London Review of Books Vol. 42 No. 5 · 5 March 2020 Wash Your Hands Rupert Beale

I first heard about coronaviruses in 1999. Their special cunning is in the huge length and complexity of their RNA genome. RNA is much less stable than DNA, so RNA viruses tend to be short. We measure them approximately in kilobases (kb) of information. Polio is a mere 7 kb, influenza stacks up at 14, and Ebola weighs in at 19. Severe Acute Respiratory Syndrome Coronavirus 2 (Sars-CoV-2), the causative agent of Covid-19, is 30 kb. That's quite normal for a coronavirus, but close to the chemical limits of information storage for RNA – about as long as a strand of RNA can be without collapsing. The viruses therefore need some clever tricks to survive. I remember being fascinated by the RNA 'pseudoknot' and 'slippery sequence', which allow the viral genome to be read in two different ways simultaneously; the virus can regulate expression of different genes according to the way they are read.

Virologists need more than clever tricks: we also need cash. Twenty years ago, funding wasn't available to study coronaviruses. In 1999, avian infectious bronchitis virus was the one known truly nasty coronavirus pathogen. Only poultry farmers really cared about it, as it kills chickens but doesn't infect people. In humans there are a number of fairly innocuous coronaviruses, such as OC43 and HKU1, which cause the 'common cold'. Doctors don't usually bother testing for them – you have a runny nose, so what?

When Sars broke out in 2002 we had no effective vaccine for any coronavirus, no antiviral drugs, minimal clues about how it caused disease and very little idea about the dynamics of transmission. It killed a reported 774 people, about 10 per cent of everyone it infected. In retrospect we were lucky that the Sars outbreak of 2002-3 was so nasty: it was easy to spot when someone had it, isolate them and treat them as best we could. There was a brief, intense flurry of funding, which rapidly subsided along with the virus. In 2012 a new, seriously pathogenic coronavirus emerged, Middle East respiratory syndrome related coronavirus (Mers). Like Sars it came to us from bats, but unlike Sars it arrived via dromedary camels – the intermediate host. It's even nastier than Sars, killing about 30 per cent of people it infects (858 in total), but it doesn't transmit well between humans. Covid-19 is especially difficult to deal with as most cases are mild. You have a cough, a sore throat, maybe a fever, maybe no symptoms at all – so what?

As the US health secretary Michael Leavitt put it in 2006, 'anything we say in advance of a pandemic happening is alarmist; anything we say afterwards is inadequate.' The Chinese government, for all its undoubted faults, instituted rational measures to contain the spread of the virus from its origin in Wuhan. Public transport, schools, large gatherings of any kind – all shut down. Known cases isolated, contacts traced and strict quarantine enforced. Enormous new hospitals built in less than a fortnight. Oxygen and ventilatory support supplied no matter the cost. Medics deployed from across the country, working extraordinary hours. Failure to comply not an option.

The current 'multi-focal epidemic', or 'pandemic' as virologists would usually describe it, has at the time of writing caused 3408 deaths. If governments move rapidly to contain and delay the spread, and effectively provide optimal medical care, we can expect a case fatality rate just under 1 per cent – though there is still a lot of uncertainty about this. South Korea is showing what a medium-sized country with a democratic government should do. They quickly ramped up their testing capacity, educated the public about self-isolation, shut down large gatherings, restricted travel, increased hospital capacity. They have allocated 30 trillion won (£19 billion) to the response. They have confirmed 6593 cases, but only 42 deaths so far – though only 41 people have been declared to have recovered. The main effort has been in rapid and efficient testing. Detecting and isolating mild cases delays the spread of the disease and reduces the proportion of the population that will be infected. 'Social distancing' – reducing human contact – can be achieved by shutting schools, universities, public transport etc, and can mitigate the undetected spread of untested mild cases. The approximately 20 per cent of severe cases requiring hospital treatment, and the roughly 5 per cent of critical cases requiring intensive care, thus do not all arrive in a short time-frame. Resources are not overwhelmed, and lives can be saved.

In countries where rapid testing and isolation do not happen, the disease will at its peak rapidly overwhelm the ability of hospitals to cope, and the case fatality rate will be much higher. The global case fatality rate is above 3 per cent at the moment, and if – reasonable worst case scenario – 30-70 per cent of the 7.8 billion people on earth are infected, that means between 70 and 165 million deaths. It would be the worst disaster in human history in terms of total lives lost. Nobody expects this, because everyone expects that people will comply with efficient public health measures put in place by responsible governments.

Things do not look good in Iran. There was a cluster of cases in Qom. No containment measures were put in place until a number of people had died. The disease spread across Iran and to neighbouring countries, destroying any lingering hope for global containment – though that was always going to be a long shot given the number of cases emerging from China in the early phase of the pandemic. Tehran's official figure of 4747 cases is likely to be between ten and a hundred times lower than the true number. The World Health Organisation is now involved and the reality may become apparent in the next few weeks. The initial lack of testing and lack of isolation of cases – denialism by the regime – is likely to lead to healthcare services being overwhelmed and tens or hundreds of thousands of deaths.

Most democratic governments will follow South Korea rather than Iran. The UK's record on testing and isolation of cases has so far been pretty good, though we need to increase testing capability. The announcement on 5 March that containment was no longer realistic and that we are moving towards a policy of delay is exactly right. Politicians will have to make some brave and possibly unpopular decisions on the advice of public health officials.

In the US the response so far has been slow. The situation isn't helped by a president who keeps suggesting that the virus isn't that bad, it's a bit like flu, we will have a vaccine soon: stopping flights from China was enough. Tony Fauci, the director of the National Institute of Allergy and Infectious Disease, deftly cut across Trump at a White House press briefing. No, it isn't only as bad as flu, it's far more dangerous. Yes, public health measures will have to be put in place and maintained for many months. No, a vaccine isn't just around the corner, it will take at least 18 months. Fauci was then ordered to clear all his press briefings on Covid-19 with Mike Pence in advance: the vice president's office is leading the US response to the virus. 'You don't want to go to war with a president,' Fauci remarked.

The Centres for Disease Control and Prevention (CDC) are in charge of testing for and responding to the outbreak in the US. Astonishingly, their website reports that 'CDC is no longer reporting the number of persons under investigation (PUIs) that have been tested, as well as PUIs that have tested negative. Now that states are testing and reporting their own results, CDC's numbers are not representative all of [sic] testing being done nationwide,' and: 'As of 4 March 2020, 1524 patients had been tested at CDC. This does not include testing being done at state and local public health laboratories, which began this week.' As a result, the US has reported only 233 cases. But by piecing together analysis of the genomes of viruses isolated from patients, virologists have shown that Sars-CoV-2 must be circulating undetected in the US. There was a very worrying case in California, where a patient was immediately suspected by his doctors to have Covid-19, but wasn't tested because he didn't meet the narrow CDC criteria. Five days later, he tested positive.

The US response will be complicated by its lack of socialised healthcare. Most cases in healthy young people will be mild. Your chance of death as a fit thirtysomething is probably much lower than 0.1 per cent. If you smoke, have diabetes, heart disease or a pre-existing lung condition, or are immunosuppressed, your chance of death is much higher. If you are in your eighties, it's approaching 15 per cent. People often don't go to the doctor in the US because they are understandably fearful of the huge costs they may incur. New York City and Washington State have already mandated that testing should be free; we must hope this becomes universal soon. Part of the public health response will have to be self-isolation of possible mild cases. You must not go to work. Will it be possible to convince the US public that they will have to endure some economic hardship to protect their vulnerable compatriots?

The US as a whole is immensely wealthy, and doesn't have an excuse not to put in place stringent testing and isolation procedures. What about poorer countries? A few cases have been reported in sub-Saharan Africa. There is infrastructure in place to monitor influenza pandemics, which can be repurposed to test for Sars-CoV-2. But to ramp it up to the scale that South Korea has achieved is probably not realistic for a country like Malawi. The test at the moment is expensive, and requires a complicated machine as well as trained staff. There are efforts beginning in the UK, and no doubt elsewhere, to develop a simple 'point-of-care' test that could be self-administered. But even a prototype is several months away. Low and middle-income countries will have to put in place measures to increase 'social distancing', which could cause significant hardship.

For all its huge genome and clever tricks, Sars-CoV-2 has significant vulnerabilities. It has a fairly feeble fatty envelope, which it needs to sneak into cells. That's destroyed by soap, and by alcohol – so washing your hands carefully or smearing them in alcohol hand gel will kill the virus. Most transmission is either by very close contact – someone coughs or sneezes in your face – or because a droplet containing the virus touches your hands, and then you touch your face; the virus gets into the body especially easily through the membranes in the eyes, nose and mouth. Expect to be bored to tears over the coming months by pious injunctions to wash your hands. It doesn't seem like much, but it's going to reduce the risk at least somewhat.

The second great vulnerability of the virus is that it has to take great pains copying its genome. All RNA viruses (influenza, for example) have a special enzyme that copies RNA into RNA. These RNA-dependent RNA polymerases are usually very sloppy copyists. They do not bother with proofreading, and make huge numbers of errors. This high mutation rate enables them to evolve very rapidly; that's one reason we need a new flu vaccine every year. Coronaviruses have to be much more careful, or else their huge genome will accumulate too many errors. Their mutation rate is therefore lower, so we may be able to develop a fairly effective vaccine – though it will take a year or two, assuming it's possible at all.

We can also target the virus with drugs. Remdesivir was developed to target the Ebola polymerase, and may also work against Sars-CoV-2. It certainly works in a Petri dish, and there are ongoing clinical trials in China and the US to see if it works in humans. Sars-CoV-2 produces many of its genes in long, multi-functional proteins that need to be chopped up – by its own 'protease' enzymes – into the right chunks. Such proteases have been successfully targeted by antiviral drugs in viruses like Hepatitis C. In my lab we are trying to work out which human proteins Sars-CoV-2 needs to replicate, and the interactions between virus and host may also be good drug targets. But we are a long way off, so in the meantime, what should we do?

I received an email from a colleague in infectious diseases. His message was in no way reassuring. He made three main points:

1. This is not business as usual. This will be different from what anyone living has ever experienced. The closest comparator is 1918 influenza.

2. early social distancing is the best weapon we have to combat Covid-19.

3. Humanity will get through this fine, but be prepared for major changes in how we function and behave as a society until either we're through the pandemic or we have mass immunisation available.

I am writing in haste. This is a fast-moving situation, and the numbers are constantly changing – certainly the ones I have given here will be out of date by the time you read this. What's very clear is that we must comply immediately with whatever measures competent public health authorities urge us to take, even if they seem disproportionate. It's time to increase 'social distance' in all sorts of ways. And wash your hands.

6 March 2020