The Coronavirus Chronicles: Emergence of a Global Pandemic

I did not realize the gravity of the situation until I was told explicitly. One of my lab mates shared an email from the Dean of Harvard Medical School on our research group's messaging system. In his email justifying the need to close research labs in his department, the dean said that COVID-19 is the single most threatening pandemic to arise in the last century and went on to compare it to the influenza pandemic of 1918, which killed tens of millions. I thought of other epidemics that had occurred during my lifetime. I was eight years old when SARS first appeared. I had heard about it but didn't know much else. I was in high school during the outbreak of H1N1, or swine flu. I recalled waiting in line at the mall to receive a vaccine and suffering from a very bad flu that winter. People panicked about these earlier outbreaks, but COVID-19 seemed like such a distant threat, something happening on the other side of the world that did not concern me, until I read that email. His words made me realize this pandemic might be one of the defining historical moments of our lifetimes.

In late 2019, several patients were appearing in Wuhan, Hubei province, China with viral pneumonia. Patients tested negative for common respiratory viruses and bacteria[1]. However, it was soon discovered that the patients were infected with a previously unknown virus, the 2019 novel corona virus (2019-nCoV, also now referred to as SARS-CoV-2). The majority of initial patients worked at or lived near Huanan seafood wholesale market[2], which in addition to fish and shellfish sold a variety of live animals[3]. Initial cases were suspected to be linked to animal-to-person spread[4]. Clusters of infected family members and medical personnel with no contact with the market, including a patient in a different city whose relatives had traveled to Wuhan, confirmed person-to-person transmission[1,4,5]. Cases were soon doubling almost every week[6].

Most common symptoms were fever and dry cough, followed by shortness of breath, muscle aches, confusion, sore throat, headaches, rhinorrhea, chest pain and diarrhea[2,4,5]. Patients also had abnormal chest CT scans[2,7]. Some patients developed acute respiratory distress syndrome and among those, some worsened and died of multiple organ failure[2]. Older patients and those with underlying conditions had more systemic symptoms and were more likely to require ICU care[4]. The new disease was termed Coronavirus disease 2019 (COVID-19).

The initial mortality rate appears to be 2-3 %[4] though it is difficult to quantify in an ongoing pandemic, as infected individuals with mild symptoms may not be tested. Additionally, some carriers of the virus can be asymptomatic[8]. Over the proceeding months, the virus would spread to every continent, infecting hundreds of thousands and killing tens of thousands, prompting the World Health Organization to label it as a global pandemic. This would become the third coronavirus outbreak in humans of the 21st century.

March 7, 2020: 105.9k confirmed cases globally

I sat waiting in my parents' hotel room as they finished getting ready. My parents had come in this weekend to see me play in the MIT Battle of the Bands which was scheduled to go on yesterday but had been cancelled due to MIT's newly implemented policy to postpone, cancel or "virtualize" any events with over 150 participants as a precaution against the spread of COVID-19. I had seen a few articles in the news about the virus but hadn't really put much thought into it until now.

"They're being overzealous" my dad had said when I had told him about the event being cancelled.

With the TV on in the background, my parents discussed the virus.

"It's being blown out of proportion. It's about creating panic and making Trump look bad" my dad exclaimed.

There was plenty of rhetoric about how this was just like the flu. I had heard that it was more infectious and more deadly than the flu but at that point, the virus seemed to barely register on America's consciousness.

Coronaviruses are thought to account for approximately 5-30 % of human respiratory tract infections[9]. Coronaviruses were first identified in the early 20th century via infections in chickens and pigs. The first human coronaviruses were discovered in the 1960s[10]. Most coronaviruses that are pathogenic to humans are mild, with the exceptions of severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV)[5] and now 2019-nCoV.

In late 2002, a novel coronavirus known now as SARS-CoV, emerged in southern China. Between 2002 and 2003, it spread to over 30 countries causing over 8000 infections and over 700 deaths giving it a mortality rate of approximately 10 %, though the mortality rate was greater than 50 % in patients 65 or older. The outbreak was finally brought under control by quarantine, patient-isolation and travel restrictions[11]. The virus originated in bats, and civets subsequently served as an intermediate which could transfer it to humans[2,5,12]. SARS-CoV recognizes angiotensin-converting enzyme 2 (ACE2), a protein expressed on the surface of epithelial cells in the lungs, as well as cells in the intestines and cardiovascular system[13]. During the epidemic, very similar strains of SARS-CoV were isolated from humans and palm civets available in live animal markets[14]. These markets may therefore have served as hubs for coronaviruses to be transmitted to human hosts from animals. Four additional outbreaks of related SARS-coronaviruses occurred in 2003 and 2004.

In 2012, MERS-CoV emerged in Saudi Arabia, which caused approximately 2500 laboratory confirmed infections and resulted in 800 deaths giving it a mortality rate of 36 %. Like SARS-CoV, MERS-CoV originated in bats and was transmitted to humans via an intermediate animal, in this case dromedary camels[2,5,12]. The virus was found to bind Dipeptidyl peptidase-4 (DPP4), a protein which is expressed in the epithelial cells of human lung tissue[15].

Including SARS-CoV, MERS-CoV and 2019-nCoV, four other coronaviruses pathogenic to humans are known and have been suggested to be circulating in humans for decades or even centuries. Generally, infections from these viruses cause mild respiratory illness but can cause more severe illness in the elderly and those with comorbidities[16].

Coronavirus infections and outbreaks are not restricted to humans. Different coronaviruses infect a variety of mammals and birds[5,12]. In 2013, porcine epidemic diarrhea coronavirus (PEDV) killed millions of piglets across the Americas and Asia with an almost 100 % fatality rate[12,16]. In 2016-2017, in a region geographically close to the original outbreak of SARS-CoV, an outbreak of swine acute diarrhoea syndrome (SADS) killed over 24,000 piglets in China. The mortality rate was as high as 90 % in very young piglets, but dropped dramatically in older pigs[17,18].

The 2019-nCoV has been found to be closely related to two coronaviruses discovered in bats from China[5] suggesting that the virus originated in bats. However, several lines of evidence suggest that, like SARS-CoV and MERS-CoV, the virus travelled through a still unknown intermediate. While Huanan market sold a variety of live animals, including mammals, birds and reptiles, as well as carcasses and meat[3], no bats were available for sale[3,5]. Furthermore, the outbreak began in December when most bats in Wuhan are hibernating and the genetic evidence suggests that the two bat-derived coronaviruses are not direct ancestors[5]. Although it has a lower mortality rate than SARS-CoV and MERS-CoV of about 2-3 %, it appears to be more infectious and has caused the greatest number of deaths of the three outbreaks[4].

March 9, 2020: 113.5k confirmed cases globally

I had lunch with a friend I hadn't seen in a while. We ran into each other a few days ago and agreed to have dinner together at some point.

"Sorry I never reached out" I said.

“It’s fine, better to stay in and be safe these days” he said.

The American Physics Society conference, which was supposed to take place that week and some of our colleagues were planning on attending, had been cancelled 24 hours before the official start to due fears of COVID-19. It seemed like the American Chemical Society meeting in a few weeks would soon follow suit. I could understand cancelling a huge conference that would bring in thousands of people from around the world, but my friend seemed to think it would be risky to go out to eat in Cambridge. I thought he was being a little overly cautious.

After been reminded of this novel virus, I grabbed a squirt of hand sanitizer from the one of MIT’s newly erected dispensers on my way back to my lab.

When viewed under an electron microscope, crown-like projections can be observed on the surface of coronaviruses[10]. These structures, from which the class of virus derives its name (“corona” is Latin for crown) are the coronavirus spike proteins (also referred to as S protein), which are the critical instrument for viral infection of cells. The protein has subunits S1, which contains a domain for binding receptors on the host cell’s surface and S2, which fuses the viral and host membranes, enabling the viral genetic material to enter the cell. Electron microscopy studies have shown that the S proteins form a trimer with three S1 subunits sitting atop the S2 subunits[19,20]. The S protein determines the range of both tissues and hosts the virus is able to infect[12].

As discussed previously, during the SARS-CoV epidemic, similar coronaviruses were isolated from human patients and palm civets. The S1 receptor-binding domain (S1-RBD) of the human and civet isolated viruses different by only two amino acids. However, the human SARS-CoV S1-RBD binds much more strongly to its target, human ACE2, than the civet SARS-CoV S1-RBD. Indeed, the civet coronavirus was found to be unable to bind human ACE2, whereas the epidemic-inducing strain was able to bind both human and civet ACE2[21]. Therefore, these mutations between the human and civet strains likely played an important role in civet-to-human and human-to-human transmission during the SARS epidemic[12]. Additionally, they demonstrate how the S protein receptor-binding domain can influence the host range. Mouse and rat ACE2 also have different structures compared to human ACE2. SARS-CoV binds poorly to mouse ACE2 and is unable to bind rat ACE2, thus it minimally infects mice cells and cannot infect rat cells[12]. Similarly, MERS-CoV cannot infect small rodents because of structural differences in the receptor DPP4, the receptor used by MERS-CoV, between rodents and humans[22].

The structural mechanisms for membrane fusion of coronaviruses to host cells are still unclear, but information can be gleaned from similar, less complex viral membrane fusion proteins, such as the influenza virus hemagglutinin glycoprotein (HA). Like the coronavirus S protein, the influenza virus HA possesses a receptor binding subunit HA1 and a membrane fusion subunit HA2. Additionally, HA also forms trimers. Host proteases cleave HA1 and HA2, though they remain associated through non-covalent interactions. During cell entry, HA1 binds to a receptor on the host cell surface and dissociates. HA2 then undergoes a conformational change. Hydrophobic fusion proteins in HA2 insert into the host membrane ultimately causing the membranes to fuse[12].

Compared with influenza HA, the coronavirus S protein has some unique features, such as its larger size and the presence of two cleavage sites. The coronavirus S protein has cleavage sites in between the S1 and S2 domains and one at the end of the fusion peptide. The S1 subunit prevents the S2 subunit from undergoing its conformational change. Additionally, the fusion peptide is internal in coronaviruses. Thus, cleavage appears necessary for the conformational changes tied to membrane fusion[12]. In fact, it has been demonstrated for SARS-CoV, MERS-CoV and other coronaviruses that cleavage at both sites is necessary for membrane fusion to occur. For SARS-CoV, in addition to lysosomal proteases, the S protein is processed by extracellular and cell surface proteases found in the respiratory tract and lungs. The cell and tissue specificities of these proteases may be why SARS-CoV causes respiratory tract infections[12].

Evidence also suggests that receptor binding triggers the conformational change of the S2 domain and membrane fusion[11,12]. After the conformational change of the S2 subunit, a six-helix bundle is formed which is used for membrane fusion[11,12].

The structure of the 2019-nCoV S protein resembles that of the SARS-CoV S protein and like SARS-CoV, 2019-nCoV binds ACE2[23]. Its S protein is able to bind ACE2 10-20 times more strongly than that of SARS-CoV[23], which is hypothesized to contribute to its higher transmissibility and contagiousness[24]. It was discovered that 2019-nCoV has a cleavage site not found in other SARS-like coronaviruses, which is cleaved by a protease highly expressed in lungs[25]. More work is needed to fully understand the membrane fusion mechanism of 2019-nCoV, but the inhibition of this enzyme could provide a possible anti-viral treatment.

Receptor binding domains and proteolysis sites of the S protein appear to be critical to the pathogenicity and cross-species transmission of coronaviruses. Due to their unique method of viral replication, coronaviruses readily undergo genetic mutations and recombination[9,12]. A small number of mutations in viral receptor-binding domains can enable access to new host species and types of tissue, potentially causing cross-species transmission and epidemic outcomes[12]. Additionally, proteolysis seems to be critical for membrane fusion and range of host cell types available as hosts[12,25]. Studies on MERS-CoV have shown that differences in proteases across hosts can serve as a barrier for cross-species transmission[12].

March 11, 2020: 125.8k confirmed cases globally

In what felt like months but was really just a few days, MIT had been turned on its head. The day before, the administration had announced that all undergraduate students would have to move off campus in just under a week, following the same announcement from Harvard. Seminar speakers were unable to or refused to travel. Essentially all events on campus were cancelled. The number of COVID-19 cases in Massachusetts had more than doubled to 92, prompting the governor to declare a state of emergency. While the MIT administration claimed there was no impending risk to the MIT community, I understood their reasoning for sending the undergrads home, considering most of them lived in dorms with shared kitchens and bathrooms.

A few years ago when I was a teaching assistant for general chemistry, I remembered the hundreds of students getting sick simultaneously from whatever ailment was circulating the dorms and classrooms at the time.

“It’s like this every year whenever something is going around” the course coordinator had told us.

“They got us sick too” one of my lab mates reminded me, as we discussed the merits of the MIT administration’s decision.

I imagined the infectious coronavirus would spread like wildfire through the undergrad dorms.

On the outside, life appeared as normal for us graduate students. Aside from our now obsessive handwashing, we reasoned among ourselves that there wouldn’t be much change for us.

That night, I began to hear the stories coming in from Italy, the second hardest hit country after China. How there are too many patients to treat. That the hospitals began to triage patients and decide who they will treat and who will be left to die.

After the outbreak of SARS-CoV, a number of SARS-like coronaviruses were discovered in Chinese horseshoe bats[26–28]. The genetic diversity of coronaviruses in bats was greater than those found in humans or civets, suggesting they are the natural coronavirus reservoir[27]. One survey found numerous SARS-like

coronaviruses in a single colony[28]. Furthermore, a bat coronavirus was discovered which is able to use human ACE2, the same receptor used by SARS-CoV, to enter host cells[28]. In addition to the bats discovered in China, SARS-like coronaviruses have been found in bats in Europe and Africa[28]. Similarly, after the MERS outbreak, bats near the home and workplace of a patient were found to have a number of coronaviruses, including one bat possessing a virus with 100 % genome sequence identity to that found in an infected human patient[29]. Bat coronaviruses related to MERS-CoV have been found in bats in Asia, Africa, Europe and the Americas[28,29]. The outbreak of SADS in pig farms in China was traced back to a nearby bat colony where a coronavirus with 98 % genome sequence identity was found[17,18]. 2019-nCoV is suggested to have originated in bats as the virus is most closely related to bat coronaviruses[5]. These findings show that bats play a critical role in pathogenic viral disease and that direct bat-to-human viral transfer without an intermediate non-human host is possible.

In addition to the many coronaviruses already discussed, bats are reservoir hosts to a number of viruses including rabies, Ebola, Hendra, Nipah and Marburg viruses[17,30]. 75 % of emerging infectious diseases are zoonoses (diseases which pathogen is maintained in a non-human vertebrate)[17]. Bats harbor a diverse set of viruses and more viruses come from bats than any other mammal[17]. However, bats are able to host viruses without displaying serious symptoms, even though the same viruses cause severe infections and death in other mammals, including humans[30].

As the only mammal capable of flight, bats require a high metabolism. Bats have developed physiological mechanisms to prevent oxidative damage related to their high metabolism. While there are many unknowns related to bat immune systems, these mechanisms may explain bats' uniquely long lifetimes and furthermore, why bats are able to host a large number of viruses.

The metabolic demands of flight can cause DNA damage and release DNA into the cytoplasm. Bats appear to have evolved a dampened inflammation immune response to cytosolic DNA compared to other mammals[31]. Cytosolic RNA and DNA can also be produced during a viral infection, activating this inflammation pathway. Bat's dampened pathway may enable them to coexist with these viruses, which can potentially cause excessive inflammation and death in other species[31].

When mammalian cells detect viral RNA or DNA in their cytoplasm, they will induce a response to make neighbouring cells essentially antiviral. Bats appear to carry out this response perpetually, even in the absence of viral RNA or DNA. While this would be harmful to most mammals, bat's reduced inflammation response reduces the risk. Epidemics are therefore less severe in bat cells compared to those of other mammals. This antiviral response protects bat cells from rapid infection and death and thus increases the likelihood for long-term persistent infections. This suggests that viruses in bats could evolve greater transmission rates within the host without severe consequences. However, if such viruses transfer to other mammalian hosts, they could cause severe infections[30].

March 13, 2020: 144.5k confirmed cases globally

I awoke to a text alert from MIT informing everyone that undergrads should now move out by Sunday.

My roommate had the idea to go to the grocery store on Friday morning rather than on the weekend as we usually did.

"It'll probably be less crowded and be cleaner in the morning" he told me the night before.

I thought it seemed like a good idea. A surreal scene greeted me when I arrived at the store. I made my way first to the canned beans and found the shelf almost completely empty. The contrast was sharp from aisle to aisle. While nothing looked out of the ordinary in some, others were picked completely clean. Most canned goods, rice and pasta was gone. The store didn't seem to have a single loaf of bread left. My mind raced and I realized I would have to make do with whatever I could find.

Campus seemed to be on the edge of hysteria, and my lab was no exception. We were all encouraged to work from home when possible and it seemed like MIT would ramp down on-campus research imminently. My lab mate and I decided we would take as much data as we could, giving us plenty to work on at home. I was hesitant to relay to my colleagues what I had seen in the grocery store that morning, worrying it would only make everyone more anxious.

With all of these events happening one after another I decided it would be wise to drop by the international student's office to get my visa signed which would permit me to re-enter the country after travel, just in case I decided to leave. The office had an air of panic and three people staffed the front desk rather than the typical one. Without even having to ask them to do so, they gave me a travel signature within minutes, a process that usually takes two business days.

I dropped off a book I had finished reading at the library and the desk was being staffed by an undergraduate I knew in her senior year. I asked her how she was holding up.

"It's just so crazy. We don't even know if we're going to have convocation or not."

She was still undecided if she would go back home to her parents or try to stay in Cambridge. I was at a loss of what to say. What could one possibly say to someone whose whole world had been turned upside down in a matter of days?

To minimize person-to-person contact, we held our usual Friday afternoon group meeting over Zoom. One of the newer lab members was very distressed since she lived with several undergrads who would soon be returning from their spring breaks after traveling all over the country or even internationally. I advised her that if she wants to leave the city and go back to her family, now would be the time to do so.

As the day progressed, our work seemed to have a more and more frantic pace. We raced to finish our last day of experiments on campus while simultaneously closing up our lab for what felt like an imminent shutdown.

That afternoon the president declared a state of emergency. What did this mean for us? Another lab member decided she wanted to leave the city.

"If we're going to be quarantined I'd rather be stuck with my mom than here."

I wished her safe travels and encouraged her to do what she thought was best. My throat felt sore. Did I have the virus or was it just stress? I tried to keep my distance from my colleagues.

Recently, Malayan pangolins being smuggled into southern China were discovered to be carrying a virus related to 2019-nCoV, suggesting they may be the missing animal link which enabled the virus to spread to humans. The pangolin coronavirus exhibited a very similar sequence in the receptor binding domain to 2019-nCov, even though this novel pangolin virus is more closely related to a bat coronavirus for the remainder of its genome[32]. Additional 2019-nCoV-like coronaviruses have subsequently been identified in pangolins[33]. Pangolins with coronavirus infections are usually in poor or critical health conditions suggesting that pangolins are an intermediate rather than original host of the virus[33]. Sequencing of genomic and protein samples from pangolins showed only the lungs contained 2019-nCoV-like samples. In addition to a similar genome revealed by the genomic sequencing, the protein sequencing results identified a partial pangolin coronavirus S protein that is highly similar to the 2019-nCoV S protein. Only 5 residues are different on the receptor-binding domain of the pangolin coronavirus compared to 2019-nCoV, in contrast with the 19 residues it differs from a similar bat coronavirus[33].

It is tempting to consider the possibility that pangolins served as the missing intermediate to transmit 2019-nCoV to humans. However, ACE2 of humans and pangolins are more similar than ACE2 of humans and bats; thus the newly discovered pangolin coronavirus may be the result of convergent evolution[32]. While

pangolins may be a possible intermediate between bats and humans for 2019-nCoV, other hosts may exist. In addition to civets, SARS-CoV is able to use racoon dogs and ferret badgers as intermediates[33].

March 15, 2020: 162.7k confirmed cases globally. The total number of cases outside of mainland China has just surpassed those of mainland China.

Since I would be working from home for the foreseeable future, I decided to bring my work desktop home. It would be of no use to me in my office.

While walking towards campus I noticed what a grim day it was. The typically busy streets were deserted. When I happened to encounter another pedestrian, there was a tacit agreement to keep as much space between us as possible as we passed. I felt my knuckles, which had become chapped and bloody from the frequent, almost fanatical, handwashing.

Approaching campus, I decided that it would be best to walk around rather than through any building to minimize any close encounters in the hallways. When I arrived, I realized this was the final move-out day for the undergrads. I walked by several shiny SUVs glittering in the sunlight, inspecting what state their licence plate was from, but cautious not to get too close. I saw a couple embrace, possibly their last for a long time.

During a regular semester, I enjoy running into my former students from when taught general chemistry years ago. Some are oblivious to me when I walk by but others flash a smile or exchange a greeting. I realized that they would be graduating this semester and would not be returning to campus after this departure. I would probably never see any of them again.

On occasion, I would go into lab on the weekend, be it to do a bit of work or just pick up my running shoes for the gym. On a typical weekend, I could expect to find one or more people working on my floor. I knew on this day, the building would reflect the vacantness of outside. Descending the stairs, I saw the darkness that awaited me in the basement though the door's window.

I walked through the empty lab spaces, making sure everything was off and safe to leave for an undetermined amount of time. We were advised to leave our lab spaces such that they would be fine for 6-8 weeks. After grabbing my computer, I ran into a colleague. We discussed how much had changed since we last spoke. Between Friday morning and that Sunday morning, about a third of our lab decided to flee the city and the president had declared a national emergency. These things don't happen every day.

Exiting the building, I ran into a maintenance worker I knew. He told me how busy he was moving and storing the students' belongings and how much work there was to do on campus. He mentioned that he saw students filling up Tupperware containers with hand sanitizer. He stood next to me as we spoke, which made me uncomfortable. What if one of us was sick and infected the other?

March 18, 2020: 194.9k confirmed cases globally

I like to use an alarm clock radio in the morning, a habit carried over from before I had a smart phone. I recently rediscovered that rather than wake up to the harsh buzzer, I could instead have it set to the radio, which happened to be set to a local news station. The morning announcer relayed that several people were calling for the governor to impose a lock-down on Boston, but he refused to do so.

This was my third day of working at home. It was still an adjustment. Upon arriving at work, the first thing I would do is check my email and Slack. Now in addition to those, I added the John's Hopkins coronavirus case tracker to my morning routine.

That afternoon, after talking with two of my friends from college over Facebook messenger, one of them had the idea to do a Zoom call between the three of us. It was nice to see their faces. I had not seen either in person in over a year. We shared the experience in our respective cities. One friend was in graduate school at Vanderbilt in Nashville. He told us about how all of the undergrads had to leave campus and how, as a TA, he would have to hold office hours over Zoom. The other friend was in Berkeley, which was imposing shelter-in-place rules. She told us she was safe and the city seemed deserted.

Later that day, my roommate, who had spent most of his day moving his brother out of his undergrad dorm, asked if I wanted to accompany him on a walk to UPS to pick up a package. On the walk there, we talked about viruses. I asked where viruses came from. He explained that unlike bacteria and eukaryotes, viruses do not share a common ancestor. I learned that while we had theories for a few types of viruses, the origins of most were still a complete mystery. When we arrived, the man behind the counter had a bad cough that worried us.

On the walk back, we discussed whether it was the right decision to send all of the undergrads home.

“New evidence is coming out that some people can carry the virus and be asymptomatic. One of these students could have the virus but not have the symptoms and be sent home to spread it to their family and community. I think we’re going to be studying whether or not this was the right decision for years.”

There are currently no therapeutic treatments available for 2019-nCoV. However, known mechanistic and structural information from other coronaviruses, as well as the genetic sequence[5] and structure of the S protein[23] for 2019-nCoV can provide insights for possible treatments. Targeting the S protein is of great interest because of its critical role in receptor binding and membrane fusion in the initial stages of infections. Inhibition the receptor-binding domain from binding ACE2, inhibition of cleavage by host proteases by blocking its cleavage sites and inhibition of its conformational change are all potential therapeutic strategies against the S protein[11,25]. Other critical processes that occur after membrane fusion, such as viral RNA replication or viral protein expression can be targeted. Viral RNA can be prevented from replicating or expressing proteins. Critical viral machinery, such as viral proteases, can be inhibited[34]. Alternatively, host processes necessary for the spread of a 2019-nCoV infection can be inhibited. Access to ACE2 could be restricted to prevent virus binding. Since host proteases are critical for the function of the S protein, inhibiting them could prevent infection[35]. Similar to SARS-CoV and MERS-CoV[11,12], 2019-nCoV enter cells through endocytosis, thus inhibitors of this process may reduce the spread of an infection[35,36]. Many known small molecules and biological compounds, which address some of these targets, are described below. An advantage of repurposing existing compounds is that the pharmacokinetics, dosing and side effects are established[34].

Lopinavir is a viral protease inhibitor, which is combined with ritonavir to increase its half-life. Together they are used to treat HIV, though they have also been tested against coronaviruses. In non-human primates infected with MERS-CoV, those treated with lopinavir/ritonavir had less lung damage and milder symptoms compared to a control group[37]. Lopinavir/ritonavir was tested in patients infected with 2019-nCov but did not seem to offer any improvement[38]. Patients in this study were critically ill, and coupled with other flaws; a larger study may be warranted. Note that 2019-nCoV and HIV have different viral proteases thus the drug’s usefulness is unclear[39].

Remdesivir is an antiviral medication currently under clinical trials to treat Ebola virus infections. It is an adenosine analog, which incorporates into new viral RNA causing premature termination during replication[40,41]. It was given to patients during both the SARS-CoV and MERS-CoV outbreaks. In mice modified to have human DPP4, those infected with MERS-CoV and treated with remdesivir had less lung damage and less viral load compared to those that did not receive this treatment[41]. In a cell assay, remdesivir was found to reduce 2019-nCoV viral infections[40]. Because it has already been used in humans,

it is known to be safe. In the first US case of 2019-nCoV, the patient was administered remdesivir because of his worsening condition[42]. Fortunately, the patient's condition improved but larger trials are needed.

Chloroquine is an anti-malarial and autoimmune disease drug. It may also act as a broad antiviral drug, and has previously been used against SARS-CoV and MERS-CoV[43]; however, its mechanism of action is unclear. It is weakly basic and thought to interfere with pH dependent processes critical for viruses. Additionally, it is known to inhibit nanoparticle endocytosis thus, it can be hypothesized that it could interfere in viral entry by endocytosis. It may also affect the host immune system by reducing the expression of factors and receptors which may cause acute respiratory distress syndrome, the primary cause of coronavirus-associated mortality[39]. Chloroquine was shown to reduce 2019-nCoV viral infections in cells[40]. The results for humans are less clear. One study showed rapid viral clearance of 2019-nCoV after administering a derivative hydroxychloroquine with antibiotics; however another found no benefit for patients infected with 2019-nCoV[43].

RNA interference is another possible strategy to combat 2019-nCoV. In RNA interference, a short interfering RNA (siRNA) strand is synthesized which can block viral gene expression or replication[11,24,34]. It is an attractive choice because RNA of any sequence can be synthesized. RNAs are known which can inhibit the expression of SARS-CoV structural proteins and machinery related to viral replication, the latter of which inhibits viral infection and replication[24]. siRNA was demonstrated to work as an antiviral agent against SARS-CoV in non-human primates. Primates given siRNA treatment had less severe symptoms and significantly less lung damage when infected with SARS-CoV compared to those who did not receive the treatment[44].

Peptides are of interest as they can block processes critical to infection such as the S protein-ACE2 interaction, S protein cleavage and the conformational transition of the S protein[12]. Small molecules are generally not effective at interrupting extended protein-protein interfaces, whereas peptides can[45]. Using computational tools and structural knowledge of the 2019-nCoV S protein, a peptide was synthesized which is able to specifically bind 2019-nCoV receptor-binding domain[45]. Such a peptide could hinder the virus from entering cells. Note that this particular work is preliminary and has not undergone peer review.

Convalescent plasma, blood serum from a patient who has recovered from an infectious disease and rich with antibodies, has previously been used as a last resort for patients infected with SARS-CoV. Those patients subsequently had lower mortality rates and shorter hospital stays compared with those that did not receive this treatment[46]. It has also been recommended or suggested as a treatment during the MERS, Ebola, H1N1 outbreaks[46,47]. Five critically ill patients infected with 2019-nCoV who were receiving antiviral medication and steroids were given convalescent plasma, and these patients' conditions improved[48]. Of course, this study is limited because it cannot be ascertained whether they would have improved without receiving the convalescent plasma and how much the other treatments aided.

Unfortunately, it may take several months to years to establish an effective treatment for those infected with 2019-nCoV. While a range of experimental and clinical data is available, much more is needed. Some antiviral medications are effective in cell cultures but do not subsequently demonstrate therapeutic benefit in animals[39], cause adverse effects or require very high doses which are not clinically feasible[37]. Additionally, animal models are imperfect, limiting the information from these trials. Infectious disease signs can be minimal, altered or absent in different animals[11,49]. Animals also undergo viral infections at different rates than humans. Generally, animals used in studies are young whereas most human patients are older. Finally, many of these viruses are specific for human receptors. For example, MERS-CoV does not replicate in the respiratory systems of small mammals[22,35].

March 20, 2020: 272.2k confirmed cases globally

"This just in the number of cases in Massachusetts has climbed to 300, and the first two death related to COVID-19 have been reported in Vermont. For today's weather…"

I climb out of bed and shut off the radio. I had almost finished my first week of working from home. For a change of pace today, I would be going to campus for the first time in almost a week.

In the event of an imminent research shutdown on short notice, the department had given us until this Friday to wrap up experiments. I was surprised we had made it the whole week without MIT announcing a total shutdown on research. I was one of the two designated personnel allowed on campus to inspect our labs during the shutdown, which we expected to start at the end of the day. Because we believed this may be the last day most of us would be able to access campus, my colleagues decided we ought to do a walk-though today.

The actual walk through itself was uneventful; no one was particularly trilled to be forced into this situation in the first place. We walked from lab to lab ensuring that everything was in a state where it could be left for weeks, but possibly months.

At the end of our inspection, we ran into a lab member finishing up his work. He was desperate to find out if anyone had any additional information. Unfortunately, we had only hypotheticals, and hoped that we could resume research, even at a reduced capacity, shortly. One colleague wondered aloud for how long this could go on; society could only function on lockdown for so long.

To date, there are no vaccines available for any coronavirus. However, several vaccines, including possible candidates for 2019-nCoV, are currently in clinical trials. Several types of vaccines exist[22,24,35]. Their functionality as well as their progress towards protection against 2019-nCov and other coronaviruses is described below.

The S protein is of great interest as a vaccine target. It was demonstrated that the S protein is the only SARS-CoV structural protein to induce an immune response[50]. Strains of the virus BHPIV3 were generated which expressed SARS-CoV S protein or other SARS-CoV structural proteins and were used to infect hamsters. Animals infected with viruses expressing the SARS-CoV S protein developed antibodies against SARS-CoV and were subsequently less susceptible to infection by SARS-CoV. In contrast, animals infected with viruses expressing other SARS-CoV structural proteins did not develop antibodies and did not become resistant to SARS-CoV[50]. Similarly, only the S protein is able to induce antibodies against MERS-CoV[22].

The immunization strategy described above is known as a viral vector-based vaccine. Because of coronaviruses' high rate of RNA recombination, attenuated coronaviruses may not be suitable for vaccines[49]. Viruses with extremely low rates of recombination, such as BHPIV3, can be modified to express coronavirus proteins. A strain of BHPIV was produced with the gene to express full-length SARS-CoV S protein. In non-human primates, use of this virus as a vaccine was able to induce the production of antibodies and protect against SARS-CoV[35,49]. An adenovirus-based vaccine against MERS-CoV was made by having the virus express the whole MERS-CoV S protein. This vaccine was shown to generate an immune response in mice[51]. Two MERS-CoV viral vector-based vaccines are currently in clinical trials[22]. An adenovirus-vectored 2019-nCoV vaccine is currently in development[35].

Virus-like particles (VLP) are nanoscale particles composed of virus structural proteins. VLPs are considered safe to produce, as no live viruses are needed in their production[22]. A MERS-CoV VLP containing S protein trimers has been shown to induce an immune response in mice and cattle[24]. A 2019-nCoV vaccine is currently being developed based on this technology[24].

DNA vaccines can be fabricated which use DNA to encode immunogens to cause a host immune response. DNA vaccines are attractive because are they easy to produce and inexpensive, as they avoid the us of virus replication or protein expression and purification[22]. A DNA vaccine encoding the SARS S protein was able to induce an immune response in mice and protect them from SARS-CoV infections[52]. A DNA-based MERS-CoV vaccine is currently in clinical trials[22]. A DNA-based vaccine for 2019-nCoV is expected to begin human trials shortly[24].

mRNA vaccines better simulate a real infection, and thus induce a stronger immune response. Additionally, multiple mRNAs can be combined into a single vaccine. mRNA vaccines encoding full-length S, as well as S1 and S2 subunits for both SARS-CoV and MERS-CoV have been developed[24]. A 2019-nCoV mRNA vaccine is currently in Phase I clinical trials[24].

Finally, vaccines against coronaviruses can be composed of the full-length S protein or key fragments of it. A vaccine composed of SARS-CoV S protein trimers was able to produce antibodies and provide significant protection from SARS-CoV in small mammals[53]. For SARS-CoV, S protein subunit vaccines appear to produce more antibodies and better protection compared to live-attenuated, full-length S protein and DNA-based S protein vaccines[24]. A fragment of the SARS-CoV S protein was able to generate antibodies in mice and protect them from SARS-CoV infections[54]. A peptide vaccine is currently under development for 2019-nCoV[24].

Vaccines against coronaviruses have faced the same hurdles as the development of therapeutics: a lack of infected patients and large financial barriers[11]. Prior to use in humans, a vaccine must be tested in non-human primates, which is extremely costly. Thus, prior experiments must be performed in small mammals, which have the limitations previously described. While human ACE2 or human DPP4 can be expressed in small mammals for SARS-CoV and MERS-CoV studies respectively, these modified animals are also expensive[22]. Because of the limited market and huge costs associated, most pharmaceutical companies are not interested in developing therapeutics and vaccines for SARS-CoV and MERS-CoV[11,22].

Although there are several vaccines for 2019-nCoV in clinical and pre-clinical trials, the development of new therapeutics generally takes years. Even with the urgency of the COVID-19 pandemic, the development, evaluation and production of therapeutics and vaccines could take months or years[34,35]. In the interim, mitigation measures such as social distancing are being used to reduce the spread of the virus[55].

Week of March 22

It no longer seems pertinent to include the number of confirmed cases. This week the number of cases passed half a million and the number of deaths 30000. The number of cases is currently trending exponentially, so any number I write now will be irrelevant in a few days.

The days seem to blur into one another as I try to adjust to this new normal. The only variation from day to day seems to be the news from my radio each morning: the hundreds of new cases in Massachusetts each day, which now total in the thousands, the unemployment numbers eclipsing the previous record, the US surpassing China for the number of confirmed cases (whether those numbers are to be believed is a different matter). My only excursions outside are to go for walks through empty streets and trips to the supermarket where everyone tries their best to keep their distance as we walk by half empty shelves. I'm slowly getting used to seeing strangers wearing gloves and masks.

I worry most about my mother, if or when she will become infected. She is a doctor at a trauma hospital. A different hospital has been designated as the city's COVID-19 center, but they have already reached capacity. Infected patients are beginning to show up at her hospital, which seems under-equipped. People still need life-saving operations but most procedures have been scaled back to a minimum. All incoming patients are tested for COVID-19 unless they are in critical condition, but the medical staff have been told that the tests are only 70 % accurate. It sounds like the personal protective equipment they've been provided is inadequate. The government has told them that they only have three to five days worth of masks and other safety equipment left. What will happen when they run out?

Some people have compared this to war. How all of humanity is fighting a common enemy. What about after the war? What will it bring? Will leaders use this calamity to tighten their grip on power? Will we see our freedoms eroded? Will we see worsening economic and social inequality? Or will change be positive?

Will more people demand greater safety nets and adequate healthcare? Will facing a common enemy reduce our perceived differences? Will it reshape how we treat and care for each other, especially the most vulnerable? For now, all we can do is wait.

References

1. Chan, J. F. W. *et al.* A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* **395**, 514–523 (2020).

2. Chen, N. *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* **395**, 507–513 (2020).

3. Wu, F. *et al.* A new coronavirus associated with human respiratory disease in China. *Nature* **579**, 265–269 (2020).

4. Sahu, K. K., Mishra, A. K. & Lal, A. Comprehensive update on current outbreak of novel coronavirus infection (2019-nCoV). *Ann. Transl. Med.* (2020) doi:10.21037/atm.2020.02.92.

5. Lu, R. *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* **395**, 565–574 (2020).

6. Li, Q. *et al.* Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. *N. Engl. J. Med.* 1199–1207 (2020) doi:10.1056/nejmoa2001316.

7. Huang, C. *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **395**, 497–506 (2020).

8. Li, Q. *et al.* Presumed Asymptomatic Carrier Transmission ofCOVID-19. *N. Engl. J. Med.* 19–20 (2020) doi:10.1056/nejmoa2001316.

9. Woo, P. C. Y. *et al.* Characterization and Complete Genome Sequence of a Novel Coronavirus, Coronavirus HKU1, from Patients with Pneumonia. *J. Virol.* **79**, 884–895 (2005).

10. Whitley, R. J. & Hayden, F. G. Clinical Virology , 2nd Edition. **35**, 23626 (2002).

11. Du, L. *et al.* The spike protein of SARS-CoV - A target for vaccine and therapeutic development. *Nature Reviews Microbiology* vol. 7 226–236 (2009).

12. Li, F. Structure, Function, and Evolution of Coronavirus Spike Proteins. *Annu. Rev. Virol.* **3**, 237–261 (2016).

13. Hamming, I. *et al.* Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J. Pathol.* **203**, 631–637 (2004).

14. Guan, Y. *et al.* Isolation and characterization of viruses related to the SARS coronavirus from animals in Southern China. *Science (80-.).* **302**, 276–278 (2003).

15. Raj, V. S. *et al.* Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature* **495**, 251–254 (2013).

16. Lau, S. K. P. & Chan, J. F. W. Coronaviruses: Emerging and re-emerging pathogens in humans and animals. *Virology Journal* vol. 12 10–12 (2015).

17. Wang, L. & Anderson, D. E. Viruses in bats and potential spillover to animals and humans. *Curr. Opin. Virol.* **34**, 79–89.

18. Zhou, P. *et al.* Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin. *Nature* **556**, 255–259 (2018).

19. Kirchdoerfer, R. N. *et al.* Pre-fusion structure of a human coronavirus spike protein. *Nature* (2016) doi:10.1038/nature17200.

20. Beniac, D. R., Andonov, A., Grudeski, E. & Booth, T. F. Architecture of the SARS coronavirus prefusion spike. *Nat. Struct. Mol. Biol.* **13**, 751–752 (2006).

21. Sheahan, T., Rockx, B., Donaldson, E., Corti, D. & Baric, R. Pathways of Cross-Species Transmission of Synthetically Reconstructed Zoonotic Severe Acute Respiratory Syndrome Coronavirus. *J. Virol.* **82**, 8721–8732 (2008).

22. Yong, C. Y., Ong, H. K., Yeap, S. K., Ho, K. L. & Tan, W. S. Recent Advances in the Vaccine Development Against Middle East Respiratory Syndrome-Coronavirus. *Front. Microbiol.* **10**, 1–18 (2019).

23. Wrapp, D. *et al.* Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science (80-.).* **367**, 1260–1263 (2020).

24. Liu, C. *et al.* Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases. *ACS Cent. Sci.* (2020) doi:10.1021/acscentsci.0c00272.

25. Coutard, B. *et al.* The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin- like cleavage site absent in CoV of the same clade. *Antiviral Res.* **176**, 104742 (2020).

26. Lau, S. K. P. *et al.* Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. *Proc. Natl. Acad. Sci. U. S. A.* **102**, 14040–14045 (2005).

27. Li, W. *et al.* Bats are natural reservoirs of SARS-like coronaviruses. *Science (80-.).* **310**, 676–679 (2005).

28. Ge, X. *et al.* Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature* **503**, 535–538 (2013).

29. Memish, Z. A. *et al.* Middle East respiratory syndrome coronavirus in Bats, Saudi Arabia. *Emerg. Infect. Dis.* **19**, 1819–1823 (2013).

30. Brook, C. E. *et al.* Accelerated viral dynamics in bat cell lines, with implications for zoonotic emergence. *Elife* **9**, 1–24 (2020).

31. Xie, J. *et al.* Dampened STING-Dependent Interferon Activation in Bats Brief Report Dampened STING-Dependent Interferon Activation in Bats. *Cell Host Microbe* **23**, 297-301.e4 (2018).

32. Lam, T. T.-Y. *et al.* Identifying SARS-CoV-2 related coronaviruses in Malayan pangolins. *Nature* 1–6 (2020) doi:10.1038/s41586-020-2169-0.

33. Zhang, C. *et al.* Protein structure and sequence re-analysis of 2019-nCoV genome refutes snakes as its intermediate host or the unique similarity between its spike protein insertions and HIV-1. *J. Proteome Res.* (2020) doi:10.1021/acs.jproteome.0c00129.

34. Pillaiyar, T., Meenakshisundaram, S. & Manickam, M. Recent discovery and development of inhibitors targeting coronaviruses. *Drug Discov. Today* **00**, (2020).

35. Dhama, K. *et al.* COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics. *Hum. Vaccin. Immunother.* **00**, 1–7 (2020).

36. Richardson, P. *et al.* Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *The Lancet* vol. 395 e30–e31 (2020).

37. Chan, J. F. W. *et al.* Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERSCoV infection in a nonhuman primate model of common marmoset. *J. Infect. Dis.* **212**, 1904–1913 (2015).

38. Cao, B. *et al.* A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N. Engl. J. Med.* 1–13 (2020) doi:10.1056/NEJMoa2001282.

39. Hu, T. Y., Frieman, M. & Wolfram, J. Insights from nanomedicine into chloroquine efficacy against COVID-19. *Nat. Nanotechnol.* 19–21 (2019) doi:10.1038/s41565-020-0674-9.

40. Wang, M. *et al.* Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research* vol. 30 269–271 (2020).

41. Sheahan, T. P. *et al.* Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat. Commun.* **11**, (2020).

42. Holshue, M. L. *et al.* First case of 2019 novel coronavirus in the United States. *N. Engl. J. Med.* **382**, 929–936 (2020).

43. Molina, J. M. *et al.* No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection. *Med. Mal. Infect.* (2020) doi:10.1016/j.medmal.2020.03.006.

44. Li, B. J. *et al.* Using siRNA in prophylactic and therapeutic regimens against SARS coronavirus in Rhesus macaque. *Nat. Med.* **11**, 944–951 (2005).

45. Zhang, G., Pomplun, S., Loftis, A. R., Loas, A. & Pentelute, B. L. The first-in-class peptide binder to the SARS-CoV-2 spike protein. *bioRxiv* 2020.03.19.999318 (2020) doi:10.1101/2020.03.19.999318.

46. Chen, L., Xiong, J., Bao, L. & Shi, Y. Convalescent plasma as a potential therapy for COVID-19. *Lancet Infect. Dis.* **20**, 398–400 (2020).

47. Dean, C. L. *et al.* Characterization of Ebola convalescent plasma donor immune response and psoralen treated plasma in the United States. *Transfusion* 3–4 (2020) doi:10.1111/trf.15739.

48. Shen, C. *et al.* Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA* 1–8 (2020) doi:10.1001/jama.2020.4783.

49. Bukreyev, A. *et al.* Mucosal immunisation of African green monkeys (Cercopithecus aethiops) with an attenuated parainfluenza virus expressing the SARS coronavirus spike protein for the prevention of SARS. *Lancet* **363**, 2122–2127 (2004).

50. Buchholz, U. J. *et al.* Contributions of the structural proteins of severe respiratory syndrome coronavirus to protective immunity. *Proc. Natl. Acad. Sci. U. S. A.* **101**, 9804–9809 (2004).

51. Kim, M. H., Kim, H. J. & Chang, J. Superior immune responses induced by intranasal immunization with recombinant adenovirus-based vaccine expressing fulllength Spike protein of Middle East respiratory syndrome coronavirus. *PLoS One* **14**, 1–20 (2019).

52. Yang, Z. Y. *et al.* A DNA vaccine induces SARS coronavirus neutralization and protective immunity in mice. *Nature* **428**, 561–564 (2004).

53. Kam, Y. W. *et al.* Antibodies against trimeric S glycoprotein protect hamsters against SARS-CoV challenge despite their capacity to mediate FcγRII-dependent entry into B cells in vitro. *Vaccine* **25**, 729–740 (2007).

54. Bisht, H., Roberts, A., Vogel, L., Subbarao, K. & Moss, B. Neutralizing antibody and protective immunity to SARS coronavirus infection of mice induced by a soluble recombinant polypeptide containing an N-terminal segment of the spike glycoprotein. *Virology* **334**, 160–165 (2005).

55. Anderson, R. M., Heesterbeek, H., Klinkenberg, D. & Hollingsworth, T. D. How will country-based mitigation measures influence the course of the COVID-19 epidemic? *The Lancet* vol. 395 931–934 (2020).