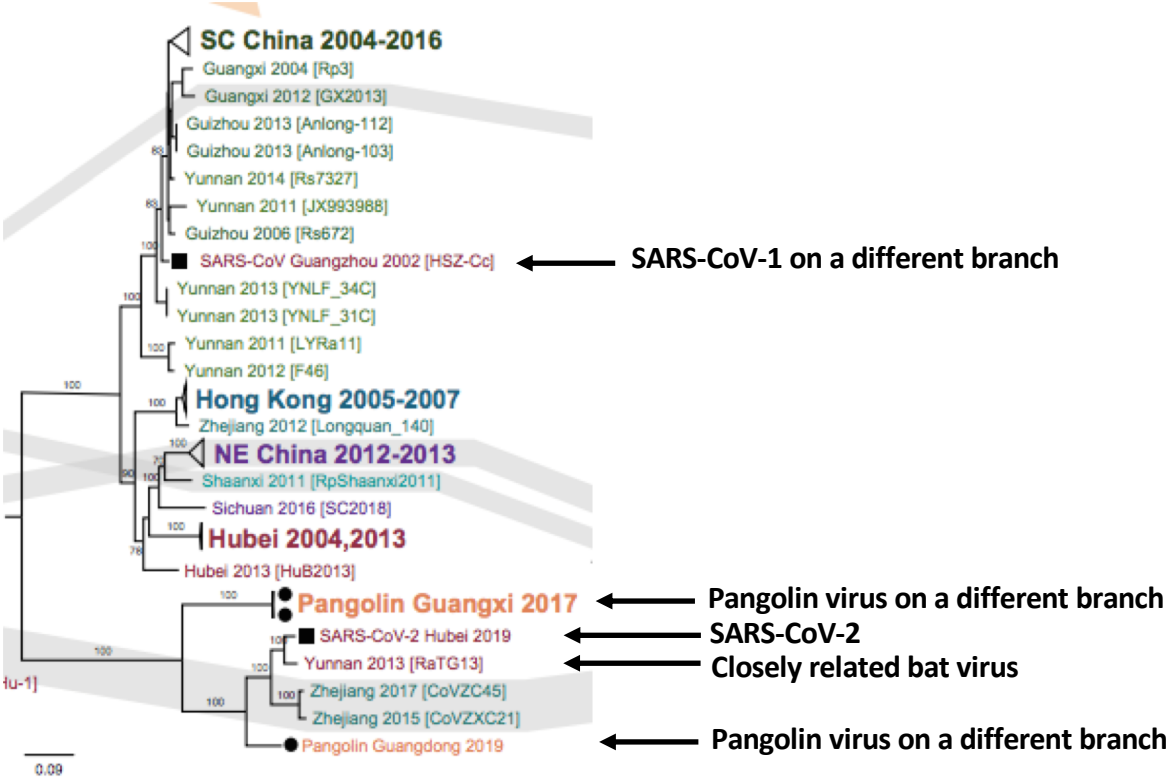
## Where did SARS-CoV-2 come from: bats, pangolins or a lab?

The best way to understand where the virus came from is to look at its genes and build a family tree. This is done in the same way that we trace our ancestors using our genes to make a tree. Family trees of viruses, or **PHYLOGENETIC** trees as they're called, allow us to see how they are related.

The complete set of a virus' genes, or any organism's genes, is called the **GENOME**. The SARS-CoV-2 genome is made of a molecule called RNA, slightly different to DNA which makes up our genes and genome. RNA is made of 4 different building blocks, which you can imagine like lego bricks, stuck together and repeated over and over again, nearly 30,000 times in total to make the SARS-CoV-2 genome. The order of these building blocks is unique in every virus, and is known as the genome sequence. We can identify the virus by its unique sequence, this is the basis for the nasal swab tests (see below). The genome contains the instructions for how to make new copies of the virus, and we can learn a lot from it, including its origins.

Coronaviruses are **ZOONOTIC**, which means they can jump between species, from animals into humans. The genome sequence of SARS-CoV-2 is a very close match (96% match) for a coronavirus that has been found in a bat, suggesting that bat viruses are the parents or ancestors of SARS-CoV-2. As we expect, this coronavirus, (called RATG13), appears next to Cov2 in the family tree. In the family tree the bat viruses are named according to where they were found in China. The size of the tree gives a sense of the variety of bat coronaviruses and how many have been identified so far. Note that SARS-CoV-1 (here called SARS-CoV) is in a completely different part of the tree (on a different

branch), showing us that this is a relatively unrelated virus to SARS-CoV-2 and an independent example of a coronavirus jumping into humans from bats. Bats can carry a whole range of zoonotic viruses which can jump from bats to humans, including coronavirus, rabies and ebola virus. We don't really understand why we catch bat viruses so often or why bats seem to be able to better tolerate infections that are lethal in human. Top tip: visiting tropical bat caves is best avoided.




*Coronavirus family tree. The bat viruses are named according to where they were identified in China. The SARS-CoV-2 is the closest match to the 'RaTG13' bat virus suggesting this is the ancestor virus. The tree is taken from Study Reference 3.*

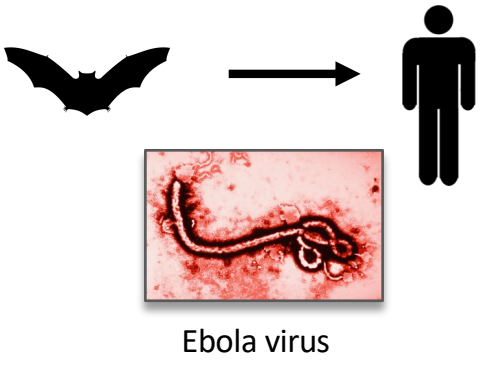
The small differences between the bat ancestor virus (RaTG13) and SARS-CoV-2 are often seen when a virus jumps species, it has to change and adapt to infecting human cells instead of bat cells, and to be able to spread effectively between humans to cause an outbreak. Sometimes viruses jump from bats to humans via an intermediate species or 'host', which acts like a stepping stone and gives the virus another chance to adapt before being able to infect humans. For SARS-CoV-1, which also came from bats, the intermediate host was civets. The MERS (Middle Eastern Respiratory Syndrome) virus, another coronavirus that causes severe respiratory disease, again originates in bats, but spreads via dromedaries *(*Arabian camels with one hump) as an intermediate host.

For SARS-CoV-2, it's been suggested that pangolins are the intermediate host, as coronaviruses have been detected in pangolins that have some similarity to SARS-CoV-2. Again looking at the family tree can help us understand this. You can also see that the pangolin coronaviruses fall into 2 separate parts of the tree. This tells us that coronaviruses have jumped into pangolins from bats at least twice. But the pangolin viruses are not the parents of the human SARS-CoV2 in the tree, they're more like a distant cousin, and that's why it's not thought that SARS-CoV-2 came from pangolins (Study Reference 3). This can't be fully excluded or that it jumped via another species, it's just that we haven't yet discovered a parent in pangolins or any other species other than bats. Until we find a SARS-CoV-2 parent virus in another species, we assume SARS-CoV2 came directly from bats.

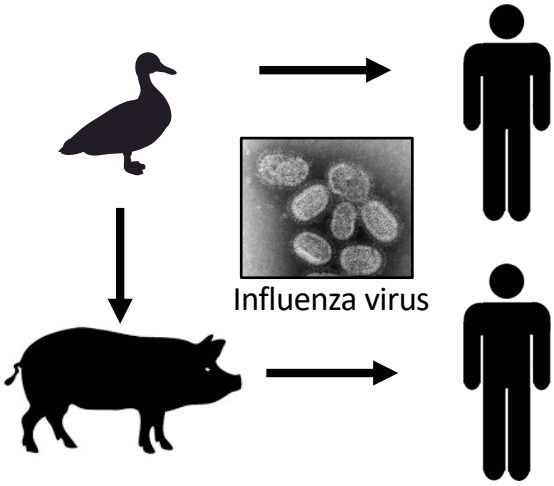
*Coronaviruses found in the horseshoe bat are the closest match to SARS-CoV-2 and are the most likely parent viruses. The pangolin coronaviruses that have been identified so far are more like a distant cousins than parent viruses, suggesting that SARS-CoV-2 did not jump via pangolins.*

There have been a number of conspiracy theories that SARS-CoV-2 was either made in a lab or was isolated from bats in a lab in Wuhan that specialises in coronavirus research and accidentally released. It is clear that the virus wasn't man-made because as we have explained, it is a typical bat virus found in humans. Although is not currently possible to completely rule out the suggestion that this virus may have infected a person in a lab, this is not the simplest explanation, or very likely especially given the level of containment needed to work with these viruses, so all evidence supports the most likely scenario that the virus jumped species in nature, a well-trodden path for coronaviruses and other zoonotic viruses.

The West African Ebola virus outbreak in 2013-2015, the largest and most lethal known Ebola outbreak to date, also began with zoonotic transmission of the virus from bats to humans. Since then research efforts have sought to understand and identify the animal hosts of ebola and other zoonotic viruses, so that we may be able to change human behaviours and interactions with certain animals to prevent or prepare for further viruses jumping species. Similarly, worldwide surveillance networks have existed for some time, for sampling emerging influenza viruses, which are also zoonotic with high potential to cause pandemics. Influenzas mainly circulate in birds but can also infect pigs before jumping into humans, as we saw in the most recent 2009 swine flu pandemic. There have been many warnings in the scientific literature since the SARS-CoV-1 (2002) and MERS outbreaks (2010) that another coronavirus outbreak was possible, and it is now clear that better surveillance networks are required for coronaviruses and other types of viruses with pandemic potential.



Ebola virus



Influenza virus

*Other known ZOONOTIC infections: Ebola virus jumps from fruit bats and free-tailed bats found in parts of Africa and Asia, and influenza viruses can spread to humans from birds and pigs.*

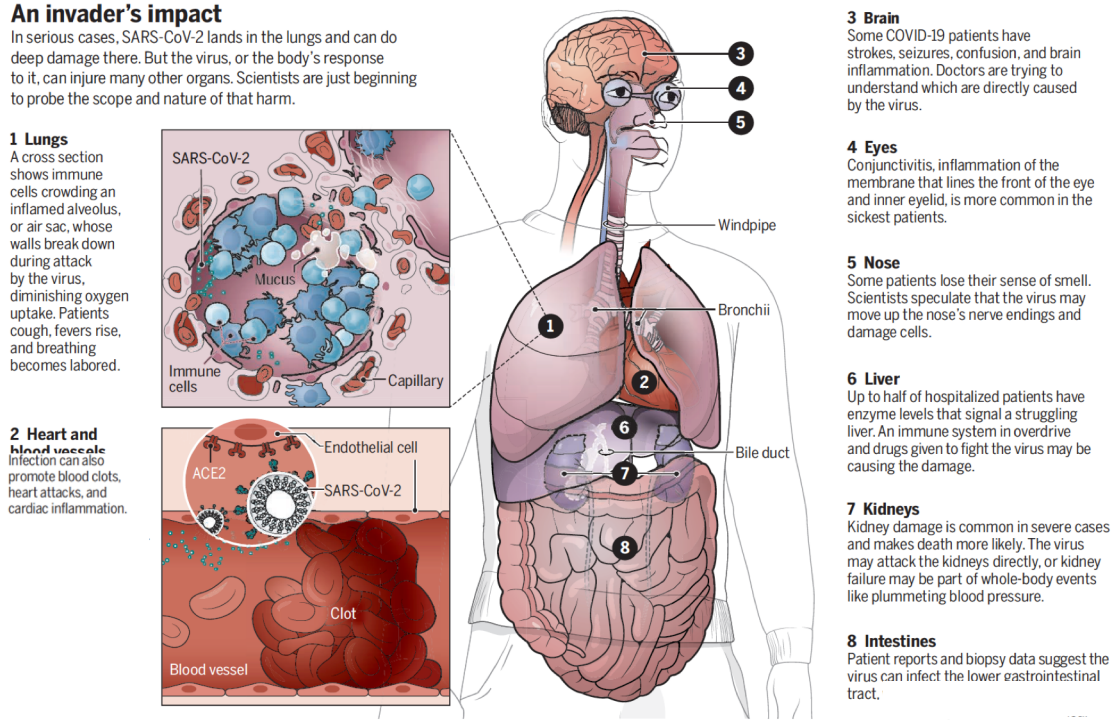
**To successfully control a zoonotic pandemic, we have to properly understand a virus in the context of its animal and human hosts, from the cellular level all the way through to the population level. As the world keeps changing in ways that affect our interactions with animals (changing habitats, deforestation, how people get their food, international travel, to give just a few examples), the viruses we encounter and their pandemic potential will change and how we prepare for and handle them must as well.**

## How does the virus cause disease and why do some people get severe disease but others have no symptoms?

This is a key question, as understanding how the virus causes disease and why infections range from asymptomatic (no symptoms) to fatal will help us develop effective treatments. Knowing this would also help us to identify and protect those most at risk from severe disease. Covid-19 is a completely new disease, unlike anything we've seen before, so doctors and scientists are trying to understand it at the same time as responding and treating it. Research in this area is incredibly fast moving.

A study from Iceland that managed, suggested that nearly 50% of infected people do not experience any symptoms (Study 4). Others develop the now well-known mild symptoms such as headache, fever, muscle aches, fatigue, loss of smell and taste senses, and a dry cough. These often resolve within the first week of infection. However, some go on to develop severe disease, which can come on suddenly between 7-10 days after infection. Severe disease is centered around the lungs and includes breathlessness, low oxygen levels, pneumonia and acute lung failure. Surprisingly for a respiratory virus, hundreds of reports now describe a range of life-threatening symptoms, different in each patient, affecting multiple organs, including the intestines (diarrhoea), kidneys (kidney failure), the brain (stroke), and damage to blood vessels and heart attacks are common.

**The key now is to understand what drives the symptoms in each organ, and whether the damage is done directly by the virus or by an unrestrained damaging immune response.**




*Summary of the range of severe COVID-19 symptoms experienced by some patients. Image taken from Refence 5.*

SARS-CoV-2 can infect cells that line the nose, airways and lungs, as well as cells that line the intestines, and most likely blood vessels. We know this by testing which cell types the virus can infect in the lab. Whilst this provides good models to study the virus, it doesn't tell us which cells are actually infected in the body. This is hard to answer as to identify infected cells we would need take biopsies from each of the affected organs, which is highly invasive. Compared to viruses that you can detect in the blood, respiratory viruses are difficult to study in the body, this makes it hard to follow the course of infection and measure the amount of virus in patients at the main site of infection.

In the lab, the virus leads to death of the cells that it infects. In the body, a lot of cell death can directly lead to tissue damage in different organs and could contribute to symptoms. It is possible that the dose of virus you are exposed to may influence the course of infection and disease severity. Being infected with a high dose of virus could mean that it has a head start on establishing infection and perhaps spreading to multiple organs before the immune system can fight back to contain and clear it. Likewise, the route of entry of the virus into the body might also influence this. For example it is possible that if you breathe virus deep into the lungs then the course of infection could be worse than initial exposure only in the nose. These questions are all currently unanswered.

However, people with no symptoms can have equally high levels of virus as those with severe disease, at least in the nose, suggesting high levels of infected cells without tissue damage and disease. This is either because they mount an effective immune response to prevent spread of the virus from the nose to the lungs and other organs, or because something else is driving disease. The onset of severe disease after 7-10 days of infection, when the immune response is really kicking in, suggests that control, or lack of control, of the immune response is a key feature of this disease.

There are numerous reports that show patients with severe disease have an overreaction of the immune system, which damages tissues and contributes to disease. However this hasn't yet been conclusively shown to be the difference between mild and severe disease. A feature of the overreaction is a **CYTOKINE STORM**. This can occur when cells that are infected release chemical danger signals, molecules known as cytokines and chemokines. These molecules signal for back up, in the form of immune cells (white blood cells), which travel to the site of infection and become activated to fight the virus. They flood into the affected area to kill infected cells in order to destroy the virus and limit its spread. In the lungs, the influx of immune cells creates excess fluid and debris, which also prevent the lungs from functioning properly, and can contribute to the symptoms of pneumonia and lung failure.

The immune response is normally a very well-regulated process to minimise this sort of damage, but in a storm this control is lost. The immune system brakes don't work, the levels of cytokines and chemokines soar and surrounding healthy cells can also be killed as collateral damage. This may explain the damage to blood vessels and other organs, contributing to some of the more severe symptoms. The storm can release molecules that affect how the blood clots, and evidence of blood clots has been found in many patients in intensive care. Blood clots have the potential to stop blood flow to the lungs and lead to lung failure, or to the brain and heart leading to stroke or cardiac arrest respectively. An effect on blood circulation might also explain the pictures of 'COVID toes' that have been reported, which look like they have frostbite, associated with reduced circulation to the extremities. Some patients are being treated with blood thinning drugs as a precaution to prevent blood clot problems.

These effects may explain why pre-existing conditions that damage blood vessels, such as high blood pressure, diabetes, and obesity, are as much risk factors for severe Covid-19 as chronic lung disease. The US Center for Disease control (CDC) found that over one third of patients in intensive care had chronic lung disease, nearly as many had diabetes, and in total half had high blood pressure (Study 6). This suggests that any existing damage makes blood vessels much less likely to withstand the effects of a cytokine storm during SARS-CoV-2 infection.

**We and others are now doing experiments to help us understand which cytokines in the storm are the most important drivers of severe disease. This is key to understanding how using existing or new drugs that dampen the storm and prevent disease. We want to know why this immune overreaction happens in some people and not others, and what triggers the storm. Is it something started by the virus or does it depend on the status of someone's immune system at the time of infection?** This is influenced by many factors, such as what other infections or recent exposures to other bacteria or viruses someone has, which may make their immune cells already activated. Does age, a key risk factor, also play a role in this? A good question is whether a storm is more likely to occur in adults over a certain age compared to children, and does this explain why children typically do not get severe symptoms? A recent study from groups at UCL found inflammatory parts of the immune response were switched on similarly in young and elderly individuals, but that response was not switched off and cleaned up properly in the elderly, suggesting they may experience prolonged inflammation (Study Reference 7). This has not yet been studied in the context of SARS-CoV-2, but is a key question.

## How does understanding the cause of disease help us to develop treatments?

To develop the most effective treatment we have to understand how the virus replicates and spreads in the body and what actually drives disease . There are two main strategies to Covid-19 treatments:

**1. Develop antiviral drugs that directly target the virus and prevent its replication**
**2. Switch off damaging immune responses.**

1. Directly targeting the virus can reduce its replication, which can also give the body a better chance to clear the virus. It is also possible that reducing viral replication would prevent virus-induced tissue damage, and stop it kicking off a cytokine storm if we find this to be the case. These drugs would probably be most effective in the early stages of infection.

2. If the early stages are missed and someone arrives in hospital with severe disease, then we may need drugs to dampen the cytokine storm, in combination with treating the virus. This is the second strategy. It's essential that we understand which particular cytokines and components of the immune response are destructive, so that we can specifically target them. Otherwise we could end up switching off good immune responses that help to clear the virus and this could make infection and disease worse.

There are currently over 75 drug trials going on worldwide that encompass these strategies. Many trials are to re-purpose existing drugs that are known to alter aspects of the immune response to treat other conditions. The advantage of this is that the drug has already been through safety trials and is licenced so it could be rolled out more quickly. Development of novel drugs may be more long-term but could lead to more potent treatments based on thorough understanding of the virus and immune processes that lead to disease. Development of drugs that target multiple coronaviruses could also prepare us for if another coronavirus were to jump from bats into humans in the future.

## Why are people of black Asian and minority ethnic (BAME) backgrounds and men more affected in the UK?

Analysis of the numbers of people hospitalised with COVID-19 in the UK have been reported to show that men and people of BAME background are up to two/three times more likely to have severe disease and and higher death rates, depending on ethnicity. The UK government has launched an inquiry into this, and whilst we await the findings many explanations have been put forward. It's a complex question and here we just summarise some of the ideas that have been put forward. It is most likely a combination of factors, and these will be different in each country. Here it has been suggested that inequalities in health and wealth in different communities is a contributing factor (described here: https://www.newscientist.com/article/2241278-an-unequal-society-means-covid-19-is-hitting-ethnic-minorities-harder/). It is possible that differences in jobs across communities and whether people of BAME background are more likely to have key worker jobs may increase risk of exposure. Likewise, differences in the level of social crowding and the number of family members living in close proximity across communities could also influence exposure rates.

It is likely that there more than socioeconomic factors at play. Certain chronic health conditions, including the cardiovascular risk factors for severe COVID-19 (diabetes and high blood pressure) are thought to be more common in men of BAME background. Finally, it is possible there are genetic risk factors that we have not yet uncovered which could vary with ethnicity. For example, during the 2009 swine flu pandemic, people with a mutation in a key antiviral protein that protects against a range of viruses, were more likely to be hospitalised with severe disease (Study Reference 8). How common this mutation is in a population varies with ethnicity. To date, no specific genetic mutations have been associated with increased risk of severe Covid-19, but this is an active area of research.

## If you've already had SARS-CoV-2, can you catch it again?

So far there are no reliable reports of anyone being infected a second time, and as the outbreak has been running for over 6 months now this is a good sign. However we can't yet rule it out, especially as there was not enough testing in the early phase of the outbreak to identify everyone who has already been infected. Regular screening of health care workers, who are most likely to be exposed multiple times, has the most potential to answer this question. Early press reports of reinfection may be explained by detection of debris from the original infection in clinical samples.

We also need to understand whether you develop a protective immune response against SARS-CoV-2 to prevent symptoms the second time you are exposed, what components of the immune system mediate the protection and crucially how long the protection lasts. SARS-CoV-1 infection generates a protective immune response, and this has been shown to last for at least 2 years in lab models, but this is not the same as showing that it's protective in the body. SARS-CoV-2 is a different virus causing a different range of disease, so it is hard to draw comparisons. Answering these questions is also key to developing an effective vaccine to induce a long-lasting protective immune response (see below).

## How has computer modelling been used in the outbreak and what can it tell us?

At the start of the outbreak, computer modelling was used to predict how many infections there would be in the UK and how many deaths. Early estimates gave a worst-case scenario of half a million deaths if no action was taken. This report was one of the factors that prompted action to prevent the worst-case scenario and stop the NHS becoming overwhelmed due to shortages of intensive care beds and ventilators, which then seemed to be increasing the death rate in other countries.

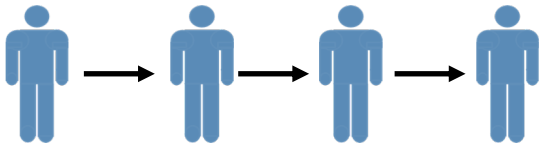
It's important to understand the uses and limitations of modelling the outbreak as it continues. Firstly, models are never completely accurate- the clue is in the name. To create a model, you have to make assumptions about the virus and how it will spread through a population, which is hard when it's a completely new virus that we don't fully understand, with no identical population to compare to. Each country has different living conditions, age and health demographics that will affect the number of infections and fatalities.

A model can be a useful starting place, but to know how accurate it is the model must be backed up with testing to provide real data about how the virus is spreading and the infection rates. By feeding real data into the computer models it is possible to see how the predictions match what is actually happening. This enables us to refine the model and test if its original predictions were accurate. This can be useful because if the model's predictions are different to what is actually happening, as we have seen during this outbreak, it tells us that the original assumptions behind it were wrong and, most importantly, it gives us a chance to learn from this. The only way to feed data in is to do thorough testing, at levels much greater than in the last few months, to know the actual rate of infections and understand how the virus is spreading through different parts of the population- studying infection spread is known as **EPIDEMIOLOGY**. By not having sufficient levels of testing during March/April, we have lost a lot of information such as the actual percentage of people in the UK who have been infected. This would allow us to more accurately predict whether we may be nearing herd immunity (see below), estimate more accurate death rates, the R number (see below), and to know how many infections there can be in the community without the NHS becoming overwhelmed.

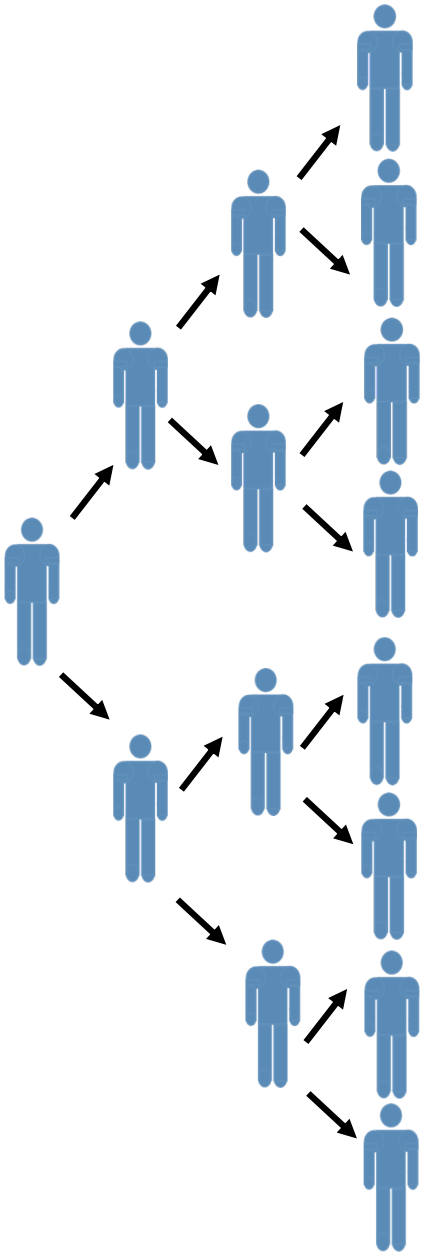
## What is the R number or reproduction rate and why does the government care so much about it?

The R number or reproduction number is a mathematical term also known as R0 (pronounced 'R naught'). It is used to describe how contagious an infectious disease is. It refers to the average number of people who will catch the disease from one infected person, so for example if R0 = 2, it means 2 people will catch the disease from 1 infected person. The higher R0 is, the faster, or further, the disease will spread and harder it will be to control an outbreak, whereas if R0 is less than 1, the spread of disease will be in decline. An R0 number less than 1 is possible because it's an average, for example if R= 0.5, it means on average 1 in 2 infected people will spread the disease to someone.

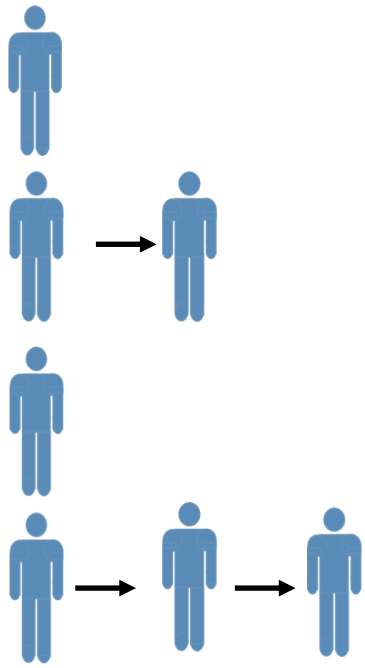
R0 is predicted when a whole population is susceptible, such as at the start of an outbreak of a new disease where no one has existing immunity. The naught is dropped and just 'R' is used when not everyone is susceptible, for example it is predicted that people may be immune now and no longer susceptible, so this changes the predictions. We think this is why the government is just calling it 'R'.



***R =1**. Each infected person gives it to one other, transmission is sustained but does not increase.*



***R= 2**. Every infected person gives it to two others, and the outbreak grows very quickly.*



***R=0.5**. For every two people infected, only one passes it onto one person. For example, 4 people are infected in the first round, only 2 are infected in the second round and only 1 is infected in the third round. When the R number is less than one, the number of infected people declines.*

An important thing to bear in mind is that R is determined by both the properties of the virus and the population it is is spreading in. First, lets consider the virus: R can be influenced by the duration of infection, where a long-lasting infection creates more opportunities for onwards spread and higher R. The more infectious the virus (the lower dose of virus needed to infect someone), the higher the R, and, finally how how the spreads is really important: airborne viruses are likely to spread better than those needing direct contact and have higher Rs. Second, the population: R is also determined by how many people come into contact with the infected person, which varies with human behaviour and in populations. For example, at the start of the outbreak, R was thought to be higher in densely populated cities like London than the Scottish Isles. Reducing contacts will therefore reduce the R, which has been in part the basis of lockdown. Developing protective immunity in the population, from natural infection or vaccination, also decreases R during an outbreak, as there are less susceptible people.

Without proper testing and contact tracing, it is unclear how government advisors have been calculating R, and on what basis they have made statements such as 'opening primary schools will increase R by …'. This is predicted by computer modelling using numbers like death rates and hospitalisations as measures of the number of infections, combined with many assumptions. As we explained earlier, computer modelling isn't always accurate. However, the government are using the R number as a way to predict the average transmission rate and convey the risk associated with easing certain lockdown measures. It's common sense that whilst there are still infected people, anything that promotes social crowding will create opportunities for spread, and will drive the number of infections up. The R number gives them a way to try and quantify virus spread to assess the risk attached to any change in policy. It's not fully clear how they will determine if and when we cross the important threshold of R=1, meaning the outbreak is growing again, but all lockdown and social distancing efforts are aimed to keep it below.

## What are the different tests and what do they tell us?

There are two types of test that we've heard about in the news:

**1. Nasal and throat swab tests** aka PCR or antigen tests
**2. Antibody test** aka serology or ELISAs

1.Nasal and throat swab tests are currently being performed in hospitals and testing centres, and as of 19th May, if you or anyone in your household has symptoms (and are >5 years), then you can apply for a home test or go to a drive through test centre, check www.gov.uk/guidance/covid-19-getting-tested for details. This was previously reserved for key workers, people who can't work at home and over 65s, so making it more widely available is a big breakthrough. Follow instructions carefully on how to do a nasal swab for it to be most accurate. It's not clear why these tests are not suitable for under 5s, most likely because taking a nasal swab has to be done carefully in small children, and so if you are worried about any children with symptoms call 111 and they will advise. So far children have not been found to develop severe disease except in rare cases. Swab tests rely on detecting the virus genes on the swab, and will tell you if you are currently infected. They are also known as PCR tests, which is the name of the technique used to detect the viral genes, and have also been called 'antigen tests' in the news. The word antigen just means a part of the virus, such as its genes, which tells you that it is present and most likely actively replicating.

2. The antibody test, also known as a serology test or ELISA, which is the name of the technique for detecting antibodies. This is a blood test and relies of detecting antibodies against the SARS-CoV-2 spike protein. This test can tell you whether you have been infected in the past rather than whether you currently have the virus, but only if you have developed **ANTIBODIES** as a result of infection. Antibodies are small molecules made as part of the immune response to fight infection. Once infected, you continue to make antibodies long after the infection is over to help protect you against the virus the next time, like an immune system memory. They are not always protective, which is something we are trying to understand for SARS-CoV-2. Either way, the levels and types of antibodies in your blood serves as a record of all of the past infections or vaccinations you have had. These tests have the potential to fill in some of the gaps from the lack of swab testing and tell us how many people have been infected in the first wave. Public Health England has just approved the use of an antibody test in the UK. It is unclear whether they will be made generally available, or at least prioritised for key workers at first. **So to summarise:**

1. **PCR is useful for diagnosis and telling us how many people in the population are infected at the moment.**
2. **Antibody testing may tell us how many people have been infected and developed an immune response.**

## Is SARS-CoV-2 mutating to become more deadly?

Stories claiming that SARS-CoV-2 has mutated to become more deadly have been doing the rounds. The word 'mutation' sparks fear. In fact, viruses are mutating all the time, it is what they do. Every time the virus makes a new copy of its genome (all of its genes), it makes mistakes or mutations, which means that every new virus produced will carry these mutations. Coronaviruses actually have lower mutation rates than other viruses like influenza, HIV and norovirus, as they take the time to proof-read and correct the newly made genomes. Nevertheless mutations still arise, and this gives the virus the chance to adapt, for example to better infect humans than bats, or to escape immune responses or develop drug resistance. If a mutation that occurs by chance gives the virus a

competitive edge, like growing faster or drug resistance, then that virus will outcompete others and we will see the particular mutation in all subsequent viruses isolated from patients. This is **EVOLUTION.**

Teams around the world are keeping track of how SARS-CoV-2 is mutating, by identifying the unique **GENOME SEQUENCE** (see page 3 for explanation) of viruses isolated from different patients and spotting the differences. There is NO evidence that any mutations have made the virus deadlier . It has been proposed that one mutation may make the virus more transmissible. The study authors presented evidence that viruses with this mutation have spread better around the world (Study reference 8). Although they have looked at 1000's of virus sequences, this is a small sample of the millions of total infections worldwide. During an outbreak it is also very hard to associate particular mutations with things like how well a virus spreads, as there are so many other factors that can influence this. For example, imagine a virus with mutation A gets into a densely crowded population (London), whereas a virus with mutation B is in a less crowded population (a small village in Cornwall). Mutant A would look like it had become better at spreading than mutant B, but this may have nothing to do with the mutation and simply reflect differences in the density of each population. This is called a **FOUNDER EFFECT,** meaning something occurs just because the founding virus in a new population was different.

An important reason to track the mutations is to inform vaccine design. We need to understand if mutations arise in the spike protein, the outer layer of the virus that the vaccine trains the immune system to recognise and mount a response against. If the virus has many mutations in the spike, then the vaccine may not give protection against all varieties and may not work so well. If we know this before a vaccine is made, then we can try and design it to recognise all spike proteins even those with different mutations to give broad protection.

**Summary: Has SARS-CoV-2 mutated to become more lethal? No.**

## Will temperature scanners at airports prevent SARS2-CoV-2 spread?

There has been talk about using temperature scanners to screen everyone coming into the country and prevent new imported waves of infection. This worked previously for SARS-CoV-1 in 2002/2003, where people had a fever when they became infectious, and also during the Ebola outbreak in 2013-2015, making it easy to identify infected people and quarantine them to prevent spread. However, SARS-CoV-2 is different in that you can spread the virus before you have symptoms, and over 50% of those infected may not develop a fever or any symptoms at all. Therefore, temperature scanning will not identify everyone who is infected. The government have proposed quarantining everyone who enters the country for at least 2weeks (the time in which you can develop symptoms after exposure) as a blanket measure to stop re-introduction of the virus into the UK.

**Summary: Temperature scanners will not identify people with asymptomatic SARS-CoV-2 infections who can still spread the virus.**

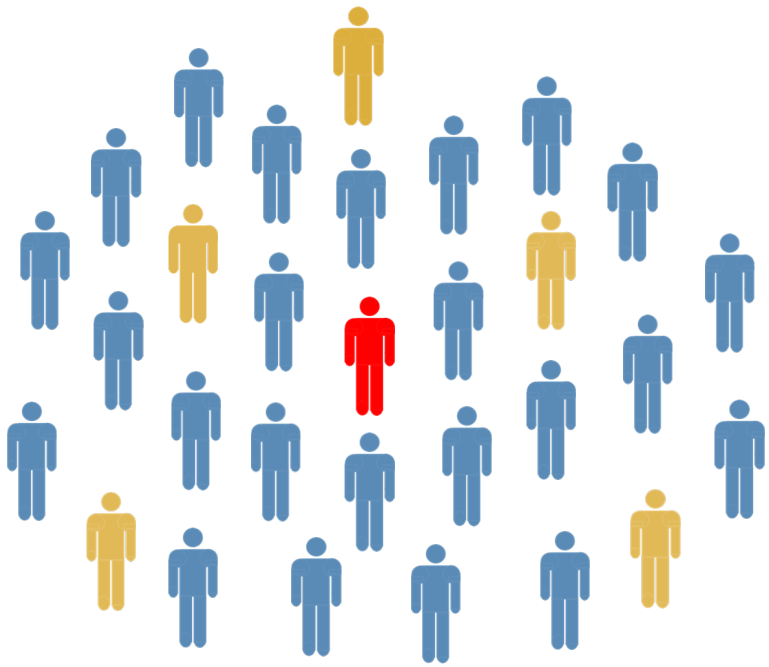
# What is herd immunity?

Herd immunity means when enough people are immune to an infectious disease to slow or stop it spreading through a population. It can be developed through natural infection, IF this leads to a protective immune response (we still don't know this for SARS-CoV-2), or by vaccination. It does not require absolutely everyone to have been infected or vaccinated, but if enough people have been then they will shield the susceptible people and stop the infectious disease from spreading. This would prevent future large waves of infection if the immunity lasts long enough. **This is why your choice to have a vaccine affects not only yourself, but your family and your whole community, protecting yourself protects others around you.**

The percentage of people that must be immune to reach herd immunity is different for each virus. The more infectious a virus is, the higher level of immunity needed, but it can also depend on the population.

We don't yet know what level of immunity against SARS-CoV-2 there is in the UK, as we don't know the percentage that have been infected so far due to lack of testing. As mentioned earlier we also still don't know if all infections (asymptomatic, mild and severe) allow you to develop a protective immune response which is key. It's also important to understand that immunity is not all or nothing, it can range from being completely protective preventing any disease and spread, to just being enough to prevent severe disease in which case spread can still occur.

Ongoing antibody testing in Spain has revealed that only ~5% of the population are thought to have developed antibodies to SARS-CoV-2 so far (Study reference 8). It is estimated that around 65% of people would need a protective immune response to prevent continued spread, so the current numbers are well below this, suggesting a vaccine would provide a better chance at achieving herd immunity as long as it induces a long-lasting protective immune response. However it's important to remember that antibodies are just one aspect of the immune response that can be protective.



***Herd Immunity is when enough people in the population are immune to an infectious disease to stop it spreading. Here the red person is infected but can't spread disease to the susceptible people (yellow) as they are shielded by the people with a protective immune response (blue), achieved by natural infection or vaccination***.

# What is the route to a vaccine and how and when will we know if it works?

**How does a vaccine work?**
Vaccines work by giving your body a chance to develop a protective immune response to a virus or bacteria before you encounter the real thing. They are often weakened, dead or just isolated parts of the virus that will not cause disease and are completely safe, but train your immune system to recognise the virus and develop a response including protective antibodies. This response lasts and creates an immune memory. This means that when you encounter the real virus/bacteria, your immune cells can recognise it, become activated and respond more quickly to shut infection down before it causes disease.

**What is the Oxford vaccine?**
There are over 100 vaccine candidates in development worldwide, and at least 10 in clinical trials. In the UK, the efforts are being headed by groups at Oxford University and Imperial College London. Their vaccine candidate is designed to give your body a chance to develop an immune response against the SARS-CoV-2 spike protein. The spike protein by itself cannot cause disease. To deliver it to your body and immune cells, the spike is inserted into a different carrier virus which gets it into cells so they can generate a response against it. The delivery also does not cause disease, it has been thoroughly tested to be safe and has been used many other times.

**Does it work?**
This vaccine has been shown to generate a protective response against SARS-CoV-2 in lab models of the disease however this is not the same as giving protection in the human body, but is enough evidence for it to go forward into clinical trials to test this.

**How is it being tested?**
Clinical trials are normally performed in three phases:
Phase 1: testing the safety of the vaccine in a small group of people for side effects.
Phase 2: testing whether the vaccine generates an immune response and what kind, in small groups .
Phase 3: larger scale testing of whether the vaccine protects against infection and developing symptoms.

The Oxford vaccine is currently in phase 1 clinical trials, but phase 2 is being run in parallel to speed up the process. If, and only if, it is safe and the team can demonstrate it induces immune responses will it move forward. Keep in mind that we don't know yet exactly what type of immune response will be protective against SARS-CoV-2.

In phase 3 trials, the team will monitor whether people given the SARS-CoV-2 vaccine are protected against natural infection compared to those given no vaccine or a different unrelated vaccine. They will be monitored for whether they become infected (i.e. can the virus be detected) and whether they develop symptoms. Depending on how much virus is circulating at that point in the pandemic, it may take time to reach an acceptable number of exposures in the control groups to compare.

**How will it be rolled out?**
Phase 3 is normally done in a large but specific group of healthy people. Next, it will be important to know if the vaccine works in people of all ages, backgrounds, and health conditions. If a vaccine can pass all of these tests then it would be licenced, and production scaled up. The question would be who gets the first doses until enough is available, health care and key workers and those most at risk from severe disease? Any vaccine would have to made globally available and there are many decisions/logistics around this and production on a global scale. The pandemic cannot be controlled without global cooperation. If the virus is in one country, there is the chance it can start spreading again in all countried. It is very difficult to put a time frame on this vaccine roll out. The UK teams have said they are optimistic there will be one towards the end of this year, but this would make it the quickest vaccine development in history, and that relies on it passing all of these tests first time. As you can see this is all very uncertain. It is important to realise that there isn't just one vaccine to be found. One thing is for sure: the more candidate vaccines and the more science and trials that are done, the better.

# Will there be a second wave and how do we emerge from lockdown without a vaccine?

The idea of a second wave is somewhat of a misnomer, as whilst the virus is in circulation we are in a continual wave of infection. The numbers do show that infection and death rates have declined, so perhaps a second peak in these figures is really what this term means.

An effective vaccine or treatment would provide a clear way out of lockdown. A vaccine could stop transmission and treatments may prevent the most serious disease and reduce death rates. As we have explained here, there are many questions we still need to understand to deliver a vaccine or drugs, and to help us tackle the pandemic from an informed position. Teams of scientists around the world are working on this, in what has become the biggest research effort ever recorded by the number of scientific articles currently being published. However, developing vaccines and treatments will still take time, and so we cannot rely on these measures to bring us out of lockdown in the near future.

All lockdown and social distancing measures have been implemented to reduce transmission. This has been effective in reducing infection and consequently death rates in hospitals, which have been our current main measurements without comprehensive testing. As we emerge from lockdown, and social contact and crowding increases, it seems inevitable that infections will rise again, as other countries have seen. Whilst there are sufficient numbers of susceptible people in a population and behaviour that facilitates transmission, viruses will spread.

We are also emerging from lockdown somewhat blind, having failed to gather a lot of this information about infection rates and who has had it in the last few months. Thankfully the government has now declared that everyone with suspected symptoms can be tested, this is a significant breakthrough and is much needed. It will now allow us to more thoroughly assess the impact of easing certain lockdown measures, without having to rely on number of infections and deaths in health care and front line workers and those most vulnerable (over 65 and existing health conditions). These are exactly the groups we are trying to protect and we need to be monitoring and tracking infections before they reach these groups. The importance of higher levels of testing cannot be repeated enough. Remember that given the incubation time of up to 2 weeks (time from exposure to developing symptoms), there will be a 2 week lag time in assessing the impact of easing any lockdown measures.

In this document, we have focussed on scientific evidence and our interpretation of it. Easing lockdown measures and the strategy behind this are largely political decisions, which are informed and guided by scientific advisers. The Government's challenge is to balance multiple factors in formulating policy for the phased release of lockdown measures. Such factors include current knowledge of the nature of the virus and disease, transmission rates, the susceptibility of vulnerable groups, economic consequences, and general health, life expectancy and mental health issues. Evidence suggests that death rates unrelated to Covid-19 have also spiked as people are afraid to seek out hospital care and many essential health care services such as cancer treatments have been affected. It is therefore of paramount importance that there is clarity in the guidance offered relating to safe working practices and the changes required in social behaviour.

So what is our take-away message? As we move towards the lifting of lockdown, we suggest that you always err on the side of caution. There will be lots of detailed debate and discussion in the press and probably lots of controversy and argument. We suggest that you try to remember what we've said about how the virus spreads, how you can catch it and how you can avoid catching it. Obviously, not getting infected is good for each one of us, and those we care about, but also it is perhaps the best contribution we can make to controlling the outbreak.

## Study References and scientific articles


1. Science Forum: SARS-CoV-2 (COVID-19) by the numbers. Bar-On et al.. eLIFE 2020. https://elifesciences.org/articles/57309

2. Stability of SARS-CoV-2 in different environmental conditions
Chin et al. Lancet. 2020.
https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30003-3/fulltext

3. Evolutionary origins of the SARS-CoV-2 sarbecovirus lineage responsible for the COVID-19 pandemic. Boni et al. Bioarchive 2020.
https://www.biorxiv.org/content/10.1101/2020.03.30.015008v1.full.pdf

4. Spread of SARS-CoV-2 in the Icelandic Population. Gudbjartsson et al. NJEM 2020.
https://www.nejm.org/doi/full/10.1056/NEJMoa2006100

5.A rampage through the body. Wadman et al.
*https://science.sciencemag.org/content/sci/368/6489/356.full.pdf*

6. *https://www.cdc.gov/mmwr/volumes/69/wr/mm6915e3.htm*

7. Blocking elevated p38 MAPK restores efferocytosis and inflammatory resolution in the elderly. De Maeyer. Nature Immunology, 2020. *https://www.nature.com/articles/s41590-020-0646-0?draft=collection*

8. IFITM3 Restricts the Morbidity and Mortality Associated With Influenza. *Everitt et al. Nature 2012. https://www.nature.com/articles/nature109219. Sheffield mutation papers*

9. https://portalcne.isciii.es/enecovid19/. National Center of Epidemiology, Spain.