

Aster Medical Journal

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Covid 19

Blood Clots: A Major Problem in Severe Cases

Clinical Case

Polymerase Gamma: Men Against a Gene

Neuroscience

Why Do You Feel Lonely?

HOW TO PREVENT THE NEXT PANDEMIC?

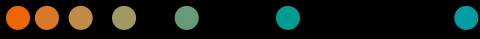
Conversation with the man who predicted COVID-19 pandemic



Meet **Dr Shi Zhengli**, a virologist from the Wuhan Institute of Virology, who is often called China's "bat woman". Shi and her lab in Wuhan have become the centre of a conspiracy theory related to the origin of the coronavirus.



Shaping the future of healthcare



SIEMENS
Healthineers 

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Q: The Wuhan Institute of Virology has received worldwide attention as the possible source of SARS CoV-2. What kind of impact has this had on your lab? And on you personally?

Dr Shi Zhengli
answers a series of
questions on her
research and the
origin of the virus.

Conversation



“Our relationship with the rest of the natural world is consumptive, intrusive, and disruptive. Those things shake loose viruses from their natural hosts. All these wild animals carry their own unique viruses.”

David Quammen

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Cover Styling: V K Haris

GO GREEN

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Prologue



Return to Normalcy

Ten plus months, and a million and more deaths. People around the world are now longing for closure of the new 'normalcy' imposed on them. The world waits in fortitude for the end of it, even if everyday life will never be quite the same as it was before we were introduced to COVID-19. So, more than six months after WHO has declared COVID-19 a pandemic, when, and how will the end of the pandemic be?

Searching out historical analogies to find a perspective on the current reality may be reassuring when facing the question of 'when or how a pandemic will end.' Medical historians have documented a lot about the 1918 pandemic and its culmination.

When enough people get immunity, the contagion will gradually die out because it's harder for the virus to find new susceptible hosts. i.e. One epidemiological end-point to a pandemic is when herd immunity is achieved.

Likewise, one end point of COVID-19 will probably happen when the percentage of society immune to COVID-19 is adequate to foil extensive and continuing transmission. Many countries hope that a vaccine will do the bulk of the work needed to achieve herd immunity. When this end point is reached, the public health emergency interventions deployed in 2020 will no longer be needed. And a fear of resurgence can be held in abeyance.

However, the COVID-19 pandemic won't really end until there's both a vaccine and a certain level of exposure in the global population. In the meantime, people can help the endeavour to contain the effect of the pandemic. A proactive approach to public health saved lives a century ago—this tactic is still acceptable.

The end of the 1918 pandemic wasn't just due to herd immunity. Social distancing was also key. Public health advice on curbing the spread of the virus was eerily similar to that of today: citizens were encouraged to stay healthy through campaigns promoting mask-wearing, frequent hand-washing, quarantining and isolating of patients, and the closure of schools, public spaces and non-essential businesses—all steps designed to cut off routes for the virus' spread.

A Markel and Navarro study of 2007 in the Journal of the American Medical Association in 2007 seems pertinent. It found that the U.S. cities that implemented more than one of these aforesaid control measures earlier during the 1918 pandemic and kept them in place for longer, had better, less deadly outcomes than cities that implemented fewer of these control measures and did not do so until later.

A pandemic has to end, following the pattern of all the other viral pandemics to date. One could be more realistic and accept the epidemiologist's view that when the pandemic does subside, it's going to be "a gradual and incremental process."

With the endless optimism that's the hallmark of the human race, we wait, debate and look forward to the 'return of normalcy'.

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"it will take months to a year or more to know whether lingering COVID-19 symptoms in young people could be chronic illnesses." – Page 32

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Editorial



There won't be a declaration that the end has come...

A pandemic has two typical endings. One, a medical ending where the curve flattens, and rates of incidence and death plummet. Two, the social ending, where the fear factor about the outbreak wanes and the people learn to live with a disease, opting out of panic mode. But this does not signify a medical ending by any means. For the people, the ending they look for is social; for the health professionals, it is both.

But beyond the when and how of it, what really signifies the end of a pandemic. Who gets to decide the end, and for whom does it end? How does that happen?

Stephen Morse, an epidemiologist at Columbia University, comments thus on the end of an epidemic, "You can't sign a treaty with a virus, so we have to settle for a kind of cease-fire".

Taking a look at the Spanish Flu that appeared in 1918, the world had believed that the Pandemic had been stopped in its tracks by the spring of 1919. Early 1920 saw the same virus strike again. By the middle of 1920, it subsided enough to assume the Pandemic was over in many places, even though there was no dramatic or memorable declaration that the end had come. Those infected either died or developed an immunity. Even after that virus died out, it would be years before scientists better understood what happened, and some mystery still remains.

Likewise, it's impossible to say with any degree of certainty just how long the COVID-19 Pandemic will last.

Our lead story for this issue unravels the possible ending of the pandemic. Additionally, we also track the progress of the COVID-19 vaccine and therapeutics. The Conversation section features an in-depth interview with David Quammen on how to prevent the next pandemic. David Quammen had predicted the Covid19 pandemic almost a decade ago and published the forecast in 2012.

The next conversation we feature is with Dr Shi Zhengli, a virologist. She is often called China's "bat woman" by her colleagues because of her virus-hunting expeditions in bat caves over the past 16 years. Shi heads a group that studies coronaviruses at the Wuhan Institute of Virology (WIV). Dr Shi Zhengli and her lab in Wuhan have become the centre of a conspiracy theory related to the origin of the coronavirus.

Before I sign off, let me leave you with the statement by the same man, David Quammen, who predicted the Pandemic: *'Science warned this would happen. Politics didn't care.'*

Happy Reading!

Dr Harish Pillai
Editor & Publisher



Nobel Prize in medicine awarded to trio for work on hepatitis C

Two Americans and a British scientist have been awarded the Nobel prize in medicine for their groundbreaking work on blood-borne hepatitis, a health problem that causes cirrhosis and liver cancer around the world.

Harvey J Alter at the US National Institutes of Health in Maryland, Charles M Rice from Rockefeller University in New York, and Michael Houghton, a British virologist at the University of Alberta in Canada, discovered the hepatitis C virus, a major cause of liver inflammation.

The three researchers share the 10m Swedish kronor award (£870,000) that was announced on Monday by the Nobel assembly from the Karolinska Institute in Stockholm.

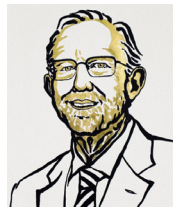
The World Health Organization estimates that more than 70 million people are infected with hepatitis C, with 400,000 dying each year from related conditions such as cirrhosis and liver cancer.



Harvey J. Alter



Michael Houghton



Charles M. Rice

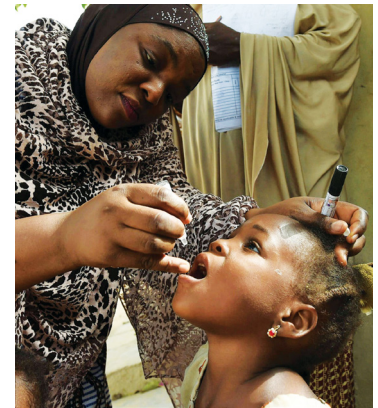
Niklas Elmehed. © Nobel Media

Africa declared free from wild polio

Africa is free from wild poliovirus, the World Health Organization (WHO) announced on 25 August — leaving just two countries where the virus remains endemic, Afghanistan and Pakistan.

The Africa Regional Certification Commission, an independent body responsible for overseeing the eradication of polio, has certified that all 47 countries in the WHO's Africa Region have eradicated the virus after a long programme of vaccination and surveillance.

There is no cure for the disease, which can cause irreversible paralysis and can be fatal if breathing muscles are affected, but vaccination can protect people for life. The certification is a "historic" achievement, says Pascal Mkanda, coordinator of the polio-eradication programme at the WHO Regional Office for Africa in Brazzaville, Republic of Congo.



Mysterious inflammatory syndrome tied to COVID-19 strikes adults as well as kids

The CDC released a report describing a "multisystem inflammatory syndrome in adults" or (MIS-A), months after a similar condition

was reported in children. MIS-A is a severe illness that targets multiple organs and causes increased inflammation in the body, the report said. And with both syndromes, many patients either test positive for SARS-CoV-2, the virus that causes COVID-19, or have antibodies against it, indicating recent infection. Currently, MIS-A appears rare, like its counterpart in children. The new CDC report identifies around two dozen cases of MIS-A.

Still, the new report, published in the CDC journal Morbidity and Mortality Weekly Report, urges doctors to consider a diagnosis of MIS-A in adults with compatible signs and symptoms.



The brief

The winner of the Wellcome Photography Prize 2020 *Medicine in Focus* category by **Julia Gunther & Sophia Mohammed.**

'Vulnerable Being'

Hadia Mundri, South Sudan, 2018

Four-month-old Hadia was born with spina bifida, hydrocephalus (fluid in the brain) and club foot. Sophia, a community rehabilitation expert, is showing her mother, Zaina, a treatment called the Ponseti method, which uses stretches and casts to correct Hadia's feet. Birth defects like Hadia's often result from a lack of folic acid during early pregnancy. Hydrocephalus, which causes the child's head to swell, is common in parts of South Sudan, but a sense of stigma surrounding the condition can deter parents from seeking treatment. Surgery and physiotherapy can help, although access may be hard, and better nutrition – like adding folic acid supplements to staple foods – can prevent it



70% of COVID-19 Patients Don't Transmit the Virus Reveals Study Conducted in Two Indian States

A new study has thrown up lesser-known findings that can help us understand the way COVID-19 spreads in India and across the globe.

The largest contact tracing study in the world has thrown up lesser-known findings that can help us understand the way COVID-19 spreads in India and across the globe.

A latest study conducted by US-based Centre for Disease, Dynamics and Economic Policy (CDDEP) in Andhra Pradesh and Tamil Nadu has revealed that not all individuals infected with COVID-19 transmit the virus.

A team of investigators from CDDEP, the Government of Tamil Nadu and Andhra Pradesh and the University of California at Berkeley studied disease transmission patterns in 575,071 individuals exposed to 84,965 confirmed cases of COVID-19. The study has found that two-thirds of the covid cases are spread by just 8% of the people and that children are active transmitters.

The study, titled 'Epidemiology and transmission dynamics of COVID-19 in two Indian states', was published in the September 30th edition of *Science* magazine.

According to the study, prospective follow-up testing of exposed contacts had revealed that 70

per cent of infected individuals did not infect any of their contacts, while 8 percent of infected individuals accounted for 60 percent of observed new infections.

The study found a high prevalence of infection among children who were contacts of cases around their own age. "Risk of transmission from an index case to a close contact ranges from 2.6 percent in the community to 9.0 percent in the household. Same-age contacts are associated with the greatest infection risk," it said.

However, mortality is higher in the age group of 40-69 years in these two states. It is 0.05 percent among the people in the age group of 5-17 years and 16.6 percent in people of above 85 years. "Men were 62 percent more likely to die than women. Similarly, 63 percent of those who died had at least one co-morbidity, while 36 percent had two or more co-morbidities. Nearly 45 percent of the deceased were diabetic," the study revealed.

"They have followed procedures including syndromic surveillance and testing for all individuals seeking care for severe acute respiratory illness or influenza-like illness at healthcare facilities,



**Dr Ramanan
Laxminarayan**

delineation of 5-km “containment zones” surrounding cases for daily house-to-house surveillance to identify individuals with symptoms,” it observed.

The study also noted that there is a daily follow-up of all contacts of laboratory-confirmed or suspected COVID-19 cases, with the aim of testing these individuals 5-14 days after their contact with a primary case, irrespective of symptoms, to identify onward transmission.

According to the director of the CDDEP, Dr Ramanan Laxminarayan, this study was made possible by the significant contact-tracing effort in Andhra Pradesh and Tamil Nadu which involved tens of thousands of healthcare workers.

“The results on disease transmission and mortality have the potential to inform policy to fight COVID-19. The study also speaks to the capacity of research emerging from India to help inform the global response to COVID-19,” he said.

Study Findings

Covid transmission

- Risk of transmission from an index case to a close contact ranges from 2.6% in the community to 9.0% in the household and does not differ significantly with respect to the age of the index case.

“Men were 62 percent more likely to die than women. Similarly, 63 percent of those who died had at least one co-morbidity, while 36 percent had two or more co-morbidities. Nearly 45 percent of the deceased were diabetic.”

- Infection probabilities ranged from 4.7-10.7% for low-risk and high-risk contact types, respectively. Same-age contacts were associated with the greatest infection risk.
- The study found a high prevalence of infection among children who were contacts of cases around their own age; this finding of enhanced infection risk among individuals exposed to similar-age cases was also apparent among adults.
- Not all infected individuals transmit COVID-19. Prospective follow-up testing of exposed contacts revealed that 70% of infected individuals did not infect any of their contacts, while 8% of infected individuals accounted for 60% of observed new infections. This study presents the largest empirical demonstration of superspreading that we are aware of.

Mortality

- Case-fatality ratios spanned 0.05% at ages 5-17 years to 16.6% at ages ≥85 years.
- Men were 62% more likely to die than women.
- 63% of those who died had at least one co-morbidity. 36% had two or more co-morbidities. 45% of those who died were diabetic.
- Unlike observations in high-income settings, deaths in India are concentrated at ages 50-64 years. The figure below shows case fatality ratios (CFR) at various age groups in India compared to other countries. The CFR is higher in the 40-70 age group in India than in any of the four comparison countries (see figure below). For the age category above 80, the CFR is India is in line with other countries indicating a potential survival effect.
- Contrary to long hospital stays reported in high-income settings, the median time to death is 6 days following admission (compared to 13 in the United States).

Effect of the Lockdown

- There are substantial reductions in the reproductive number, R_t , associated with the implementation of India's country-wide shutdown, which had not previously been shown empirically.
- Case-fatality ratios (proportion of cases that died) have decreased over the course of the epidemic. Individuals who tested positive in July were 26% less likely to die than those tested in March and April. Those who tested positive in May and June were 13% less likely to die than those tested in March and April.

Post Covid, Kids Too Get Diabetes

Evidence suggests that the virus may enter the pancreas through the ACE2 receptor and damage the pancreatic beta islet cells which produce insulin.

by **Iffath Fathima**

Doctors in Bengaluru have come across cases of children, who have developed diabetes after contracting COVID-19. In a person with Type 1 diabetes, the body doesn't produce enough insulin which breaks down sugar and turns it into energy.

Dr Srikanta J T, a consultant of paediatric pulmonology at Aster CMI Hospital reported that his team has seen three cases of children developing diabetic ketoacidosis (DKA), a life-threatening build-up of acid in the blood.

Dr Srikanta said there is evidence to suggest that the virus may have entered the pancreas through the ACE2 receptor and damaged the pancreatic beta islet cells which produce insulin. This can cause transient or new-onset of Type 1 diabetes. The long-term effects on children's health are a cause for concern, said Dr Yogesh Gupta, paediatrician at Fortis Hospital, Bannerghatta Road.

"We have found Type 1 diabetes in children after a Covid infection. It can cause long-term morbidity, mortality and can lead to poor quality of life. Since COVID-19 cases are on the rise,

we may see more children with these problems." So far, 20,008 children between the age of 0-10 years in Karnataka have contracted COVID-19.

Dr Manu Chaudhary, a consultant for paediatric infectious diseases at Rainbow Children's Hospital, recently treated a 10-year-old who developed diabetes soon after she was diagnosed with COVID-19. While most children with COVID-19 are asymptomatic or have a mild infection, this child's condition turned severe, and they had to be prescribed Remdesivir. "As this is a new virus, we don't know much yet. Children who have already been diagnosed with Type 1 diabetes need to be careful as their condition could worsen (if they contract COVID-19)," Dr Chaudhary added.

This study, published in the *Diabetes Care* journal, analysed data from 30 children in London hospitals diagnosed with new-onset Type 1 diabetes during the first peak of the pandemic—around double the cases seen in this period in previous years.

While the study is based on only a handful of cases, it is the first to link COVID-19 and new-onset Type 1 diabetes in children, and doctors should be on the look-out, the Imperial College London researchers said.

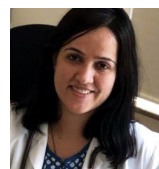
"Our analysis shows that during the peak of the pandemic the number of new cases of Type 1 diabetes in children was unusually high in two of the hospitals (we studied) compared to previous years," said Karen Logan, who co-led the study.



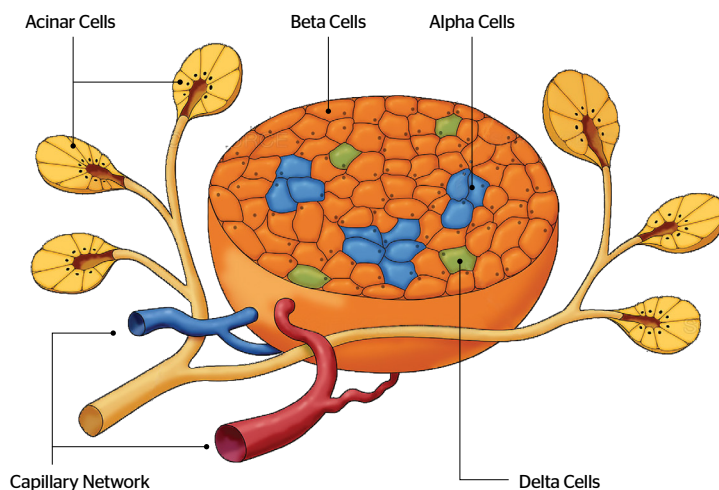
Dr Srikanta J T



Dr Yogesh Gupta



Dr Manu Chaudhary



In focus

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WHEN WILL THE COVID-19 PANDEMIC END? AND HOW?

An infectious outbreak can conclude in more ways than one, historians say. But for whom does it end, and who gets to decide?

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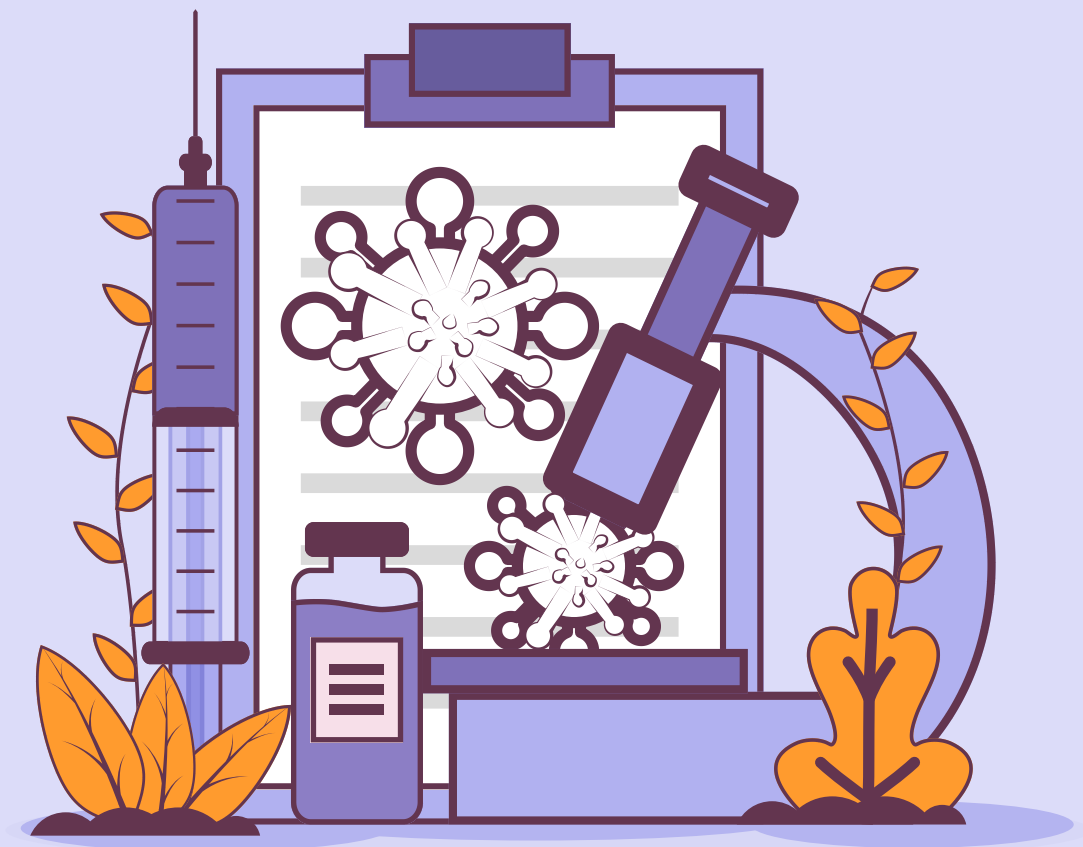
VACCINE: WHERE WE ARE, WHAT'S NEXT?

Researchers are testing 44 vaccines in clinical trials on humans, and at least 91 preclinical vaccines are under active investigation in animals.

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CORONAVIRUS DRUG & TREATMENT TRACKER

Doctors and scientists are scrambling to find treatments and drugs that can save the lives of infected people and perhaps even prevent them from getting sick in the first place.



by **Gina Kolata**

WHEN WILL THE COVID-19 PANDEMIC END? AND HOW?

Bubonic plague has struck several times in the past 2,000 years, killing millions of people and altering the course of history. Each epidemic amplified the fear that came with the next outbreak.

An epidemic of fear can occur even without an epidemic of illness. Dr. Susan Murray, of the Royal College of Surgeons in Dublin, saw that firsthand in 2014 when she was a fellow at a rural hospital in Ireland.

In the preceding months, more than 11,000 people in West Africa had died from Ebola, a terrifying viral disease that was highly infectious and often fatal. The epidemic seemed to be waning, and no cases had occurred in Ireland, but the public fear was palpable.

“On the street and on the wards, people are anxious,” Dr. Murray recalled recently in an article in *The New England Journal of Medicine*. “Having the wrong color skin is enough to earn you the side-eye from your fellow passengers on the bus or train. Cough once, and you will find them shuffling away from you.”

The Dublin hospital workers were warned to prepare for the worst. They were terrified, and worried that they lacked protective equipment. When a young man arrived in the emergency room from a country with Ebola patients, no one wanted to go near him; nurses hid, and doctors threatened to leave the hospital.

Dr. Murray alone dared treat him, she wrote, but his cancer was so advanced that all she could offer was comfort care. A few days later, tests confirmed that the man did not have Ebola; he died an hour later. Three days afterward, the World Health Organization declared the Ebola epidemic over.

Dr. Murray wrote: “If we are not prepared to fight fear and ignorance as actively and as thoughtfully as we fight any other virus, it is possible that fear can do terrible harm to vulnerable people, even in places that never see a single case of infection during an outbreak. And a fear epidemic can have far worse consequences when complicated by issues of race, privilege, and language.”

A Sicilian fresco from 1445. In the previous century, the Black Death killed at least a third of Europe's population.



Werner Forman/Universal Images Group/Getty Images

Bubonic plague has struck several times in the past 2,000 years, killing millions of people and altering the course of history. Each epidemic amplified the fear that came with the next outbreak.

The disease is caused by a strain of bacteria, *Yersinia pestis*, that lives on fleas that live on rats. But bubonic plague, which became known as the Black Death, also can be passed from infected person to infected person through respiratory droplets, so it cannot be eradicated simply by killing rats.

Historians describe three great waves of plague, said Mary Fissell, a historian at Johns Hopkins: the Plague of Justinian, in the sixth century; the medieval epidemic, in the 14th century; and a pandemic that struck in the late 19th and early 20th centuries.

The medieval pandemic began in 1331 in China. The illness, along with a civil war that was raging at the time, killed half the population of China. From there, the plague moved along trade routes to Europe, North Africa and the Middle East. In the years between 1347

and 1351, it killed at least a third of the European population. Half of the population of Siena, Italy, died.

"It is impossible for the human tongue to recount the awful truth," wrote the 14th-century chronicler Agnolo di Tura. "Indeed, one who did not see such horribleness can be called blessed." The infected, he wrote, "swell beneath the armpits and in their groins, and fall over while talking." The dead were buried in pits, in piles.

In Florence, wrote Giovanni Boccaccio, "No more respect was accorded to dead people than would nowadays be accorded to dead goats." Some hid in their homes. Others refused to accept the threat. Their way of coping, Boccaccio wrote, was to "drink heavily, enjoy life to the full, go round singing and merrymaking, and gratify all of one's cravings when the opportunity emerged, and shrug the whole thing off as one enormous joke."

That pandemic ended, but the plague recurred. One of the worst outbreaks began in China in 1855 and

spread worldwide, killing more than 12 million in India alone. Health authorities in Bombay burned whole neighborhoods trying to rid them of the plague. “Nobody knew if it made a difference,” the Yale historian Frank Snowden said.

It is not clear what made the bubonic plague die down. Some scholars have argued that cold weather killed the disease-carrying fleas, but that would not have interrupted the spread by the respiratory route, Dr. Snowden noted.

Or perhaps it was a change in the rats. By the 19th century, the plague was being carried not by black rats but by brown rats, which are stronger and more vicious and more likely to live apart from humans.

“You certainly wouldn’t want one for a pet,” Dr. Snowden said.

Another hypothesis is that the bacterium evolved to be less deadly. Or maybe actions by humans, such as the burning of villages, helped quell the epidemic.

The plague never really went away. In the United States, infections are endemic among prairie dogs in the Southwest and can be transmitted to people. Dr. Snowden said that one of his friends became infected after a stay at a hotel in New Mexico. The previous occupant of his room had a dog, which had fleas that carried the microbe.

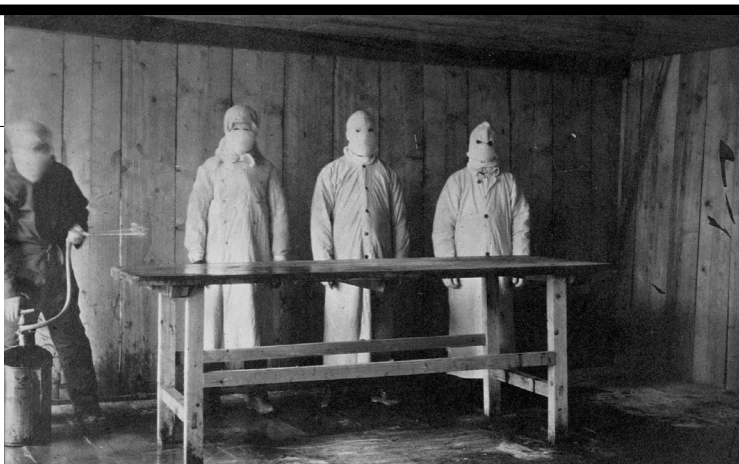
Such cases are rare, and can now be successfully treated with antibiotics, but any report of a case of the plague stirs up fear.

ONE DISEASE THAT ACTUALLY ENDED

Among the diseases to have achieved a medical end is smallpox. But it is exceptional for several reasons: There is an effective vaccine, which gives lifelong protection; the virus, *Variola major*, has no animal host, so eliminating the disease in humans meant total elimination; and its symptoms are so unusual that infection is obvious, allowing for effective quarantines and contact tracing.

But while it still raged, smallpox was horrific. Epidemic after epidemic swept the world, for at least 3,000 years. Individuals infected with the virus developed a fever, then a rash that turned into pus-filled spots, which became encrusted and fell off, leaving scars. The disease killed three out of 10 of its victims, often after immense suffering.

In 1633, an epidemic among Native Americans “disrupted all the native communities in the north-east and certainly facilitated English settlement



Disinfecting an autopsy table at a plague hospital in Mukden, China, in 1910, during a wave of pneumonic plague, also caused by the bacteria *Yersinia pestis*.



Dissecting rats in New Orleans in 1914 for signs that they might be carrying bubonic plague.

in Massachusetts,” said Harvard historian Dr. David S. Jones. William Bradford, leader of the Plymouth colony, wrote an account of the disease in Native Americans, saying the broken pustules would effectively glue a patient’s skin to the mat he lay on, only to be torn off. Bradford wrote: “When they turn them, a whole side will flay off at once as it were, and they will be all of a gore blood, most fearful to behold.”

The last person to contract smallpox naturally was Ali Maow Maalin, a hospital cook in Somalia, in 1977. He recovered, only to die of malaria in 2013.

FORGOTTEN INFLUENZAS

The 1918 flu is held up today as the example of the ravages of a pandemic and the value of quarantines and social distancing. Before it ended, the flu killed 50 million to 100 million people worldwide. It



Red Cross volunteers in Piedmont, Calif., making masks in October 1918.



Edward Jenner, one of the early developers of the smallpox vaccine, inoculating a child from the disease in 1796.

preyed on young to middle-aged adults — orphaning children, depriving families of breadwinners, killing troops in the midst of World War I.

In the autumn of 1918, Victor Vaughan, a prominent doctor, was dispatched to Camp Devens near Boston to report on a flu that was raging there. He saw “hundreds of stalwart young men in the uniform of their country, coming into the wards of the hospital in groups of ten or more,” he wrote. “They are placed on the cots until every bed is full, yet others crowd in. Their faces soon wear a bluish cast, a distressing cough brings up blood stained sputum. In the morning the dead bodies are stacked up in the morgue like cord wood.”

The virus, he wrote, “demonstrated the inferiority of human inventions in the destruction of human life.”

After sweeping through the world, that flu faded away, evolving into a variant of the more benign flu that comes around every year.

“Maybe it was like a fire that, having burned the available and easily accessible wood, burns down,” Dr. Snowden said.

It ended socially, too. World War I was over; people were ready for a fresh start, a new era, and eager to put the nightmare of disease and war behind them. Until recently, the 1918 flu was largely forgotten.

Other flu pandemics followed, none so bad but all nonetheless sobering. In the Hong Kong flu of 1968, one million people died worldwide, including 100,000 in the United States, mostly people older than 65. That virus still circulates as a seasonal flu, and its initial path of destruction — and the fear that went with it — is rarely recalled.

HOW WILL COVID-19 END?

One possibility, historians say, is that the coronavirus pandemic could end socially before it ends medically. People may grow so tired of the restrictions that they declare the pandemic over, even as the virus continues to smolder in the population and before a vaccine or effective treatment is found.

“I think there is this sort of social psychological issue of exhaustion and frustration,” the Yale historian Naomi Rogers said. “We may be in a moment when people are just saying: ‘That’s enough. I deserve to be able to return to my regular life.’”

It is happening already; in some states, governors have lifted restrictions, allowing hair salons, nail salons and gyms to reopen, in defiance of warnings by public health officials that such steps are premature. As the economic catastrophe wreaked by the lockdowns grows, more and more people may be ready to say “enough.”

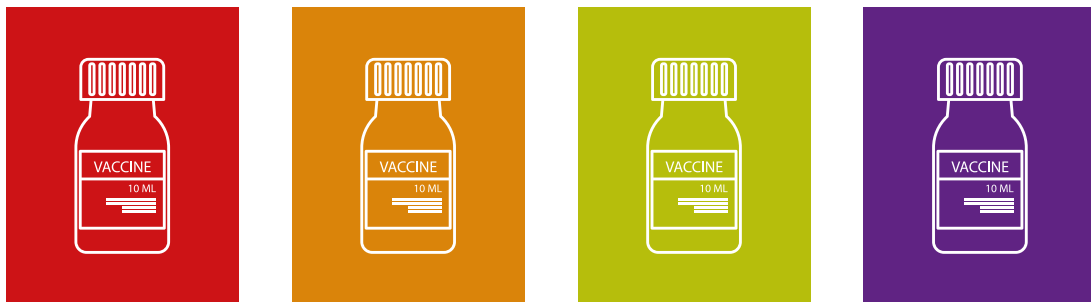
“There is this sort of conflict now,” Dr. Rogers said. Public health officials have a medical end in sight, but some members of the public see a social end.

“Who gets to claim the end?” Dr. Rogers said. “If you push back against the notion of its ending, what are you pushing back against? What are you claiming when you say, ‘No, it is not ending.’”

The challenge, Dr. Brandt said, is that there will be no sudden victory. Trying to define the end of the epidemic “will be a long and difficult process.”

VACCINE

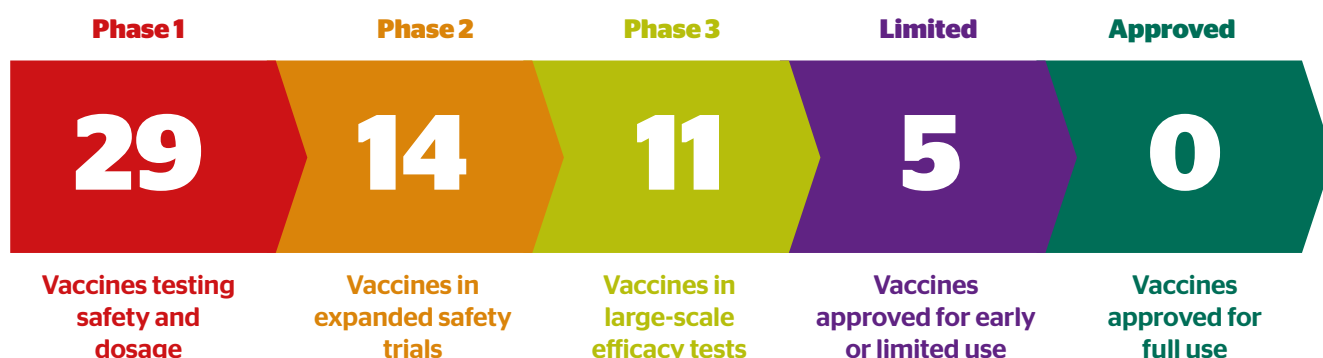
WHERE WE ARE, WHATS NEXT?



Researchers are testing 44 vaccines in clinical trials on humans, and at least 91 preclinical vaccines are under active investigation in animals.



by **Jonathan Corum, Denise Grady, Sui-Lee Wee & Carl Zimmer**



Vaccines typically require years of research and testing before reaching the clinic, but scientists are racing to produce a safe and effective coronavirus vaccine by next year. Work began in January with the deciphering of the SARS-CoV-2 genome. The first vaccine safety trials in humans started in March, but the road ahead remains uncertain. Some trials will fail, and others may end without a clear result. But a few may succeed in stimulating the immune system to produce effective antibodies against the virus. Here is their progress.

HOW ARE VACCINES TESTED?

The development cycle of a vaccine, from lab to clinic.

PRECLINICAL TESTING

Scientists test a new vaccine on cells and then give it to animals such as mice or monkeys to see if it produces an immune response. We have confirmed 91 preclinical vaccines in active development.

PHASE 1 SAFETY TRIALS

Scientists give the vaccine to a small number of people to test safety and dosage as well as to confirm that it stimulates the immune system.

PHASE 2 EXPANDED TRIALS

Scientists give the vaccine to hundreds of people split into groups, such as children and the elderly, to see if the vaccine acts differently in them. These trials further test the vaccine's safety and ability to stimulate the immune system.

PHASE 3 EFFICACY TRIALS

Scientists give the vaccine to thousands of people and wait to see how many become infected, compared with volunteers who received a placebo. These trials can determine if the vaccine protects against the coronavirus. In addition, Phase 3 trials are large enough to reveal evidence of relatively rare side effects that might be missed in earlier studies.

EARLY OR LIMITED APPROVAL

China and Russia have approved vaccines without waiting for the results

of Phase 3 trials. Experts say the rushed process has serious risks.

APPROVAL

Regulators in each country review the trial results and decide whether to approve the vaccine or not. During a pandemic, a vaccine may receive emergency use authorisation before getting formal approval. Once a vaccine is licensed, researchers continue to monitor people who receive it to make sure it's safe and effective.

COMBINED PHASES

One way to accelerate vaccine development is to combine phases. Some coronavirus vaccines are now in Phase 1/2 trials, for example, in which they are tested for the first time on hundreds of people.

Types of Vaccines ●●●

Genetic Vaccines

Vaccines that use one or more of the coronavirus's own genes to provoke an immune response.

Viral Vector Vaccines

Vaccines that use a virus to deliver coronavirus genes into cells. The cells make viral proteins, provoking an immune response, but the virus cannot replicate.

Protein-Based Vaccines

Vaccines that use a coronavirus protein or a protein fragment to provoke an immune response.

Whole-Virus Vaccines

Vaccines that use weakened or inactivated viruses to provoke an immune response

Repurposed Vaccines

Vaccines already in use for other diseases that may also protect against COVID-19

PHASE 1

Inovio ●●●

The American company Inovio has developed DNA-based vaccines which are delivered into the skin with electric pulses from a hand-held device. They have vaccines in clinical trials for a number of diseases, and in June they announced interim data from a Phase 1 trial on COVID-19. They found no serious adverse effects, and measured an immune response in 34 out of 36 volunteers.

Genexine ●●●

The Korean company Genexine started testing the safety of a DNA-based vaccine in June. They anticipate moving to Phase 2 trials in the fall.

ARCoV ●●●

In June, Chinese researchers at the Academy of Military Medical Sciences, Suzhou Abogen Biosciences and Walvax Biotechnology announced they would start their country's first safety trials on a mRNA-based vaccine, called ARCoV. Earlier studies on monkeys reportedly showed protective effects.

ChulaCov19 ●●●

Researchers at Thailand's Chulalongkorn University have been developing several potential vaccines for the coronavirus. The furthest along is an mRNA-based vaccine known as ChulaCov19. On Sept. 29, the Chula Vaccine Research Center registered a Phase 1 trial to test it in humans.

GRAd-COV2 ●●●

The Italian biotechnology company ReiThera has developed a COVID-19 vaccine, called GRAd-COV2, that is based on an adenovirus that infects gorillas. Working in collaboration with the Lazzaro Spallanzani National Institute for Infectious Diseases in Rome, they launched a Phase 1 trial at the end of July.

Vaxart ●●●

While many vaccines are given as injections, some vaccines can be taken as a pill. Oral vaccines have been approved for diseases including polio, cholera, and

typhoid fever. Earlier this year, the small San Francisco-based company Vaxart began work on an oral vaccine for COVID-19. It contains an adenovirus called Ad5 (the same viral vector in CanSinoBio's vaccine and in Russia's Sputnik V). In September, Vaxart reported that mice given the pill produced antibodies against the coronavirus. On September 24, they registered a Phase 1 clinical trial.

Merck + Themis ●●●

The American company Merck acquired the Austrian firm Themis Bioscience in June and is working on a vaccine originally developed at Institut Pasteur. The vaccine uses a weakened measles virus that carries a gene for the coronavirus spike protein. Researchers launched a Phase I trial in August.

University of Hong Kong + Xiamen University ●●●

In 2019, researchers at the University of Hong Kong and Xiamen University created a nasal-spray vaccine for the flu based on a genetically weakened form of the influenza virus. Earlier this year, they engineered the vaccine to produce part of the coronavirus spike protein as well. On September 9, they received approval to start clinical trials in partnership with Beijing Wantai Biological Pharmacy.

German Center for Infection Research ●●●

Three decades ago, the German Center for Infection Research developed a smallpox vaccine from a harmless virus called Modified Vaccinia Ankara, or MVA for short. In recent years, they modified it to create a vaccine for MERS, a disease caused by another coronavirus. This spring, they made an MVA-based vaccine for the coronavirus that is causing the COVID-19 pandemic. It carries the gene for the spike protein, which is produced inside cells that it invades. On September 29, the center and a consortium of German universities registered a Phase 1 trial.

Merck + IAVI ●●●

In addition to its project with Themis, Merck is partnering with IAVI on a second viral vector vaccine. It is based on vesicular stomatitis viruses, the same approach

Merck successfully used to produce the first approved vaccine for Ebola. They have designed their coronavirus vaccine as a pill, which could potentially make it easier to distribute than syringes for injections. Merck and IAVI received \$38 million from the United States government to support their research, and on September 30 they registered a Phase 1 trial.

Clover Biopharmaceuticals ●●●

Clover Biopharmaceuticals has developed a vaccine containing the spike protein from coronaviruses. To further stimulate the immune system, the vaccine is being given in conjunction with so-called adjuvants made by British drugmaker GSK and the American company Dynavax. Investments from CEPI will support the development of manufacturing that could lead to the production of hundreds of millions of doses a year.

Clover launched a Phase 1 trial in June. In September the company announced that it was expanding the trial and anticipated starting a Phase 2 trial by the end of 2020.

University of Queensland ●●●

A vaccine from Australia's University of Queensland delivers viral proteins altered to draw a stronger immune response. Experiments on hamsters showed that the vaccine protected them from the coronavirus. The university launched Phase 1 trials in July, combining the proteins with an adjuvant made by CSL. If the results are positive, CSL will advance late stage clinical trials by the end of 2020.

Medicago ●●●

Canada-based Medicago, partly funded by the cigarette maker Philip Morris, uses a species of tobacco to make vaccines. They deliver virus genes into leaves, and the plant cells then create protein shells that mimic viruses. In July, Medicago launched Phase 1 trials on a plant-based COVID-19 vaccine in combination with adjuvants from drug makers GSK and Dynavax. If the trial goes well, they plan to start Phase 2/3 trials in October.

Vaxine ●●●

The Australian company Vaxine developed a vaccine that combines viral proteins with an adjuvant that stimulates the immune system. Phase 1 trials began over the summer, and Phase 2 trials are expected to commence by the end of the year.

Kentucky BioProcessing ●●●

A second tobacco-based vaccine is in development at Kentucky BioProcessing, an American subsidiary of British American Tobacco, the maker of Lucky Strike and other cigarettes. Like Medicago, Kentucky BioProcessing engineers a species of tobacco called *Nicotiana benthamiana* to make viral proteins. The company previously used this technique to make a drug called Zmapp

for Ebola. After preclinical testing in the spring, they registered a Phase 1 trial for their coronavirus vaccine in July.

Medigen ●●●

Taiwan-based vaccine maker Medigen is making a vaccine made of a combination of spike proteins and an adjuvant from Dynavax. They have registered a Phase 1 trial set to start in September.

Adimmune ●●●

Taiwan-based vaccine manufacturer Adimmune got permission to launch a Phase 1 trial on August 20. The vaccine contains the RBD section of the virus's spike protein.

West China Hospital of Sichuan University ●●●

In July, researchers at West China Hospital of Sichuan University published a study in *Nature* describing a vaccine made from the RBD region of the spike protein that could protect mice and monkeys from the coronavirus. On August 24, they got approval to run a Phase 1 trial. To make the vaccine, researchers encode the RBD region in a gene, which they insert into a virus. They then infect insect cells with the virus, causing them to make the molecule in huge amounts.

COVAXX ●●●

New York-based COVAXX, a subsidiary of United Biomedical, has created a vaccine containing parts of several viral proteins. On Sept. 11 they registered a Phase 1 trial in Taiwan. They have reached an agreement with authorities in Brazil to run their Phase 2/3 trial there.

University of Tübingen ●●●

In the spring, researchers at the University of Tübingen in Germany created a vaccine made of eight parts of two viral proteins, along with an immune-stimulating adjuvant. In September they launched a Phase 1 trial.

North Korea's State Commission ●●●

On July 18, North Korea's State Commission of Science and Technology announced on their web site that they had started clinical trials on a vaccine based on part of the coronavirus spike protein. The commission claimed to have tested the vaccine on animals, but provided no data. It stated that effectiveness trials would have to be carried out in another country "since there is no case of Covid-19 in DPR Korea." Outside experts find this claim highly doubtful.

QazCovid ●●●

The Central Asian nation of The Republic of Kazakhstan began research on a vaccine made from inactivated coronaviruses over the summer. On August 28, their Research Institute for Biological Safety Problems registered a Phase 1 trial on the vaccine, known as QazCovid.

PHASE 1 PHASE 2 COMBINED PHASE

Imperial College London ●●●

Imperial College London researchers have developed a “self-amplifying” RNA vaccine, which boosts production of a viral protein to stimulate the immune system. They began Phase 1/2 trials on June 15 and have partnered with Morningside Ventures to manufacture and distribute the vaccine through a new company called VacEquity Global Health.

AnGes + Osaka University ●●●

On June 30, the Japanese biotechnology company AnGes announced they had started Phase 1 trials on a DNA-based vaccine, developed in partnership with Osaka University and Takara Bio. The company will announce initial results of the trials in November and are planning for a Phase 3 trial by the end of the year.

Arcturus + Duke-NUS Singapore ●●●

The California-based company Arcturus Therapeutics and Duke-NUS Medical School in Singapore have developed an mRNA vaccine. It has a “self-replicating” design that leads to a greater production of viral proteins. Tests on animals showed that it protected them against infection. In August, Arcturus launched a Phase 1/2 trial at Singapore General Hospital.

Soberana 1 ●●●

On August 18, the head of epidemiology at Cuba's public health ministry announced that the Finlay Vaccine Institute in Havana would start a clinical trial on a vaccine for COVID-19. The vaccine, called Soberana 1, contains a part of the spike protein, called RBD, along with an adjuvant to boost the immune response.

EpiVacCorona ●●●

On August 26, a Russian biological research centre, The Vector Institute, registered a Phase 1/2 trial for a coronavirus vaccine they call EpiVacCorona. The vaccine contains small portions of viral proteins, known as peptides. According to newspaper reports, the EpiVacCorona trials had already begun by then, with plans for distribution of the vaccine by the end of the year.

Sanofi ●●●

In addition to their mRNA vaccine, Sanofi developed a COVID-19 vaccine based on viral proteins. They produced the proteins with engineered viruses that grow inside insect cells. GSK supplemented these proteins with adjuvants that stimulate the immune system. The vaccine is based on the same design Sanofi used to create Flublok, an approved vaccine for influenza. The companies launched a Phase 1/2 clinical trial in September. They plan to start a Phase 3 trial in December and hope to know if the vaccine is safe and effective by the middle of 2021.

SpyBiotech ●●●

SpyBiotech, a company spun off from the University of Oxford, announced in September that the first volunteers in an Australian Phase 1/2 trial were receiving their COVID-19 vaccine. The researchers created the vaccine from a mixture of proteins. Some of the proteins, from hepatitis B viruses, assemble themselves into hollow shells. The researchers decorated these shells with part of the coronavirus spike protein. The Serum Institute of India, which licensed the technology from SpyBiotech, is running the trials.

PHASE 2

Zyklus Cadila ●●●

In July, the Indian vaccine-maker Zyklus Cadila began testing a DNA-based vaccine delivered by a skin patch. They launched a Phase 2 trial on Aug. 6.

CureVac ●●●

CureVac launched its clinical trials of an mRNA vaccine, gave injections in September to volunteers and Panama and Peru for a Phase 2 study, and planned for a Phase 3 trial by the end of 2020. In an interview, the chief executive of CureVac said that the company would make 100 million doses by the end of 2020 and hoped to gain approval some time in 2021. CureVac has collaborated with Elon Musk's company Tesla on creating mRNA “micro-factories,” which could potentially be deployed around the world to make billions of doses of the vaccine.

Anhui Zhifei Longcom ●●●

In July, the Chinese company Anhui Zhifei Longcom began Phase 2 trials for a vaccine that is a combination of viral proteins and an adjuvant that stimulates the immune system. The company is part of Chongqing Zhifei Biological Products and has partnered with the Chinese Academy of Medical Sciences.

Chinese Academy of Medical Sciences ●●●

Researchers at the Institute of Medical Biology at the Chinese Academy of Medical Sciences, which has invented vaccines for polio and hepatitis A, started a Phase 2 trial of an inactivated virus vaccine in June.

ICMR + Bharat Biotech ●●●

In collaboration with the Indian Council of Medical Research and the National Institute of Virology, the Indian company Bharat Biotech designed a vaccine called Covaxin based on an inactivated form of the coronavirus. Studies on monkeys and hamsters found that it provided protection against infection. When the company launched clinical trials in July, reports circulated that the vaccine would be ready by August 15. But the C.E.O. of Bharat told reporters it would be available no sooner than early 2021.

PHASE 2 PHASE 3 COMBINED PHASE**BioNTech + Pfizer + Fosun Pharma ●●●**

The German company BioNTech entered into collaborations with Pfizer, based in New York, and the Chinese drug maker Fosun Pharma to develop an mRNA vaccine to be given in two doses. In May they launched a Phase 1/2 trial on two versions of the vaccine. They found that both versions caused volunteers to produce antibodies against SARS-CoV-2, as well as immune cells called T cells that respond to the virus. They found that one version, called BNT162b2, produced significantly fewer side effects, such as fevers and fatigue, and so they chose it to move into Phase 2/3 trials. On July 27, the companies announced the launch of a Phase 2/3 trial with 30,000 volunteers in the United States and other countries including Argentina, Brazil, and Germany.

In September, the chief executive of Pfizer said they would know if the vaccine works as soon as October 2020. If approved, Pfizer has said they expect to manufacture over 1.3 billion doses of their vaccine worldwide by the end of 2021.

AstraZeneca + University of Oxford ●●●

A vaccine in development by the British-Swedish company AstraZeneca and the University of Oxford is based on a chimpanzee adenovirus called ChAdOx1. A study on monkeys found that the vaccine provided them protection. In May, the United States awarded the project \$1.2 billion in support. In their Phase 1/2 trial, the vaccine developers did not detect any severe side effects. They found that the vaccine raised antibodies against the coronavirus as well as other immune defenses. The vaccine began Phase 2/3 trials in England and India, as well as Phase 3 trials in Brazil, South Africa, and the United States.

In August the European Union reached an agreement for AstraZeneca to deliver 400 million doses if the trials yield positive results. AstraZeneca has indicated they might be able to start delivering emergency vaccines as early as October, depending on the outcome of the studies. The company has said their total manufacturing capacity for the vaccine, if approved, stands at two billion doses. India's Serum Institute has already produced millions of doses to be used in trials.

On Sept. 6, AstraZeneca halted global trials of the vaccine to investigate one volunteer, who developed a form of inflammation called transverse myelitis. Within a week, the trials began resuming. As of now, however, the United States is still keeping its trial on pause as the F.D.A. investigates.

PHASE 3**National Institutes of Health + Moderna ●●●**

Moderna develops vaccines based on messenger RNA (mRNA) to produce viral proteins in the body. They have yet to bring one to the market. In January, they began developing a vaccine for the coronavirus and since then the government has bankrolled Moderna's efforts, providing nearly \$1 billion. In partnership with National Institutes of Health, they found that the vaccine protects monkeys from the coronavirus. In March, the company put the first COVID-19 vaccine into human trials, which yielded promising results. The vaccine has progressed into Phase 3 testing, which began on July 27. The final trial is enrolling 30,000 healthy people at about 89 sites around the United States. On August 11, the government awarded the company an additional \$1.5 billion in exchange for 100 million doses if the vaccine proves safe and effective. Canada agreed in September to acquire 20 million doses.

In July, Moderna lost a patent dispute over some of their vaccine technology. The following month, the company stated that it could not be certain it was the first to make the inventions claimed in their patents, including its coronavirus vaccine.

On Sept. 17, Moderna shared their protocol for determining if their vaccine was safe and effective. They planned to wait until a significant number of volunteers became sick with COVID-19 and then see how many had been vaccinated. It may take till the end of 2020 or early 2021 to reach the necessary numbers.

Johnson & Johnson ●●●

A decade ago, researchers at Beth Israel Deaconess Medical Center in Boston developed a method for making vaccines out of a virus called Adenovirus 26, or Ad26 for short. Johnson & Johnson developed vaccines for Ebola and other diseases with Ad26 and have now made one for the coronavirus. In March they received \$456 million from the United States government to support their move towards production. The vaccine has provided protection in experiments on monkeys. Johnson & Johnson began Phase 1/2 trials in July and launched a Phase 3 trial with up to 60,000 participants in September.

In August, the federal government agreed to pay \$1 billion for 100 million doses if the vaccine is approved. The company is aiming for production of at least a billion doses in 2021.

Novavax ●●●

Maryland-based Novavax makes vaccines by sticking proteins onto microscopic particles. They've taken on a number of different diseases this way; their flu vaccine finished Phase 3 trials in March. The company launched trials for a COVID-19 vaccine in May, and the Coalition for Epidemic

Preparedness Innovations has invested \$384 million in the vaccine. In July the U.S. government awarded \$1.6 billion to support the vaccine's clinical trials and manufacturing.

After getting promising results from preliminary studies in monkeys and humans, Novavax launched a Phase 2 trial in South Africa in August. The blinded, placebo-controlled trial on 2,900 people will measure not just the safety of the vaccine but its efficacy. The following month, Novavax launched a Phase 3 trial enrolling up to 10,000 volunteers in the United Kingdom. It could potentially deliver results by the start of 2021. A larger Phase 3 trial is in development to launch in the United States in October.

If the trials succeed, Novavax expects to deliver 100 million doses for use in the United States by the first quarter of 2021. In September Novavax reached an agreement with the Serum Institute of India, a major vaccine manufacturer, that they said would enable them to produce as many as 2 billion doses a year.

BCG Vaccine ●●●

The Bacillus Calmette-Guerin vaccine was developed in the early 1900s as a protection against tuberculosis. The Murdoch Children's Research Institute in Australia is conducting a Phase 3 trial called the BRACE to see if the vaccine partly protects against the coronavirus.

PHASE 3 APPROVED FOR LIMITED USE

CanSino Biologics ●●●

The Chinese company CanSino Biologics developed a vaccine based on an adenovirus called Ad5, in partnership with the Institute of Biology at the country's Academy of Military Medical Sciences. In May, they published promising results from a Phase 1 safety trial, and in July they reported that their Phase 2 trials demonstrated the vaccine produced a strong immune response. In an unprecedented move, the Chinese military approved the vaccine on June 25 for a year as a "specially needed drug." CanSino would not say whether vaccination would be mandatory or optional for soldiers. Starting in August, CanSino began running Phase 3 trials in a number of countries, including Saudi Arabia, Pakistan and Russia.

Sputnik V, ●●●

The Gamaleya Research Institute, part of Russia's Ministry of Health, launched clinical trials in June of a vaccine they called Gam-Covid-Vac. It is a combination of two adenoviruses, Ad5 and Ad26, both engineered with a coronavirus gene.

On Aug. 11, President Vladimir V. Putin announced that a Russian health care regulator had approved the vaccine, renamed Sputnik V, before Phase 3 trials had even begun. Vaccine experts decried the move as risky, and Russia later walked back the announcement, saying that the approval

was a "conditional registration certificate," which would depend on positive results from Phase 3 trials. Those trials, initially planned for just 2,000 volunteers, were expanded to 40,000. On September 4, three weeks after Putin's announcement, Gamaleya researchers published the results of their Phase 1/2 trial. In a small study, they found that Sputnik yielded antibodies to the coronavirus and mild side effects. Meanwhile, Russia negotiated agreements to supply the vaccine to countries including Brazil, Mexico and India.

Wuhan Institute of Biological ●●●

The Wuhan Institute of Biological Products developed an inactivated virus vaccine, which the state-owned Chinese company Sinopharm put into clinical tests. The Phase 1/2 trial showed that the vaccine produced antibodies in volunteers, some of whom experienced fevers and other side effects. They launched Phase 3 trials in the United Arab Emirates in July, and in Peru and Morocco the following month. Over the summer, the company later said, the government gave it approval to inject hundreds of thousands of people with its two experimental vaccines. On Sept. 14, the U.A.E. gave emergency approval for Sinopharm's vaccine to be used on health care workers.

Sinopharm ●●●

Sinopharm also began testing a second inactivated virus vaccine, this one developed by the Beijing Institute of Biological Products. After running early clinical trials in China, they launched Phase 3 trials in the United Arab Emirates and Argentina. Over the summer, the company later said, the government gave it approval to inject hundreds of thousands of people with its two experimental vaccines. On Sept. 14, the U.A.E. gave emergency approval for Sinopharm's vaccine to use on health care workers before Sinopharm shared data indicating it was safe and effective.

Sinovac Biotech ●●●

The private Chinese company Sinovac Biotech is testing an inactivated vaccine called CoronaVac. In June the company announced that Phase 1/2 trials on 743 volunteers found no severe adverse effects and produced an immune response. Sinovac then launched a Phase 3 trial in Brazil in July, followed by others in Indonesia and Turkey. On September 16, they registered a Phase 1/2 trial of the vaccine for children.

Reuters reported that the Chinese government gave the Sinovac vaccine an emergency approval for limited use in July. Meanwhile, Sinovac has been preparing to manufacture the vaccine, reaching an agreement to supply Indonesia with at least 40 million doses by March 2021. In September, Yin Weidong, the CEO of SinoVac, said the company planned on worldwide distribution of the vaccine in early 2021 — including the United States.

COVID-19by **Jonathan Corum, Katherine J. Wu and Carl Zimmer**

Coronavirus Drug & Treatment Tracker



Doctors and scientists are scrambling to find treatments and drugs that can save the lives of infected people and perhaps even prevent them from getting sick in the first place.



The COVID-19 pandemic is one of the greatest challenges modern medicine has ever faced. Doctors and scientists are scrambling to find treatments and drugs that can save the lives of infected people and perhaps even prevent them from getting sick in the first place. Below is an updated list of 22 of the most-talked-about treatments for the coronavirus. While some are accumulating evidence that they're effective, most are still at early stages of research. We also included a warning about a few that are just bunk. We are following 22 coronavirus treatments for effectiveness and safety.

WHAT THE LABELS MEAN

WIDELY USED

These treatments have been used widely by doctors and nurses to treat patients hospitalized for diseases that affect the respiratory system, including COVID-19.

PROMISING EVIDENCE

Early evidence from studies on patients suggests effectiveness, but more research is needed. This category includes treatments that have shown improvements in morbidity, mortality and recovery in at least one randomized controlled trial, in which some people get a treatment and others get a placebo.

TENTATIVE OR MIXED EVIDENCE

Some treatments show promising results in cells or animals, which need to be confirmed in people. Others have yielded encouraging results in retrospective studies in humans, which look at existing datasets rather than starting a new trial. Some treatments have produced different results in different experiments, raising the need for larger, more rigorously designed studies to clear up the confusion.

NOT PROMISING

Early evidence suggests that these treatments do not work.

PSEUDOSCIENCE OR FRAUD

These are not treatments that researchers have ever considered using for COVID-19. Experts have warned

against trying them, because they do not help against the disease and can instead be dangerous. Some people have even been arrested for their false promises of a COVID-19 cure.

EVIDENCE IN CELLS, ANIMALS OR HUMANS

These labels indicate where the evidence for a treatment comes from. Researchers often start out with experiments on cells and then move onto animals. Many of those animal experiments fail; if they don't, researchers may consider moving on to research on humans, such as retrospective studies or randomized clinical trials. In some cases, scientists are testing out treatments that were developed for other diseases, allowing them to move directly to human trials for COVID-19.

WIDELY USED**Prone positioning**

The simple act of flipping COVID-19 patients onto their bellies opens up the lungs. The manoeuvre has become commonplace in hospitals around the world since the start of the pandemic. It might help some individuals avoid the need for ventilators entirely. The treatment's benefits continue to be tested in a range of clinical trials.

WIDELY USED**EMERGENCY USE AUTHORIZATION****Ventilators and other respiratory support devices**

Devices that help people breathe are an essential tool in the fight against deadly respiratory illnesses. Some patients do well if they get an extra supply of oxygen through the nose or via a mask connected to an oxygen machine. Patients in severe respiratory distress may need to have a ventilator breathe for them until their lungs heal. Doctors are divided about how long to treat patients with noninvasive oxygen before deciding whether or not they need a ventilator. Not all COVID-19 patients who go on ventilators survive, but the devices are thought to be lifesaving in many cases.

PROMISING EVIDENCE**EVIDENCE IN CELLS, ANIMALS AND HUMANS
EMERGENCY USE AUTHORIZATION****Remdesivir**

Remdesivir, was the first drug to get emergency authorization from the F.D.A. for use on COVID-19. It interferes with the creation of new viruses by inserting itself into new viral genes. Remdesivir was originally tested as an antiviral against Ebola and Hepatitis C, only to deliver lackluster results. However, a randomized controlled trial published in May concluded the drug reduced the recovery time of people hospitalized with COVID-19 from 15 to 11 days. (The study defined recovery as "either discharge from the hospital or hospitalization for infection-control purposes only.") The trial did not show any effect on mortality, though retrospective data released in July hints that the drug might reduce death rates among those who are very ill.

The F.D.A. responded to this data in May by issuing an emergency authorization in May for remdesivir's use in critically ill patients who need supplemental oxygen. In August, they expanded that approval after researchers found that patients with less severe forms of COVID-19 seemed to benefit modestly from a five-day treatment course of remdesivir. The revised approval

allows the use of the drug on all patients hospitalized with COVID-19, regardless of how severe their disease is. The move was criticized by some experts who said the F.D.A. had expanded remdesivir's use without strong evidence to back the change.

**PROMISING EVIDENCE
EVIDENCE IN HUMANS****Dexamethasone and Other Corticosteroids**

Corticosteroids — often called steroids for short — are used to tamp down inflammation and for conditions such as allergies and asthma. In the 1960s, doctors began using them as a treatment for pneumonia and other severe respiratory illnesses, but the results of clinical trials were inconclusive. The COVID-19 pandemic brought a new interest in these drugs, and a raft of new clinical trials were launched.

In June, a steroid called dexamethasone was the first shown to reduce COVID-19 deaths. A study of more than 6,000 people found that dexamethasone reduced deaths by one-third in patients on ventilators, and by one-fifth in patients on oxygen. It may be less likely to help — and may even harm — patients who are at an earlier stage of COVID-19 infection, however. In its COVID-19 treatment guidelines, the National Institutes of Health recommends only using dexamethasone in patients with COVID-19 who are on a ventilator or are receiving supplemental oxygen.

In September, researchers reviewed the results of trials on dexamethasone, along with two other steroids, hydrocortisone and methylprednisolone. Overall, they concluded, steroids were linked with a one-third reduction in deaths among COVID-19 patients.

**TENTATIVE OR MIXED EVIDENCE
EVIDENCE IN CELLS, ANIMALS AND HUMANS****Favipiravir**

Originally designed to beat back influenza, favipiravir blocks a virus's ability to copy its genetic material. A small study in March indicated the drug might help to purge the coronavirus from the airway. Larger, randomized trials are now underway.

**TENTATIVE OR MIXED EVIDENCE
EVIDENCE IN CELLS, ANIMALS AND HUMANS****MK-4482**

MK-4482 is another antiviral originally designed to fight the flu. Ridgeback Biotherapeutics and Merck are collaborating to develop it as a treatment for COVID-19. The drug, (previously known as EIDD-2801) produced promising results against the new coronavirus in studies this spring in cells and on animals. Clinical

trials started this summer, with a large Phase 3 trial expected to start by October.

TENTATIVE OR MIXED EVIDENCE EVIDENCE IN CELLS

Recombinant ACE-2 -

To enter cells, the coronavirus must first unlock them — a feat it accomplishes by latching onto a human protein called ACE-2. Scientists have created artificial ACE-2 proteins which might be able to act as decoys, luring the coronavirus away from vulnerable cells. Recombinant ACE-2 proteins have shown promising results in experiments on cells, but not yet in animals or people.

TENTATIVE OR MIXED EVIDENCE EVIDENCE IN CELLS, ANIMALS AND HUMANS

Ivermectin

For decades, ivermectin has served as a potent drug to treat parasitic worms. Doctors use it against river blindness and other diseases, while veterinarians give dogs a different formulation to cure heartworm. Studies on cells have suggested ivermectin might also kill viruses. But scientists have yet to find evidence in animal studies or human trials that it can treat viral diseases. As a result, Ivermectin is not approved for use as an antiviral.

In April, Australian researchers reported that the drug blocked coronaviruses in cell cultures, but they used a dosage that was so high that might have dangerous side effects in people. The FDA immediately issued a warning against taking pet medications to treat or prevent COVID-19. “These animal drugs can cause serious harm in people,” the agency warned.

Since then a number of clinical trials have been launched to see if a safe dose of ivermectin can fight COVID-19. In Singapore, for example, the National University Hospital is running a 5,000-person trial to see if it can prevent people from getting infected. As of now, there’s no firm evidence that it works. Nevertheless ivermectin is being prescribed increasingly often in Latin America, much to the distress of disease experts.

TENTATIVE OR MIXED EVIDENCE EVIDENCE IN CELLS

Oleandrin

Oleandrin is a compound produced by the oleander shrub. It can cause irregular heartbeats, making the plant dangerous to ingest. But many plant compounds — even some potentially lethal ones — have proven to be medically useful, and so researchers have investigated oleandrin as a potential treatment for cancer. The U.S.

Army Medical Research Institute of Infectious Diseases tested oleandrin on coronavirus-infected cells in May but the experiments were inconclusive. Researchers at Phoenix Biotechnology, a San-Antonio based company, and the University of Texas Medical Branch at Galveston then released a study finding that it was effective in a culture of monkey kidney cells infected with the coronavirus. The study has not yet been published in a scientific journal.

In July, Mike Lindell, the chief executive of My Pillow, a donor to President Trump and a Phoenix investor, attended a meeting at the White House to discuss oleandrin’s use against COVID-19.

But most compounds that kill viruses in cell cultures fail in further testing in animals or humans. What’s more, experts worry about the safety of oleandrin as a treatment for the coronavirus, given the toxicity of the plant. Phoenix Biotechnology is considering selling oleandrin as an over-the-counter supplement. Consumers should be aware that there is no evidence that it’s safe or effective against the coronavirus in people.

TENTATIVE OR MIXED EVIDENCE EVIDENCE IN CELLS AND HUMANS EMERGENCY USE AUTHORIZATION

Convalescent plasma

A century ago, doctors filtered plasma from the blood of recovered flu patients. So-called convalescent plasma, rich with antibodies, helped people sick with flu fight their illness. Now researchers are trying out this strategy on COVID-19.

In August, top government scientists reportedly stopped the F.D.A. from giving emergency authorization to convalescent plasma, arguing the evidence was still too weak for such a step. But President Trump announced on August 23 that the authorization would go ahead — a move that generated immediate controversy. In a statement, the N.I.H.’s COVID-19 Treatment Guidelines Panel underscored the importance of further investigation into convalescent plasma’s effectiveness. Despite the F.D.A.’s emergency authorization, the panel said “there are insufficient data to recommend either for or against the use of convalescent plasma for the treatment of COVID-19.”

A study of the Mayo Clinic’s program suggested that the treatment provided a modest benefit, but only to patients who got treated early in their disease with plasma packed with high levels of antibodies. Outside experts warned that only randomized clinical trials could confirm such a benefit.

Few randomized clinical trials have yet delivered results, and what evidence they’ve produced is mixed.

On September 10, for example, Indian researchers reported on a trial of 464 patients who were moderately ill — the point at which many researchers suspect plasma may provide its biggest benefit. The people who got the plasma fared no better than those that didn't.

Larger randomized clinical trials are underway, but they've struggled to enroll enough participants, some of whom worry they will receive a placebo instead of the treatment itself. Experts say that it's vital to complete these trials to determine if convalescent plasma is safe and effective. The treatment may only be a stopgap measure until more potent therapies become widely available.

TENTATIVE OR MIXED EVIDENCE EVIDENCE IN CELLS, ANIMALS AND HUMANS

Monoclonal antibodies

Convalescent plasma from people who recover from COVID-19 contains a mix of billions of different kinds of antibodies. Some of the molecules can attack the coronavirus, but the vast majority are directed at other pathogens. When the pandemic began, scientists began sifting through this slurry of antibodies and picked out a few dozen types that provide a potent defense against COVID-19 in cells and animals according to preclinical studies.

These potent molecules, known as monoclonal antibodies, have a long track record in medicine. Monoclonal antibodies were first investigated in the 1970s, and since then the F.D.A. has approved them for 79 diseases, ranging from cancer to AIDS. Over the summer, companies and universities began giving monoclonal antibodies for COVID-19 to patients in a number of clinical trials. On September 16, Eli Lilly announced promising preliminary results from a monoclonal antibody trial on 452 patients newly diagnosed with COVID-19. The drug reduced their risk of getting hospitalized by 72 percent compared to a placebo. Eli Lilly are continuing their trials, and results from other studies are expected to come out through the end of the year.

On October 2, the White House announced that President Trump received a dose of an experimental antibody cocktail from the drug maker Regeneron.

TENTATIVE OR MIXED EVIDENCE EVIDENCE IN CELLS, ANIMALS AND HUMANS

Interferons

Interferons are molecules our cells naturally produce in response to viruses. They have profound effects on the immune system, rousing it to attack the invaders, while also reining it in to avoid damaging

the body's own tissues. Injecting synthetic interferons is now a standard treatment for a number of immune disorders. Rebif, for example, is prescribed for multiple sclerosis.

As part of its strategy to attack our bodies, the coronavirus appears to tamp down interferon. That finding has encouraged researchers to see whether a boost of interferon might help people weather COVID-19, particularly early in infection. Early studies, including experiments in cells and mice, have yielded encouraging results that have led to clinical trials.

An open-label study in China suggested that the molecules could help prevent healthy people from getting infected. On July 20, the British pharmaceutical company Synairgen announced that an inhaled form of interferon called SNG001 lowered the risk of severe COVID-19 in infected patients in a small clinical trial. The full data have not yet been released to the public, or published in a scientific journal. On August 6, the National Institute of Allergy and Infectious Diseases launched a Phase III trial on a combination of Rebif and the antiviral remdesivir, with results expected by fall 2020.

TENTATIVE OR MIXED EVIDENCE EVIDENCE IN HUMANS

Cytokine Inhibitors

The body produces signaling molecules called cytokines to fight off diseases. But manufactured in excess, cytokines can trigger the immune system to wildly overreact to infections, in a process sometimes called a cytokine storm. Researchers have created a number of drugs to halt cytokine storms, and they have proven effective against arthritis and other inflammatory disorders. Some turn off the supply of molecules that launch the production of the cytokines themselves. Others block the receptors on immune cells to which cytokines would normally bind. A few block the cellular messages they send. Depending on how the drugs are formulated, they can block one cytokine at a time, or muffle signals from several at once.

Researchers are now trying out a number of different cytokine inhibitors against COVID-19 in clinical trials. So far, the results are mixed. In some trials, the drug tocilizumab has shown some evidence of reducing deaths, but has failed to help in others. A similar drug, sarilumab, did not appear to benefit patients in Phase 3 clinical trials.

Another drug, baricitinib, which can affect many types of cytokines at once, has shown some promise when doctors used it in combination with the antiviral drug remdesivir.

TENTATIVE OR MIXED EVIDENCE
EVIDENCE IN HUMANS
EMERGENCY USE AUTHORIZATION

Blood filtration systems

The F.D.A. has granted emergency use authorization to several devices that filter cytokines from the blood in an attempt to cool cytokine storms. One machine, called Cytosorb, can reportedly purify a patient's entire blood supply about 70 times in a 24-hour period. A small study in March suggested that Cytosorb had helped dozens of severely ill COVID-19 patients in Europe and China, but it was not a randomized clinical trial that could conclusively demonstrate it was effective. A number of studies on blood filtration systems are underway, but experts caution that these devices carry some risks. For example, such filters could remove beneficial components of blood as well, such as vitamins or medications. In September, a team of experts urged that blood filtration for COVID-19 be limited to randomized clinical trials.

TENTATIVE OR MIXED EVIDENCE
EVIDENCE IN HUMANS

Stem cells

Certain kinds of stem cells can secrete anti-inflammatory molecules. Over the years, researchers have tried to use them as a treatment for cytokine storms, and now dozens of clinical trials are under way to see if they can help patients with COVID-19. But these stem cell treatments haven't worked well in the past, and it's not clear yet if they'll work against the coronavirus.

TENTATIVE OR MIXED EVIDENCE
EVIDENCE IN HUMANS

Anticoagulants

The coronavirus can invade cells in the lining of blood vessels, leading to tiny clots that can cause strokes and other serious harm. Anticoagulants are commonly used for other conditions, such as heart disease, to slow the formation of clots. Doctors sometimes use them on patients with COVID-19 who have clots, but there's no clear evidence of what benefits and risks they offer to people with the disease. On September 10, the National Institutes of Health announced three large randomized clinical trials to evaluate anticoagulants on people with COVID-19 who have not yet been hospitalized, people who are being treated in hospitals, and people who have been sent back home.

TENTATIVE OR MIXED EVIDENCE
EVIDENCE IN HUMANS

Vitamin and mineral supplements

Our bodies need vitamins and minerals to work properly. Some researchers are investigating whether supplements might help against COVID-19, but there's no strong evidence yet that they prevent infections or speed up recovery from them.

Vitamin C is known to tamp down inflammation, and so some researchers are investigating whether it can help with the immune system's overreaction to COVID-19 in several clinical trials. No convincing data showing a benefit has emerged yet. It's also important to bear in mind that it's possible to ingest too much vitamin C, causing symptoms including diarrhea and nausea.

Vitamin D has also attracted attention. Along with promoting good bone health, it may play some role in helping immune cells function. Some studies have found an association between low levels of vitamin D and higher rates of COVID-19. But such studies cannot establish that this deficiency was the cause of those disease rates. It may be that populations who suffer high rates of vitamin D deficiency are getting hit harder by the coronavirus for other reasons, including poorer access to health care or underlying conditions like obesity. Some clinical trials are underway to test whether vitamin D can help COVID-19 patients.

A 2010 study on the coronavirus that causes SARS found that zinc can put the brakes on the replication of the virus in cultures of cells. Small clinical trials are now underway to see if zinc can provide any benefit to people with COVID-19 or even prevent it. As of yet, however, there is no evidence that it does either.

NOT PROMISING
EVIDENCE IN CELLS AND HUMANS

Lopinavir and ritonavir

Twenty years ago, the F.D.A. approved this combination of drugs to treat H.I.V. Recently, researchers tried them out on the new coronavirus and found that they stopped the virus from replicating. But clinical trials in patients proved disappointing. In early July, the World Health Organization suspended trials on patients hospitalized for COVID-19. They didn't rule out studies to see if the drugs could help patients not sick enough to be hospitalized, or to prevent people exposed to the new coronavirus from falling ill. The drug could also still have a role to play in certain combination treatments.

NOT PROMISING EVIDENCE IN CELLS, ANIMALS AND HUMANS

Hydroxychloroquine and chloroquine

German chemists synthesized chloroquine in the 1930s as a drug against malaria. A less toxic version, called hydroxychloroquine, was invented in 1946, and later was approved for other diseases such as lupus and rheumatoid arthritis. At the start of the COVID-19 pandemic, researchers discovered that both drugs could stop the coronavirus from replicating in cells.

Since then, they've had a tumultuous ride. A few small studies on patients offered some hope that hydroxychloroquine could treat COVID-19. The World Health Organization launched a randomized clinical trial in March to see if it was indeed safe and effective for COVID-19, as did Novartis and a number of universities. Meanwhile, President Trump repeatedly promoted hydroxychloroquine at press conferences, touting it as a "game changer," and even took it himself. The F.D.A. temporarily granted hydroxychloroquine emergency authorization for use in COVID-19 patients — which a whistleblower later claimed was the result of political pressure. In the wake of the drug's newfound publicity, demand spiked, resulting in shortages for people who rely on hydroxychloroquine as a treatment for other diseases.

But more detailed studies proved disappointing. Studies on animals such as monkeys and mice found no evidence that hydroxychloroquine stopped the disease. Randomized clinical trials found that hydroxychloroquine didn't help people with COVID-19 get better or prevent healthy people from contracting the coronavirus. Another randomized clinical trial found that giving hydroxychloroquine to people right after being diagnosed with COVID-19 didn't reduce the severity of their disease. (One large-scale study that concluded the drug was harmful as well was later retracted.) The World Health Organization, the National Institutes of Health and Novartis have since halted trials investigating hydroxychloroquine as a treatment for COVID-19, and the F.D.A. revoked its emergency approval. The F.D.A. now warns that the drug can cause a host of serious side effects to the heart and other organs when used to treat COVID-19.

In July, researchers at Henry Ford hospital in Detroit published a study finding that hydroxychloroquine was associated with a reduction in mortality in COVID-19 patients. The study was not a randomized controlled trial, in which some people got a placebo instead of hydroxychloroquine. The study's

results might therefore not be due to the drug killing the virus. Instead, doctors may have given the drug to people who were less sick, and thus more likely to recover anyway.

Despite negative results, a number of hydroxychloroquine trials have continued, although most are small, testing a few dozen or a few hundred patients. A recent analysis by STAT and Applied XL found more than 180 ongoing clinical trials testing hydroxychloroquine or chloroquine, for treating or preventing COVID-19. Although it's clear the drugs are no panacea, it's theoretically possible they could provide some benefit in combination with other treatments, or when given in early stages of the disease. Only well-designed trials can determine if that's the case.

PSEUDOSCIENCE OR FRAUD

Drinking or injecting bleach and disinfectants

Disinfectants can help slow the spread of the coronavirus, but only when used properly for cleaning your house and hands. Washing with soap is the best way to keep your hands clean, but alcohol-based sanitizers will do if you're not near a sink.

It's important to only use the right products. Never mix bleach and ammonia to disinfect surfaces, for example, because it can release toxic gas. As for hand-sanitizers, make sure to use brands with greater than 60% ethanol or 70% isopropanol. The FDA has warned that some sanitizers contain wood alcohol, or methanol, which can be dangerous.

PSEUDOSCIENCE OR FRAUD

UV light

Researchers have used UV light to sterilize surfaces, including killing viruses, in carefully managed laboratories. But UV light would not be able to purge the virus from within a sick person's body. This kind of radiation can also damage the skin. Most skin cancers are a result of exposure to the UV rays naturally present in sunlight.

PSEUDOSCIENCE OR FRAUD

Silver

Several metals do have natural antimicrobial properties, but none has been shown to be effective against the coronavirus. As for silver, the National Institutes of Health warns that "scientific evidence doesn't support the use of colloidal silver dietary supplements for any disease or condition." It can also be dangerous, causing people's skin to turn blue and making it difficult for them to absorb antibiotics and other drugs.

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“I’m a COVID-19 long-hauler and an epidemiologist – here’s how it feels when symptoms last for months

I imagine being young and healthy, a nonsmoker with no preexisting health conditions, and then waking up one morning feeling like you were being suffocated by an unseen force. Back in March, this was my reality.

I had just returned from Europe, and roughly 10 days later started having flu-like symptoms. I became weak overnight and had trouble breathing. It felt like jogging in the Rocky Mountains without being in condition, only I wasn’t moving. I went to the hospital, where I was tested for COVID-19.

More than four months later, the symptoms have not gone away. My heart still races, even though I am resting. I cannot stay in the sun for long periods; it zaps all of my energy. I have gastrointestinal problems, ringing in the ears and chest pain.

I’m what’s known as a long-hauler – part of a growing group of people who have COVID-19 and have never fully recovered. Fatigue is one of the most common persistent symptoms, but there are many others, including the cognitive effects people often describe as brain fog.

The frustration of not knowing

What made matters worse in the beginning was that my doctors were not certain I had COVID-19. My test was negative, and I had no fever, so my symptoms did not fit into early descriptions of the disease. Instead, I was diagnosed with a respiratory illness, prescribed the Z-pack antibiotic and a low dosage of an anti-inflammatory medication normally used for arthritis patients.

A Yale study released in May shows COVID-19 deaths in America do not reflect the pandemic’s true mortality rate. If I had died at home, my death would not have been counted as COVID-19.

By the end of March, I was on the road to recovery. Then I had a seizure. In the ER, the doctor said I had COVID-19 and that I was lucky – tests showed my organs did not have lasting damage. After the seizure, I lay in my bedroom for weeks with the curtains drawn, because light and sound had started to hurt.

The search for answers

I did not understand why I was not recovering. I began searching for answers online. I found a support group for people struggling with COVID-19 long-term. They called themselves long-haulers.

COVID-19 support groups show that there are many people not considered sick enough to be hospitalized – yet they are experiencing symptoms worse than the flu. It is possible COVID-19 is neurotoxic and is one of the first illnesses capable of crossing the blood-brain barrier. This might explain why many people like me have neurological problems. Many long-haulers are experiencing post-viral symptoms similar to those caused by mononucleosis and myalgic encephalomyelitis/chronic fatigue syndrome.

A common frustration is that some medical doctors dismiss their complaints as psychological. One woman in the support group wrote: “140 days later, so many are hard to breathe, and no doctors will take me seriously as I was diagnosed with a negative swab and negative antibodies.”

Like many long-haulers, my goal is to resume a normal life. I still grapple with a host of post-viral issues, including extreme fatigue, brain fog and headaches. I spend the majority of my day resting.

A big challenge long-haulers face may be sustaining employment.

Ultimately, it is too early to classify long-haulers as having a disability. Anthony Fauci reported that “it will take months to a year or more to know whether lingering COVID-19 symptoms in young people could be chronic illnesses.”

“it will take months to a year or more to know whether lingering COVID-19 symptoms in young people could be chronic illnesses.”



Margot Gage Witvliet
Assistant Professor of
Social Epidemiology,
Lamar University

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Conversation with *David Quammen*:

**HOW TO PREVENT THE NEXT
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Meet *Dr Shi Zhengli*, a virologist
who is often called China's
"bat woman":

**WAS THE CORONAVIRUS
ACCIDENTALLY RELEASED
FROM THE LAB?**

“Under the deployment of Hubei Provincial Government, our team, alongside researchers from Huazhong Agricultural University, collected environmental samples and frozen animal samples in Huanan seafood market. We detected SARS-CoV-2 nucleic acids only in the environmental samples such as roller shutter door handles, the ground and sewage, but not in the animals.”

- DR SHI ZHENGLI

HOW TO PREVENT THE NEXT PAN- DEMIC



Author David Quammen, wrote the book on coronavirus almost a decade ago. He published it in 2012. It's called *Spillover: Animal Infections and the Next Human Pandemic* and it expounds on a threat that epidemiologists have known about for decades, animal-borne or zoonotic diseases jumping the species barrier and becoming global disasters. The title 'spillover' was the result of five years of research on scientists who were looking into the possibility of another Ebola-type disease emerging.

David Quammen predicted everything. There would indeed be a new disease, likely from the coronavirus family, coming out of a bat, and it would likely emerge in or around a wet market in China. But what was not predictable was how unprepared we would be.

After the appearance of COVID-19 many dashed to the bookshops, for no other reason than the fact that Quammen had described the way in which the pandemic would arise, identifying a wet-market as the place from where the contagion would spread. COVID-19, however, is already a reality. What can we expect from the future? We discussed this and other matters with the American science journalist. To avoid future pandemics, he says, we must rethink our relationship with nature and recognize how our choices can lead to dangerous disruptions of the natural world.

When you wrote *Spillover* in 2012, you warned that we were going to face the same situation we're faced with now — a virus that spills over from animals into humans and spreads around the globe. And scientists warned us three years ago about the emerging novel coronavirus. Yet the world now finds itself unprepared for this outbreak. Has that surprised you at all?

David Quammen: Yes, the lack of preparedness is the only thing about this whole situation that has surprised me. I didn't have any illusions that the people who control the wheels of power and government were listening carefully to the scientists, but I thought they were listening at least enough to have some preparedness. Everything about this outbreak was predictable, to the scientists I was listening to, and to me 10 years ago.

New virus coming out of an animal, yes, predictable. Animal was a bat, yes, predictable. Virus is a coronavirus, yes, predictable. Happens in or around a wet market in China, yes, predictable.

What was not predictable was how completely unprepared we would be.

Still, I am surprised at how unprepared we've been and how badly we have managed this thing. It's appalling.

You've been out in the field with the scientists who go searching for new viruses in wild animal populations. This virus was actually discovered and then identified in China in 2017. How did researchers come upon this virus?

Scientists have known that coronaviruses are dangerous because SARS was a coronavirus. Coronaviruses have been one of the groups at the top of the watch list. It has also been known that small bats, insectivorous bats, such as horseshoe bats, carry coronaviruses in some variety, unknown, and that those bats live, among other places, in Southern and Central China where they roost in caves. If a bat roosts together with thousands of other bats in these cozy huddles or scrums, that is a great situation for passing viruses. So a team from the Wuhan Institute of Virology, among other institutions, led by a woman named Dr. Shi Zhengli, went to caves in Yunnan Province and captured bats. They took blood samples. They looked for coronaviruses, and in 2017, they came out with a paper announcing that they had found a new coronavirus and identified its genome sequence.

It seems like many of these viruses originate in bats. Is there any sense of why that is so?

A couple of things make bats more likely to seem as though they are overrepresented as the reservoir hosts of these viruses. First of all, bats are an incredibly diverse order of mammals. One in every four species of mammal on the planet is a species of bat. They would naturally seem overrepresented because they are overrepresented in mammal diversity.

Beyond that, there are actual physiological reasons. Bats tend to live a long time — some of them can live 18 to 20 years. If a bat lives 18 to 20 years, and if it roosts together with thousands of other bats in these cozy huddles or scrums on the wall of a cave, 60,000 bats, essentially, in a pileup on the wall of a cave, then that is a great situation for passing viruses from one individual to another endlessly, round and round, so that the virus continues circulating in the bat population.

In the case of novel coronavirus and others, these bats made their way into animal markets and then spread from there to humans. I know you've been to one of those markets in China. Can you describe what it was like?

I was there during one of the periods of suppression of the [wild animal] trade [after the 2003 SARS outbreak]. But frogs were still legal. Turtles were still legal. I didn't see bats. But I saw a ton of wild birds of all sorts that had been captured, not for pets but for food, and all caged in a great jumble, with water flowing and blood flowing, and butchery happening in a pretty unhygienic environment.

There is a vogue in China now for what's called



Spillover: Animal Infections and the Next Human Pandemic
by David Quammen

"wild flavor." There's this vogue for eating wild animals: porcupines, bamboo rats, palm civets, pangolins, bats, frogs, snakes, tortoises, turtles, et cetera, and more. There are these markets that periodically operate in the open. Then sometimes, the Chinese enact regulations against them, which they did after the SARS outbreak. This wild animal trade was driven underground. It never disappeared, but it was happening out the back doors of restaurants and other places. Some people say, "Well, this is an ancient tradition in China. This is going to take a lot of education to move people away from it." But I have a Chinese colleague who looked into this and read some of the ancient Chinese sources. Those ancient Chinese sources were saying the opposite. They were saying, "Don't eat wild animals. You're liable to get sick. No, wild animals are not healthy."

I think it's a myth that this is an ancient and revered tradition. What it is more likely is a vogue. It's not like what we call bushmeat in Africa, which to a considerable degree is consumed by people in the countryside, people in villages who live close to the forest who desperately need protein. It's true that bushmeat in Africa is also traded commercially. There are chimpanzees being killed, and shipped, or trucked to capital cities where people with money pay fancy prices to be able to eat chimpanzee meat. It's a vogue in parts of Africa. But of course, in Montana, where I live, it's also a vogue. We eat deer and elk, and we call it wild game.

What underlies this whole issue, really, is our relationship with nature, how it's changed, and the way we keep pushing more and more into habitat and increasing human contact with animals. Do you see that as the heart of the issue?

That is absolutely the heart of the issue, yes. Our relationship with the rest of the natural world, which is consumptive, and intrusive, and disruptive. Those things shake loose viruses from their natural hosts. All these wild animals carry their own unique viruses. When we go into a tropical forest with its great diversity, and we start cutting down trees, and capturing animals, or killing animals for food, then we offer those viruses the opportunity to become our viruses, to jump into us and find a new host, a much more abundant host. And when a virus moves from an infected animal into a human, it's won the sweepstakes. It can now spread around the world and become one of the world's most successful viruses, which this coronavirus now is.

The problem is that when there's no outbreak, there's no interest in discovering new viruses, and there's no money for it.

Why don't these viruses affect their animal hosts, but they do affect humans?

The reason they don't seem to affect their animal hosts is because they probably, in most cases, have lived in that animal host for thousands or millions of years. There has been a coadaptation. The animal host is called the reservoir host, and the usual relationship between a virus and a reservoir host is that the virus exists at relatively low levels. It's not fulminating inside the reservoir hosts' individual bodies. It's not replicating as fast as it might. It's not causing organ shutdown in that animal. It's just living there.

Then it happens to spill over into a new host, say, a human. It's a new environment. If the virus has the broad adaptive capacity, a relatively wide niche, it might already be adapted, and it finds that, okay, I can get along in this other mammal pretty well. I can get into the cells of this new mammal, this one that's wearing a wristwatch and clothes. I can replicate in that first cell and come busting out of that cell, and I can get into another one. And I can even do that in the respiratory tract which means, holy cow, now I have the opportunity to come flying out of this host the next time I succeed in making him cough, and maybe I can get into a new host.

Now I'm a human virus traveling from one human to another. But it's a new relationship. I don't have an old co-evolved relationship with this host. I'm going to replicate as fast as I damn well can, and make myself abundant and seize this new opportunity for vast, evolutionary success by going from one host to another at high levels. Before you know it, I'm going to be one of the most successful viruses in the world. It's all ecology and evolutionary biology.

This whole subject seems to fuse the two overarching topics of your work, which are ecology and evolution. Do you see it that way?

Absolutely. That's the reason I got interested in this whole crazy field 20 years ago or so. I started reading about Ebola, and I realized there was the question of Ebola and where it goes when it's not killing humans. Oh, it's got a reservoir host. What's the reservoir host? Well, we don't know. We haven't found it yet. There's a mystery story there. I realized that it was all about ecology and evolutionary biology, the ecology of scary viruses, and the evolutionary biology of scary viruses, and the hosts that they live in. That was right over the plate for me, that was in my wheelhouse of evolutionary biology.

You've been out with the scientists who are virus hunters, people who are looking for the origins of these viruses. Funding for this kind of work, not to mention for preparedness for outbreaks, has been cut. There's not enough?

No, there's not enough. There's never enough money for this kind of important research. Some call it viral discovery, finding out what's out there that might be

dangerous. The problem is that when there's no outbreak, there's no interest in discovering new viruses, and there's no money for it. When there's an outbreak, it's a medical emergency, so you can't get money to go out there and do the basic ecological research to identify the host. If there are people dying in Liberia, Sierra Leone, or Guinea, you can't go in there with your white suits and say, "Oh, we're not dealing with people. We want to go into the forest, and trap some bats, and take blood samples."

There's never enough money. There are organizations that are doing this and doing wonderful work. But there's not enough, just the way there's not enough money for actual preparedness for various reasons, including the fact that if you spend \$5 billion on preparedness against the pandemic and then the pandemic doesn't happen during your first presidential term, then when you run for your second term, people are going to criticize you for having wasted that money.

When do you think this pandemic will be over?

Somebody made the casual statement that, "In six months or a year maybe this virus will be gone." This virus is not going to be gone. This virus is never going to be gone. We have friends who have children and grandchildren, and their great-grandchildren will be vaccinated against this virus.

Vaccine development takes a long time, and a lot of luck. And then vaccine manufacturing at scale takes another truckload of time... There's a ridiculous amount of hoopla for a tiny sample size at a very preliminary stage.

It's important to remember that responsibility for this includes everybody; it's not just the fault of some Chinese people who eat pangolins or bats. Nor is it the fault of African people who eat bushmeat that sometimes includes primates. This is the responsibility of all 7.8 billion of us, because we are all consumers of food, resources, and energy. Each of the choices that we make

about what we're going to eat, wear, or buy draws on these wild ecosystems.

What's new is that there's 7.8 billion of us on this planet—four times the number of humans at the time of the 1918 influenza. And we have quadrupled the speed we travel around the planet; we have quadrupled the size of some of our cities. So there are a lot more of us large-bodied vertebrate animals, living in dense aggregations, moving fluidly from one place to another.

We're the world's greatest target for a virus—a great ecosystem for them to colonize. So when a virus does get into a human and finds it can replicate and transmit to the next human, that virus has opened the door to vast opportunity.

Consequently, in the last 60 years, there's been this drumbeat of what are called spillovers, where new viruses get into humans and cause trouble: Machupo, or Bolivian hemorrhagic fever, in 1959. Marburg, 1967, coming out of monkeys that were sent to Marburg, Germany for research purposes. Ebola first emerging in 1976, MERS in 2012, Zika in 2015, and this. So it's happening more, with greater consequences, and greater potential to spread worldwide.

Is there anything we can do to reduce the chances of the next big pandemic or at least be better prepared for it?

Yes. We can reduce the chances both of spillovers occurring and of spillovers turning into outbreaks, epidemics, pandemics. The less disruptive contact that we have with wild animals, the less chance there is for there to be a spillover of a dangerous new virus into the first human. We can do some things about that: cutting down on the wild animal trade, cutting down probably on the meat that we eat, cutting down on our disruption of wild animals and diverse ecosystems. We'll then bring a lessening of the opportunities for these viruses to spill over into a single human. Once a spillover happens, we can improve our scientific and technological ways of detecting that very quickly, and our public health measures for isolating an outbreak before it becomes an epidemic.

The big events don't happen every year, but they may happen once every 10 years. A new, really dangerous virus comes blasting out of some particular country. It gets on airplanes with people, and it rides around the world. When we know this virus is getting loose, our responses at that point can be much better. We can have real-time detecting, screening of people, positive or negative, at airport security points, if we develop the technology to do that. I thought that was going to be done by now. I heard about that 10 years ago, and it still hasn't happened.

Do you think that this will finally spur action on that?

I hope so, but I'm not confident. Still, I am hopeful that this should make a difference, that this will shock us into better preparedness.

“What’s new is that there’s 7.8 billion of us on this planet—four times the number of humans at the time of the 1918 influenza.”

Was the coronavirus accidentally released from the lab?

Meet Dr Shi Zhengli, a virologist who is often called China's "bat woman" by her colleagues because of her virus-hunting expeditions in bat caves over the past 16 years. The COVID-19 pandemic has thrust Shi Zhengli into a fierce spotlight.

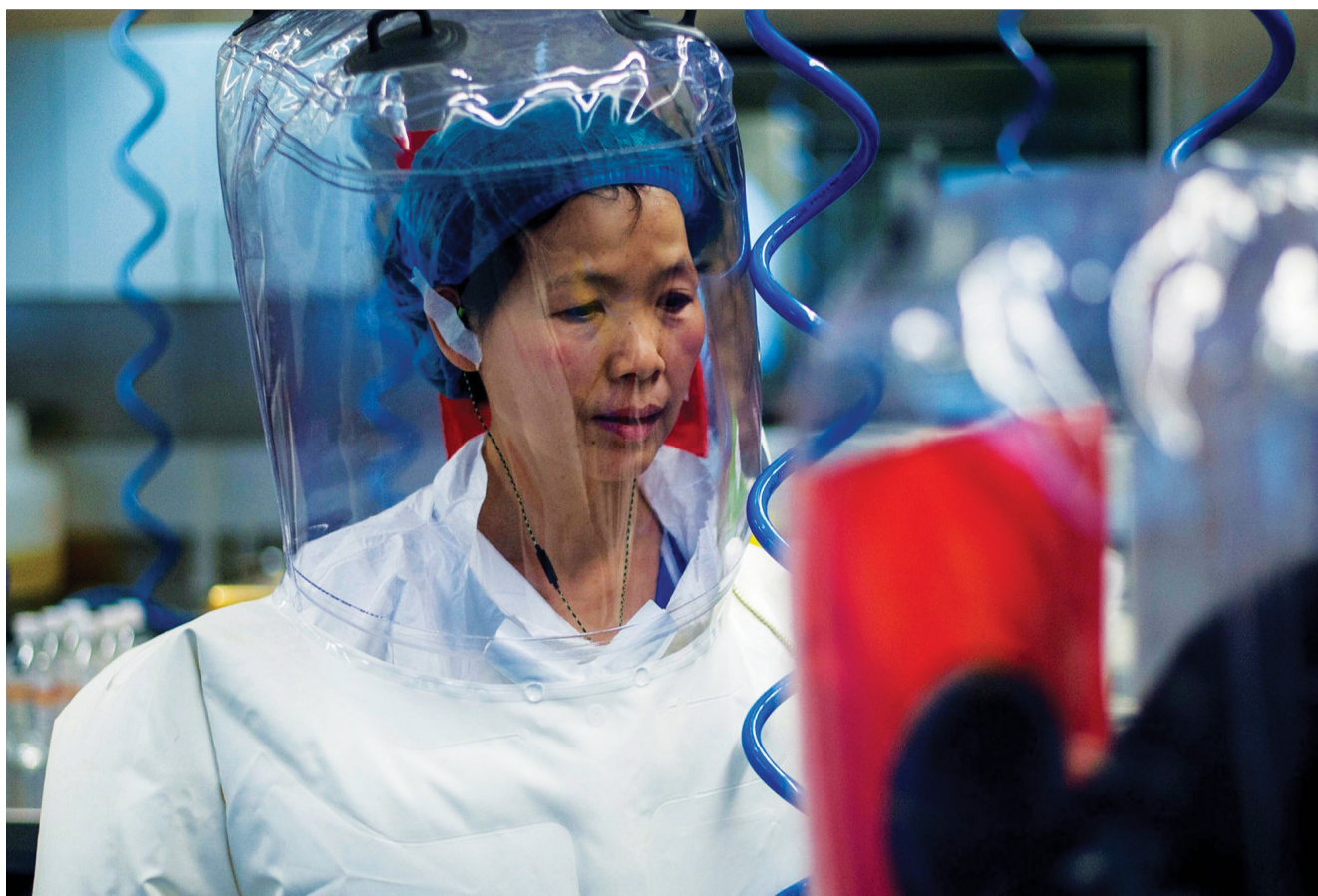
A bat virus specialist known as China's "batwoman" and her lab in Wuhan have become the centre of a conspiracy theory related to the origin of the coronavirus. The U.S. President Donald Trump insists he has seen evidence coronavirus was leaked from the Wuhan Institute of Virology, in the city where the outbreak began in January.

Meet Dr Shi Zhengli, a virologist who is often called China's "bat woman" by her colleagues because of her virus-hunting expeditions in bat caves over the past 16 years. The COVID-19 pandemic has thrust Shi Zhengli into a fierce spotlight. Shi heads a group that studies bat coronaviruses at the Wuhan Institute of Virology (WIV), in the Chinese city where the pandemic began. Many have speculated that SARS-CoV-2, the pathogen that causes COVID-19, accidentally escaped from her lab. Some have even suggested it could have been engineered there. China has forcefully rejected such claims, but Shi herself has said very little publicly—until now. In this interview, Shi emailed answers to a series of questions about the virus' origin and her research. In them, Shi hit

back at speculation that the virus leaked from WIV. Shi and her colleagues discovered the virus in late 2019, Shi says, in samples from patients who had a pneumonia of unknown origin. "Before that, we had never been in contact with or studied this virus, nor did we know of its existence," Shi wrote.

Shi Zhengli, the 55-year-old scientist had been looking to make a mark on bat-linked virology, an area to which she has dedicated her life. For years, Ms Shi has collected strains of coronaviruses from bats. In 2004, she identified a reservoir for such diseases in bat caves in Yunnan province in southern China and she has been at the forefront of research on how viruses such as Sars may have jumped to humans.

Wuhan Institute of Virology was set up in 1956 as a microbiology lab, one of the first of its kind in the country following the communist takeover of China seven years earlier. As a level-4 biosafety facility, the highest level of security in China, it is allowed to handle the world's deadliest viruses. Scientists at the facility are known to have created hybrid versions of a bat coronavirus that could infect human cells. *Nature*, the



scientific journal, published an article in 2015 that raised questions about the level of risk associated with such research. This has contributed to theories that the virus could have originated as a leak from the lab. However, the journal added a note to the report in March this year stating: “We are aware that this story is being used as the basis for unverified theories that the novel coronavirus causing COVID-19 was engineered. There is no evidence that this is true; scientists believe that an animal is the most likely source of the coronavirus.”

You have published many papers on coronaviruses and even warned of the possibility of a serious spill-over event from animals to humans. Do you feel like your warnings were not appropriately heeded and how does what you imagined compare to the scale of this pandemic?

The risk of cross-species infection always exists. With regards to this issue, China has undertaken scientific research projects, created facilities and equipment, and built teams of experts. With global environmental change and the expansion of human activity, the risk of infection continues to increase, which is confirmed

and supported by our research. However, our study did not involve an investigation into the pandemic’s scale.

How has the pandemic affected you, personally and professionally?

This pandemic has made me realize the importance of our work and the necessity of pursuing it. I think if we could do more basic research and technological development on vaccines and therapeutic drugs, we would do better in this regard.

What are your leading theories about the origin of SARS-CoV-2 and has your own research shed any light on the question?

According to the findings of our team and our international peers, SARS-CoV-2 is very likely to have originated from bats. It may have evolved in one or more intermediate hosts, become adapted to humans, and eventually spread among humans. However, it remains unclear which animals were the intermediate hosts and how it spilled over to humans.

Assuming this was natural event, a virus jumping species somewhere, how do you think this likely happened? Do you think it’s possible that a bat in

or close to Wuhan infected someone? If not, where could this have taken place? What do you think of the theory that infected people who lived near mines were the index cases and that they traveled to Wuhan?

There are two possibilities for the cross-species transmission from the natural host to humans. One is that the virus was transmitted directly from a bat to a human, while the other is that the virus spread to humans via one or more intermediate hosts. For SARS-CoV-2, though the first possibility cannot be ruled out, its likelihood is very low. I tend to support the second scenario.

When and where the earliest cross-species transmission of SARS-CoV-2 occurred from the intermediate host to humans has not been scientifically uncovered yet. We know from historical experience like HIV that the places where big emerging diseases first break out usually are not their place of origin (where the spillover originally happened). Tracing the origin of a virus is a very challenging scientific task. As for the origin and transmission routes of SARS-CoV-2, it needs a pioneering vision, and the collective efforts of scientists all around the world, and it needs time as well.

We have done bat virus surveillance in Hubei Province for many years, but have not found that bats in Wuhan or even the wider Hubei Province carry any coronaviruses that are closely related to SARS-CoV-2. I don't think the spillover from bats to humans occurred in Wuhan or in Hubei Province.

I guess you are referring to the bat cave in Tongguan town in Mojiang county of Yunnan Province. To date, none of the nearby residents is infected with coro-

“I think the coronavirus carried by the natural host would have undergone transmission by at least one intermediate before it evolved into SARS-CoV-2.”

naviruses. Thus the claim that the so-called "patient zero" was living near the mining area and then went to Wuhan is false.

An early cluster at the Huanan seafood market in Wuhan led many to think that an animal there somehow infected humans. How has your thinking about the seafood market's role evolved as it became clear that many of the earliest cases are not linked to it?

As you pointed out, some early patients do not have a history of Huanan seafood market exposure. We detected SARS-CoV-2 nucleic acids in environmental samples from sources such as rolling door handles, the ground and sewage in that market, but we did not detect any SARS-CoV-2 nucleic acids in frozen animal samples. The Huanan seafood market may just be a crowded location where a cluster of early novel coronavirus patients were found.

Do you know whether anyone tested animals from the market? If not, why not?

Under the deployment of Hubei Provincial Government, our team, alongside researchers from Huazhong Agricultural University, collected environmental samples and frozen animal samples in Huanan seafood market. We detected SARS-CoV-2 nucleic acids only in the environmental samples such as roller shutter door handles, the ground and sewage, but not in the animals.

Is there an attempt to use registries from the market to test farms that supplied animals to the market? Has your group or any other done testing of domesticated animals or wild animal farms at any farms for SARS-CoV-2 like viruses? If so, what has research found?

Under the deployment of the Hubei Provincial Government, our team and researchers from Huazhong Agricultural University collected samples of farmed animals and livestock from farms around Wuhan and in other places in Hubei Province. We did not detect any SARS-CoV-2 nucleic acids in these samples.

Were you ever given environmental or animal samples from the market to test yourself? If so, what did you find? If not, what do you know about the market samples tested?

We detected SARS-CoV-2 nucleic acids in environmental samples from the Wuhan seafood market, including on rolling door handles, on the ground and in sewage, but the detected numbers of viral genome copies were very low.

The earliest case report I'm aware of has a patient, unlinked to the seafood market, who had symptoms on December 1. One news story suggests there were cases in November. What is the earliest confirmed

case you are aware of and what are the demographics?

I did not participate in the epidemiological survey and I don't know much about it. It was on December 30, 2019 that our Institute first received the clinical samples of a "pneumonia with unknown etiology".

Where do you think the zoonotic transmission most likely occurred? Wuhan? Hubei? Elsewhere?

I can't make any conclusions before we have solid evidence. Tracing the virus's origins is a scientific question, which ought to be answered by scientists based on solid data and scientific evidence. However, the historical experience I mentioned above is worth attention.

You have reported the existence of a bat coronavirus, RaTG13. It's clear that this is a distant ancestor of SARS-CoV-2 that differs by 1100 nucleotides. Using molecular clocks, other researchers have estimated that RaTG13 and SARS-CoV-2 shared a common ancestor at least 20 years ago. Have you made your own estimates? Do you think there was an intermediate species between bats and humans, and, if so, what do you think is most likely and why? What do you think of the pangolin data and suggestions that it might be an intermediary?

I am not an expert in bioinformatics, so I did not calculate the evolutionary distance between RaTG13 and SARS-CoV-2. I think the coronavirus carried by the natural host would have undergone transmission by at least one intermediate before it evolved into SARS-CoV-2.

The gene sequences of pangolin coronavirus, RaTG13 and SARS-CoV-2, are relatively close and they may have a common ancestor. But with the data currently available, I can't determine whether pangolins are the natural host or an intermediate host.

Have you or anyone else you're aware of contacted veterinarians about possible illnesses in animals that occurred that could be SARS-CoV-2 relatives? If so what have you learned?

No. I don't have any information on that.

Your group did a fascinating study with cats, showing that 15% of 102 stray and house cats in Wuhan had antibodies for SARS-CoV-2. A research group in Harbin separately showed cats could readily be infected and transmit the virus. Cats have been infected presumably by infected humans in homes, and even big cats were infected, at a zoo in New York. How likely do you think it is that cats might be more involved in spread than is commonly thought?

The results of our tests of SARS-CoV-2 antibodies in cat sera, collected in Wuhan after the COVID-19 outbreak, revealed that the infection rate and antibody

titers of SARS-CoV-2 in house cats was higher than in stray cats. So I think the SARS-CoV-2 infections in cats were very likely to have been transmitted by humans.

Could cats have been the intermediate species between bats and humans? Have you thought of this possibility? Has anyone studied it? I know in your study sera from cats pre-outbreak didn't harbor SARS-CoV-2 antibodies, but that was a small sample. Have you considered broadening that investigation?

Further research needs to be conducted to investigate whether cats are potential intermediate hosts of SARS-CoV-2. Currently our lab is not continuing with the studies on cats. Based on the current findings of our lab and other teams, it is probable that the viruses were transmitted from humans to cats.

Do you know which Chinese labs are investigating origin possibilities and what are they studying? Do you know why so few papers have been published that have new data?

Many groups in China are carrying out such studies. We are publishing papers and data, including those about the virus's origins. We are tracing the origin of the virus in different directions and through multiple approaches.

The Wuhan Institute of Virology has received worldwide attention as the possible source of SARS-CoV-2. President Donald Trump has said he has "high confidence" the virus came from the lab. What kind of an impact has this had on your lab? And on you personally?

We first received the clinical samples of SARS-CoV-2 on December 30 2019, which were called back then samples of "pneumonia with unknown etiology". Subsequently, we rapidly conducted research in parallel with other domestic institutions, and quickly identified the pathogen. The complete genome sequence of SARS-CoV-2 was submitted and published via WHO on January 12. Before that, we had never been in contact with or studied this virus, nor did we know of its existence.

Scientists from around the world have overwhelmingly concluded that SARS-CoV-2 originated naturally rather than from any institution. The US President Trump's claim that SARS-CoV-2 was leaked from our institute totally contradicts the facts. It jeopardizes and affects our academic work and personal life. He owes us an apology.

Many scientists who have analyzed the sequence of SARS-CoV-2 have concluded that it does not have the signatures of a lab-engineered virus. But even some of these researchers say it remains possible that SARS-CoV-2 existed in your lab and accidentally infected a

lab worker. They note that several labs had accidental infections with the virus that causes SARS. So how can you rule out this possibility?

We have isolated three closely-related bat coronaviruses over the last 15 years (here an isolated virus is a live virus which can grow in cultured cells in the laboratory) and all of them are SARS-related coronaviruses. These bat viruses share 79.8% sequence identity and are distantly related to SARS-CoV-2. On February 3, we published a paper in *Nature* and reported that SARS-CoV-2 is 96.2% identical at the whole-genome level to a bat coronavirus named RaTG13 (I would like to emphasize that we have only the genome sequence and didn't isolate this virus). With about 30,000 nucleotides, coronaviruses have a larger genome size than most animal RNA viruses. The 3.8% difference in genome sequence is a significant difference for coronaviruses. Five renowned virologists from Scripps Research Translational Institute, Columbia University, Tulane University, the University of Edinburgh and the University of Sydney published a paper titled "The proximal origin of SARS-CoV-2" in *Nature Medicine* on March 18. The authors stated that "although RaTG13 is 96% identical overall to SARS-CoV-2, its spike diverges in the receptor binding domain." On April 23, the US news site "VOX" quoted opinions from Prof. Edward Holmes, an expert in virus evolution at the University of Sydney. "The level of genome sequence divergence between SARS-CoV-2 and RaTG13 is equivalent to an average of 50 years (and at least 20 years) of evolutionary change," said Professor Holmes. The genomes of RaTG13 carried by bats and SARS-CoV-2 differ in 1,177 nucleotide positions. It would have taken a very long time to accumulate suf-

“We tested all bat samples that we collected, including bat anal swabs, oral swabs and fecal samples, and 2,007 samples were positive for coronavirus.”

ficient numbers of mutations through natural evolution. The probability is extremely tiny that the mutations occurred exactly in these 1,100-plus positions to be identical to SARS-CoV-2. Therefore, RaTG13 evolving into SARS-CoV-2 in nature is only theoretically possible.

Meanwhile, the research and experiments in our institute are in strict accordance with the international and national management requirements of biosafety laboratories and experimental activities, which are conducted in the required biosafety laboratories. Both the facilities and management of P3 and P4 laboratories are very strict. For example, personal protective equipment must be worn by the research staff. The air in the laboratory can only be discharged after highly efficient filtration. Waste water and solid waste must be sterilized under high temperatures and high pressure. The entire process of the experimental activities is video-monitored by biosafety management personnel. Every year, the lab's facilities and equipment must be tested by a third-party institution authorized by the government. Only after passing the test can the lab continue to run. The high-level biosafety laboratories at our institute have been operated safely and stably. To date, no pathogen leaks or personnel infection accidents have occurred.

The people who have floated these theories have proposed several ways in which the virus could have escaped from the Wuhan Institute of Virology. I'd like to ask some detailed, factual questions about the work at your lab that could shed more light on those scenarios:

(1) Are bat coronaviruses grown at the institute?

We have only isolated three strains of live SARS-related coronaviruses (SARSr-CoV) from bats, which shared 95-96% genome sequence similarity with SARS-CoV and less than 80% similarity with SARS-CoV-2. These results were published in *Nature* [2013, 593(7477):535-538], the *Journal of Virology* [2016, 90(6), 3253-3256] and *PLoS Pathogens* [2017, 13(11):e1006698], respectively.

(2) Does your group extract viruses from biological samples and do the sequencing or does that take place elsewhere?

We isolated viruses or extracted virus RNA from biological samples in the lab. The sequencing was done mostly in Wuhan.

(3) Has your lab done any animal experiments with SARS-related viruses recently? If so, can you provide any details?

We performed in vivo experiments in transgenic (human ACE2 expressing) mice and civets in 2018 and 2019 in the Institute's biosafety laboratory. The viruses

Wuhan Institute of Virology



we used were bat SARSr-CoV close to SARS-CoV. Operation of this work was undertaken strictly following the regulations on biosafety management of pathogenic microbes in laboratories in China. The results suggested that bat SARSr-CoV can directly infect civets and can also infect mice with human ACE2 receptors. Yet it showed low pathogenicity in mice and no pathogenicity in civets. These data are being sorted and will be published soon.

(4) Is it possible that someone associated with the institute became infected in some other way, for instance while collecting, sampling, or handling bats?

Such a possibility did not exist. Recently we tested the sera from all staff and students in the lab and nobody is infected by either bat SARSr-CoV or SARS-CoV-2. To date, there is "zero infection" of all staff and students in our institute.

(5) Is it possible that you have biological samples from bats in your lab that you have yet to test for viruses? If so, how many samples have you tested and how many remain untested? If some remain untested, how do you know for certain that none contain SARS-CoV-2 or a close relative?

We tested all bat samples that we collected, including bat anal swabs, oral swabs and fecal samples, and 2,007 samples were positive for coronavirus. We did not find any viruses whose gene sequence is more similar to SARS-CoV-2 than RaTG13.

(6) Your lab was one of the first to sequence and isolate the virus. When and where did you first sequence it?

We received the first batch of samples from seven patients on December 30 2019. Using pan-coronavirus RT-PCR and quantitative RT-PCR, which can detect all SARS-related coronaviruses, we found samples from five patients were positive. On December 31, when analyzing the sequencing result of the RT-PCR product, we identified that it was a novel SARS-related coronavirus. We

then confirmed the result via different methods and performed full-length genome sequencing as well as virus isolation. We released the genome sequence to the global public on January 12 via WHO.

(7) What about the cave at Mojiang in 2013? When did you first isolate RaTG13? When did you complete the full sequencing of it?

We detected the virus by pan-coronavirus RT-PCR in a bat fecal sample collected from Tongguan town, Mojiang county in Yunnan province in 2013, and obtained its partial RdRp sequence. Because of the low similarity of this virus to SARS-CoV, we did not pay special attention to this sequence. In 2018, as the NGS sequencing technology and capability in our lab was improved, we did further sequencing of the virus using our remaining samples, and obtained the full-length genome sequence of RaTG13 except the 15 nucleotides at the 5' end. As the sample was used many times for the purpose of viral nucleic acid extraction, there was no more sample after we finished genome sequencing, and we did not do virus isolation and other studies on it. Among all the bat samples we collected, the RaTG13 virus was detected in only one single sample. In 2020, we compared the sequence of SARS-CoV-2 and our unpublished bat coronavirus sequences and found it shared a 96.2% identity with RaTG13. RaTG13 has never been isolated or cultured.

(8) Some people who suspect a lab accident occurred have suggested that BtCoV/4991, a bat virus you described in 2016, is SARS-CoV-2. When you published, you only had the sequence of one protein, RNA dependent RNA polymerase (RdRp). A blast analysis on GenBank shows that the RdRp of BtCoV/4991 and RaTG13 are 100% homologous. Is BtCoV/4991 actually RaTG13, which would be consistent with your 2020 report that described how you did the full sequence of a virus you only had done the RdRp sequence for earlier? If so, why did you rename the virus? What does "TG" stand for in RaTG13?

Ra4991 is the ID for a bat sample while RaTG13 is the ID for the coronavirus detected in the sample. We changed the name as we wanted it to reflect the time and location for the sample collection. 13 means it was collected in 2013, and TG is the abbreviation of Tongguan town, the location where the sample was collected.

(9) Why do you have RdRp sequences for some viruses and not their full sequences? How many full-length sequences are there of the samples you've tested and how many are just RdRp?

Due to financial and manpower constraints, it is impossible for us to do the whole genome sequencing

of all samples. We hope to conduct further full-length coronavirus genome sequencing in some other samples within the next two years. However, for some samples, it is impossible to obtain the whole virus genome sequences because of the low quantity of the viral nucleic acids in them.

(10) Were you ever instructed to destroy any viruses after the outbreak surfaced?

No.

(11) Is it possible that there was an accidental release at another lab in Wuhan? The Wuhan Center for Disease Control has been mentioned. If you have ruled this out as a possibility, why?

Based on daily academic exchanges and discussion, I can rule out such a possibility.

(12) What haven't I asked you that you would like people to know?

With the continuing occurrences of emerging infectious diseases all over the world, scientists are beginning to study the viruses carried by wild animals, which is not only the key to having early warnings of the diseases from those origins, but also an important scientific basis for disease prevention. In this context, I have conducted collaborative research with Dr. Peter Daszak, President and PI of EcoHealth Alliance. We have established a good relationship in the fields of virus surveillance and pathogen discovery. Our research team has found a variety of coronaviruses with different sequences in bat populations. Some of them have the potential to spread to humans and animals, such as SARS-related coronavirus, MERS-related coronavirus, SARS-related coronavirus, etc. The findings provide important clues for the prevention and control of infectious diseases.

We don't understand the NIH termination of funding

support for our collaborative project and feel it is absolutely absurd. This project should be an international cooperative work aiming to gather scientists from different countries to jointly explore early warnings and predictions of infectious diseases, which will help vaccine design and drug development to protect us from coronavirus threats.

Over the past 20 years, coronaviruses have been disrupting and impacting human lives and economies. Here, I would like to make an appeal to the international community to strengthen international cooperation on research into the origins of emerging viruses. I hope scientists around the world can stand together and work together. The purpose of the search for the origin of a virus is to prevent the recurrence of similar outbreaks which will harm human society, and in this way, we can respond more effectively when an outbreak happens.

Did you do or collaborate on any gain-of-function experiments with coronaviruses that were not published, and, if so what are the details?

No.

Given that coronavirus research in most places is done in BSL-2 or BSL-3 labs--and indeed, you WIV didn't even have an operational BSL-4 until recently--why would you do any coronavirus experiments under BSL-4 conditions?

The coronavirus research in our laboratory is conducted in BSL-2 or BSL-3 laboratories.

After the BSL-4 laboratory in our institute has been put into operation, in accordance with the management regulations of BSL-4 laboratory, we have trained the scientific researchers in the BSL-4 laboratory using the low-pathogenic coronaviruses as model viruses, which aims to prepare for conducting the experimental activities of highly pathogenic microorganisms.

After the COVID-19 outbreak, our country has stipulated that the cultivation and the animal infection experiments of SARS-CoV-2 should be carried out in BSL-3 laboratory or above. Since the BSL-3 laboratories in our institute do not have the hardware conditions to conduct experiments on non-human primates, and in order to carry out the mentioned research, our institute had applied to the governmental authorities and obtained the qualification to conduct experiments on SARS-CoV-2 for Wuhan P4 laboratory, in which the rhesus monkey animal model, etc. have been carried out.

The experimental activities are supervised by our institute's biosafety committee and complied with the biosafety regulations.

“Over the past 20 years, coronaviruses have been disrupting and impacting human lives and economies.”

Research

**The Etiological Spectrum
of Dizziness Observed at
a Vertigo Clinic: A Study
of a Dubai Outpatient
Population**

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**Lung Transplantation for
COVID-19-Associated Acute
Respiratory Distress
Syndrome in a PCR-Positive
Patient**

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Analyses for preexisting antibodies showed high levels of class I and class II HLA antibodies, probably due to the previous administration of multiple blood products, including convalescent plasma.

The Etiological Spectrum of Dizziness Observed at a Vertigo Clinic: A Study of a Dubai Outpatient Population

There is little data available describing the incidence of vestibular disorders in the Dubai population.⁴ This study therefore aims to report the etiological spectrum of vertigo and dizziness from a vertigo speciality clinic in Dubai.

Dr Vishal Pawar, Specialist Neurologist, Aster specialty clinic, International city, Dubai, UAE

Introduction

Dizziness is a common complaint in medical outpatients, with vestibular disorders being the most common cause of dizziness.^{1,3} However, there is little data available describing the incidence of vestibular disorders in the Dubai population.⁴ This study therefore aims to report the etiological spectrum of vertigo and dizziness from a vertigo speciality clinic in Dubai.

Material and methods

The study was conducted at the Vertigo clinic, Aster Specialty Medical Centre, International city, Dubai, which is equipped with Video-Oculography (VOG) goggles. All patients suffering from dizziness who visited the Vertigo clinic during the study period (27th Jan-25th Dec 2019) were included in the study (n=601). Detailed history taking and neurotological examination were performed in every patient. Video-oculography (VOG), Neuroimaging studies and other investigations were also conducted where appropriate.

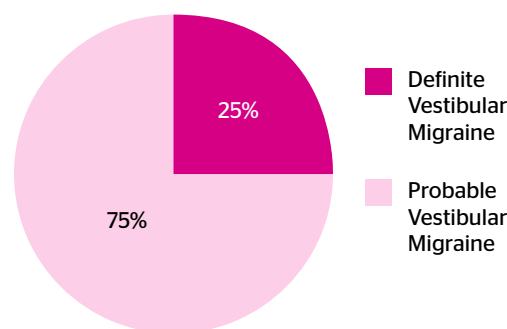
Results

During the 11 month study period, 601 patients (359 males and 242 females) were evaluated. The mean age was 38 years (Range 14-83 years).

Overall, central causes were responsible for 47% cases; peripheral causes were seen in 31% cases, functional and psychiatric causes in 12% of patients and other causes in 9% of cases. Vestibular migraine was the most common central cause, Benign paroxysmal positional vertigo (BPPV) was the most common peripheral cause, and persistent-postural-perceptual dizziness (PPPD) was the most common cause of dizziness due to functional aetiology.

1) Vestibular migraine

- ▶ Vestibular migraine is the leading cause of spontaneous episodic vertigo.
- ▶ The International classification of headache disorders (ICHD-3) criteria was used to diagnose vestibular migraine.⁵
- ▶ Due to the stringent nature of the diagnostic criteria, only 25% patients with vestibular migraine were diagnosed to have 'definite' vestibular migraine, and 75% were diagnosed to have 'probable' vestibular migraine (Fig 1).
- ▶ Patients with 'definite vestibular migraine' had vertigo as a presenting complaint which affected their quality of life. The duration of the dizziness was more than 5 minutes per episode.

Figure 1. Vestibular migraine distribution

- Patients with 'probable vestibular migraine' did not have vertigo as a presenting complaint, and many reported that it did not affect their quality of life. A large proportion of patients had a duration of dizziness of less than 5 minutes. Some patients had had fewer than 5 attacks of vestibular symptoms. Of those who had more than 5 attacks, fewer than 50% of the attacks were associated with 2 or more of the four migrainous features mentioned in the diagnostic criteria². All of these patients were categorized as 'probable vestibular migraine'.

A statistical analysis showed the following findings.

- 258 patients were diagnosed with vestibular migraine.
- 69 patients presented with migrainous positional vertigo mimicking BPPV.
- 15 patients presented with Meniere's syndrome.
- 51 patients presented with pseudo- acute unilateral vestibulopathy, and 5 patients presented with bilateral vestibulopathy (Fig 3).
- The mean age of onset of vestibular migraine was 38 years.
- Vestibular migraine can affect children as young as 14 years, and can present as late as 83 years.
- It is slightly more common in females (53.48% of cases) than in males.
- Video-oculography showed dizziness and discomfort on optokinetic stimulation in 90% of patients.
- 13.5% (35/258) patients with vestibular migraine had comorbid/triggered persistent-postural-perceptual dizziness
- 22% of patients had a history of motion sickness in childhood (39/258).

2) BPPV

Overall, BPPV was the second most common cause of vertigo. However, it remains the most common cause of positional vertigo if 'probable vestibular migraine' patients are discounted.

108 patients had typical symptoms suggestive of BPPV (Fig 3).

11 patients did not undergo positional testing. Of those who underwent positional testing (97 patients), 49 patients had nystagmus which was characteristic of one of the canal types (objective BPPV).

30 patients had symptoms without any characteristic nystagmus during the positional testing (subjective BPPV). 10 patients with Subjective BPPV (sBPPV) had sitting-up vertigo (or Type 2 BPPV), and 20 patients were classified as having sBPPV forms other than type 2 BPPV.

7 patients did not have symptoms or nystagmus during the positional testing. They were classified as 'probable BPPV spontaneously resolved' as per the Barany society criteria.

The most common type of objective BPPV was posterior

canal (65%), followed by the lateral canal (24%). Anterior canal BPPV was seen in 10% of patients.

30 out of 32 patients with posterior canal BPPV had a typical form, and two patients had an apogeotropic form (Fig 4). 10 out of 12 patients with lateral canal BPPV had the geotropic form, and two patients had the apogeotropic form.

3) Persistent postural perceptual dizziness:

86 patients were diagnosed to have 'persistent postural perceptual dizziness' (P3D). P3D presents with chronic vestibular syndrome.

Symptoms are usually triggered in specific situations such as crowded places (malls, supermarkets), which can be classified as agoraphobia. Symptoms can also be triggered in open places during active or passive head motion (especially while driving). The symptoms usually present with the patient in an upright posture, and are relieved in the supine position.

In 34 patients, the precipitating disorder for the P3D could not be established. Fifty-two patients had P3D secondary to another vestibular, neurologic or medical disorder.

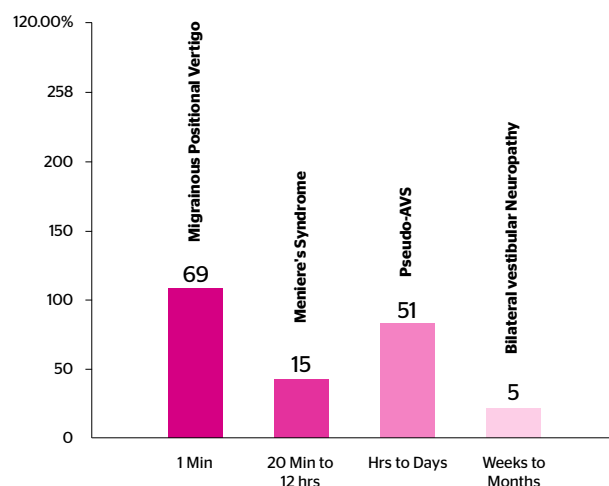
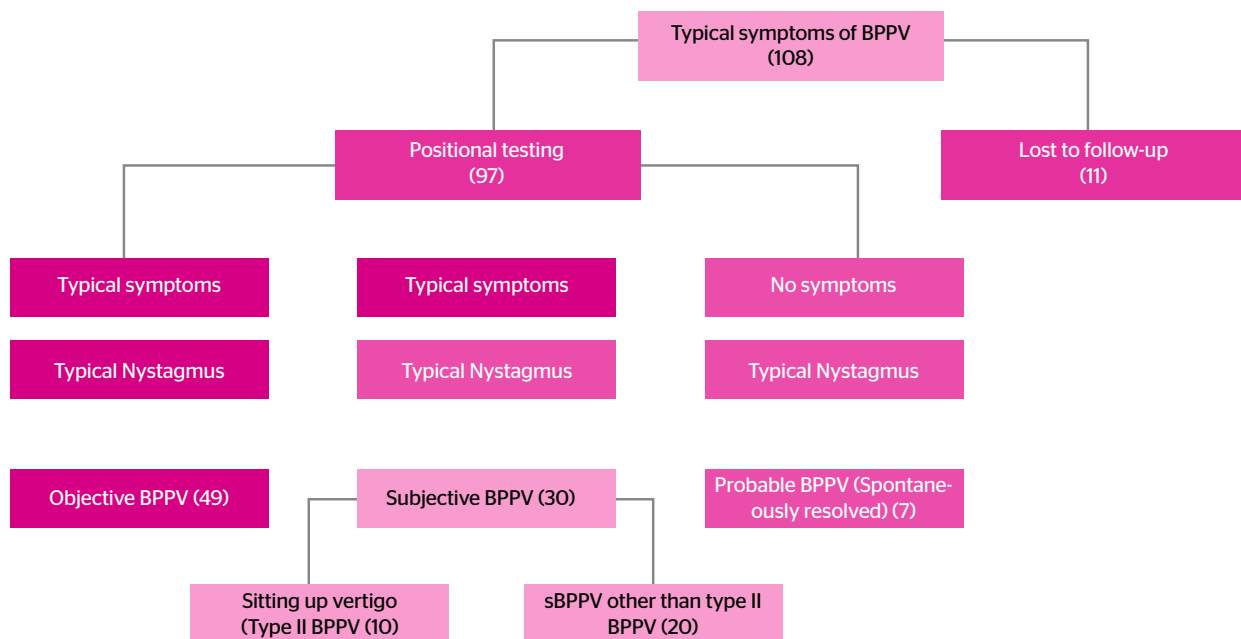
Figure 2. Vestibular migraine symptom overlap with common vestibular syndromes

Figure 3. Distribution of patients with BPPV



The most common precipitating disorder for P3D was vestibular migraine. Other vestibular disorders identified included BPPV, Meniere's disease, Acute unilateral vestibulopathy and vestibular paroxysmia. However, it was observed that P3D could also be triggered by non-vestibular disorders including epilepsy and depression.

The most common oculographic finding in patients with P3D was 'dizziness during a hyperventilation test without any characteristic nystagmus.'

4) Meniere's disease:

30 patients were diagnosed with Meniere's disease. This can trigger persistent-postural-phobic dizziness. It closely mimics vestibular migraine and differentiation from vestibular migraine can sometimes be challenging.

5) Acute unilateral vestibulopathy

18 cases were diagnosed with acute unilateral vestibulopathy due to peripheral aetiology (p-AUV). Patients with p-AUV presented with acute vestibular syndrome. Following the HINTS examination protocol is essential in these cases to exclude central causes. All patients had a positive head impulse test, unidirectional nystagmus without fixation, absence of skew deviation and absence of acute hearing loss.

The nystagmus of p-AUV is not seen under light during a routine clinical examination, or is of mild intensity when gazing contralateral to the side of a vestibulopathy.

Examination of the eyes in the dark (especially with videonystagmography (VNG) goggles and visor), or with Frenzel lenses, is the key to the diagnosis of a unidirectional nystagmus.

Three cases were diagnosed to have Ramsay Hunt syndrome

presented with an acute unilateral vestibulopathy. They had ipsilateral facial weakness and herpetic lesions in-ear (Fig 5).

6) Post-traumatic vertigo-

16 cases of dizziness were secondary to trauma. 8 were diagnosed with BPPV and 5 had a labyrinthine concussion. Patients with labyrinthine concussion presented with 'acute vestibular syndrome'. Two patients had both BPPV and labyrinthine concussion.

7) Psychiatric causes

Dizziness of psychiatric origin was seen in 14 out of 601 patients (2.3%). The most common cause was anxiety disorder.

8) Vestibular paroxysmia

13 cases were diagnosed with vestibular paroxysmia. They commonly presented with a spontaneous episodic syndrome of chronic onset.

All patients had stereotypical symptoms lasting less than one minute per episode.

Two cases had co-existent trigeminal neuralgia.

Two cases had positionally triggered attacks of vertigo.

3 out of 6 patients who underwent VNG showed hyperventilation nystagmus.

MRI brain showed an arterial loop in 9 patients (Fig 6), a venous loop in 1 patient and 3 cases of secondary paroxysmia (multiple sclerosis, vertebral dolichoectasia and an arachnoid cyst in the cerebello-pontine angle respectively)

All patients with vestibular paroxysmia showed a complete response to carbamazepine and/or gabapentin.

9) Posterior circulation stroke

9 cases had vestibular symptoms originating from a vascu-

lar cause. 4 patients had an infarction in the vertebro-basilar distribution. Three cases had transient ischaemic attacks; one patient had a cerebellar bleed, and one case had vertebral artery compression syndrome.

10) Tumours

6 patients were diagnosed to have posterior fossa tumours. Three had a cerebellopontine angle tumour; the three remaining cases were respectively diagnosed to have an arachnoid cyst, a colloid cyst of the third ventricle and retro-cerebellar meningioma.

11) Drug-induced

6 patients had drug-induced dizziness. The incriminating drugs were as follows.

- ▶ Pregabalin
- ▶ Combination of gabapentin and tramadol
- ▶ Amitriptyline
- ▶ Budesonide inhaler
- ▶ Phenytoin
- ▶ Combination of candesartan, dutasteride and alfuzosin

12) Syncopal dizziness

20 patients had syncopal (Type-2) dizziness. The causes were as follows:

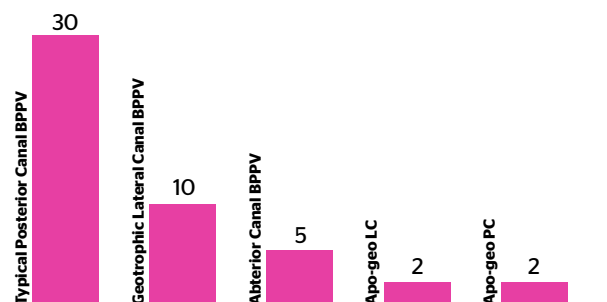
- ▶ Pre-syncope- 6
- ▶ Neuro-cardiogenic syncope -4
- ▶ Micturition syncope- 2
- ▶ Orthostatic hypotension- 2
- ▶ Carotid sinus hypersensitivity- 1
- ▶ Defecation syncope-1
- ▶ Postural orthostatic tachycardia syndrome- 3
- ▶ Migraine- 2

13) Other disorders

16 patients were diagnosed to have other disorders as follows.

- ▶ Migraine with brainstem aura- 6
- ▶ Rotational vertebral artery syndrome- 2
- ▶ Vitamin B12 deficiency - 1

Figure 4. Distribution of patients with objective BPPV



(BPPV: Benign paroxysmal positional vertigo, Apo-geo: Apogeotrophic, LC- Lateral canal, PC- Posterior canal)

Figure 5. The first image shows herpetic vesicles in the right ear and the second image shows facial weakness on the right side.



Figure 6. MRI CISS image showing vascular loop around the left vestibulocochlear nerve.



- ▶ Cervical myelopathy - 1
- ▶ Otolith dysfunction- 1
- ▶ Veisalgia (Alcohol hangover) - 1
- ▶ Diabetic neuropathy - 1
- ▶ Chronic fatigue syndrome- 1
- ▶ Essential head tremor - 1
- ▶ Parkinson's disease -1

14) Unknown causes

The cause could not be established in 21 cases, despite a detailed history and relevant investigations.

CONCLUSION:

Vestibular migraine is one of the most common causes of spontaneous dizziness. BPPV is the most common cause of positional vertigo. This study is probably one of the most extensive studies of vertigo patients in a Dubai population from a neurology clinic. The etiological spectrum of vertigo seen in this study is similar to spectra reported from other countries³⁻⁵.

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Lung Transplantation for COVID-19-Associated Acute Respiratory Distress Syndrome in a PCR-Positive Patient

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Most patients with COVID-19 have a mild or asymptomatic disease course; however, about 10% require admission to an intensive care unit (ICU) because of acute respiratory distress syndrome (ARDS).^{1,2} Mortality rates of up to 60% have been reported for this subgroup.^{3,4} Lung transplantation remains the ultimate treatment option for various chronic end-stage lung diseases. In addition, it can be considered as a salvage therapy for carefully selected patients who have severe treatment-refractory ARDS.⁵ However, wide uncertainty exists as to whether lung transplantation could have a place in the treatment of severe COVID-19 and, if so, what the optimal timing for such a treatment should be. Herein, we report the first case of lung transplantation for a patient with a persistently positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) real-time RT-PCR test result.

On March 21, 2020, at a time when the first COVID-19 cases were reported in Austria, a 44-year-old woman was admitted to Klinikum Klagenfurt am Wörthersee (Klagenfurt, Austria) with symptoms of fever and cough, and tested positive for SARS-CoV-2 by nasopharyngeal swab real-time RT-PCR on the same day (day 0).

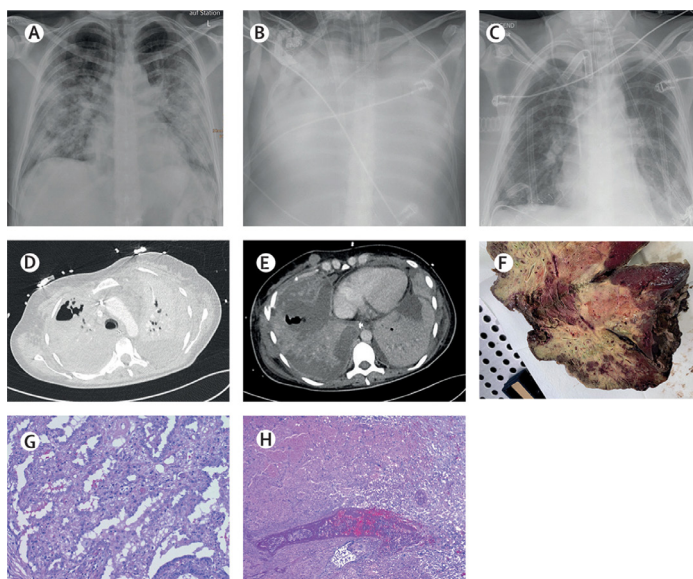
Her medical history was unremarkable, except that she had mild psoriatic arthritis, which did not require any systemic treatment, and a diagnosis of

idiopathic CD4 lymphocytopenia without any clinical relevance. On day 6 after the first positive SARS-CoV-2 test, the patient's respiratory condition worsened, requiring transfer to the ICU and subsequent intubation. Therapy was further escalated by femorofemoral venovenous extracorporeal membrane oxygenation (ECMO), initiated on day 13. Administration of immunoglobulins, tocilizumab, and lopinavir, and use of prone positioning did not improve the patient's condition. On day 20, the patient developed spontaneous bleeding from the right thoracic cavity, which required surgical opening of her chest and haematoma evacuation. A small, self-limiting intracerebral bleed in the left temporal lobe did not require any intervention. During this episode of bleeding, the patient required multiple transfusions. A final treatment attempt with convalescent plasma therapy (day 32) was initiated, which offered no benefit, and the patient was subsequently transferred to the Medical University of Vienna (Vienna, Austria) on day 48 as a possible candidate for lung transplantation.

On arrival, the patient required moderate doses of vasopressors (0.3 µg/kg per min norepinephrine), presented with normal kidney function, and had a bilirubin level of 48 µmol/L. Partial pressure of arterial oxygen was about 70 mm Hg while ventilated with airway pressure release ventilation of 25 mbar over 8 mbar positive end-expiratory pressure and a fractional concentration of oxygen in inspired air of 1.0. With these settings, her tidal volume was only around 50 mL and she was fully dependent on the venovenous ECMO support (blood flow 3.8 L/min and sweep gas flow 6 L/min). Subsequent reduction of the sedation levels led to spontaneous opening of her eyes. When turning the patient, repeated episodes of desaturation accompanied by bradycardia occurred and the ECMO cannulation had to be changed to a femorojugular configuration using larger cannulas (25F/21F). The changes to the cannulation resulted in stabilisation of the patient; however, ECMO run with regular physiotherapy while the patient was awake to avoid further deconditioning, as previously described in the setting of bridge to transplant,^{6,7} was not feasible.^{6,7} A complete investigation was initiated to consider the possibility of lung transplantation.

Pulmonary CT angiography revealed complete consolidation of the lungs with large necrotic areas and air inclusions, raising high suspicion of bacterial superinfection.

Figure 1. Radiological imaging and pathological examinations

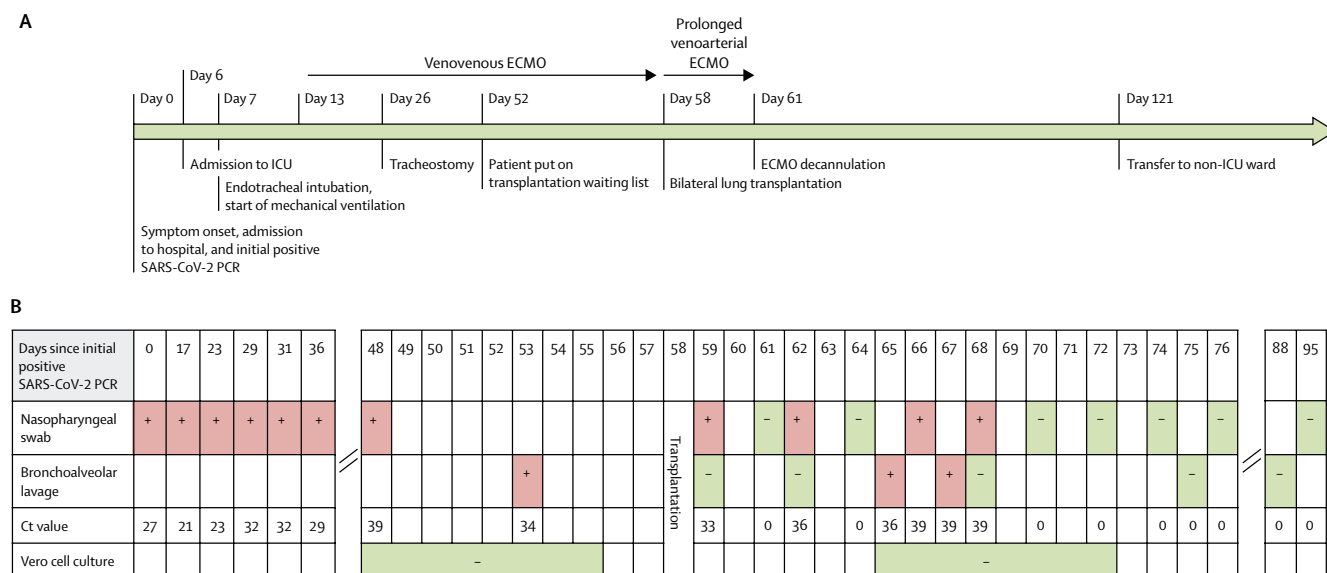


Chest x-rays of the patient on day 6 after the initial SARS-CoV-2-positive PCR result, on admission to the intensive care unit (A); and on day 52, when she was put on the transplantation waiting list (B). Chest x-ray after lung transplantation on day 62 (postoperative day 4; C). CT on day 49 showed air-filled cystic spaces, indicating necrotic lung tissue (D); and missing contrast enhancement in the periphery of the right lower lobe, suggesting thrombosis of small pulmonary vessels (E). Macroscopic appearance of the explanted lungs showed extensive necrosis (F). Microscopic images of haematoxylin and eosin staining of the explanted lungs showed diffuse alveolar damage, inflammatory granulation (original magnification × 40; G) and thrombosis of middle-sized arteries (original magnification × 16; H). SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Additionally, there was almost no perfusion in large parts of the lower lobes, suggesting extensive infarctions of the peripheral parts of the lung parenchyma and thrombosis of small and medium-sized pulmonary arteries (figure 1). CT of the CNS showed a reduction in the size of the lesion corresponding to the previously reported small left-temporal haemorrhage. On day 52, an increase of acute-phase proteins and a positive *Candida albicans* blood culture were noted. Furthermore, bilirubin increased to 170 µmol/L, so a superinfection of the necrotic lung with subsequent sepsis-associated liver dysfunction was assumed (appendix p 4).

During the whole course of treatment from day 0, RT-PCR testing for SARS-CoV-2 was repeatedly positive, both in nasopharyngeal swabs and in bronchoalveolar lavage samples (figure 2). However, real-time RT-PCR cycle threshold (Ct) values were exceptionally high, with some values greater than 33, suggesting that these positive results could have derived from nucleic acid

Figure 2. Patient timeline



(A) Clinical events. (B) SARS-CoV-2 tests, including PCR and Vero cell culture. Ct=cycle threshold. ECMO=extracorporeal membrane oxygenation. ICU=intensive care unit. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

segments of residual virus without actual infectivity.⁸ To better define the presence of an active SARS-CoV-2 infection, Vero cell cultures were used,⁹ which turned out to be negative after 7 days of culture (three passages).

Analyses for pre-existing antibodies showed high levels of class I and class II HLA antibodies, probably due to the previous administration of multiple blood products, including convalescent plasma. Cytological analysis of bronchoalveolar lavage fluid exposed predominantly necrotic material, and flow cytometric analysis showed the absence of alveolar macrophages but high abundance of immature neutrophils and cell debris (appendix p 2). These findings further corroborated the profound damage to the lungs.

On the basis of all these examinations, a comprehensive interdisciplinary discussion on the direction of treatment was held on day 52, which resulted in a consensus that the lungs of the patient had no potential for recovery. Consequently, the alternatives of terminating the treatment or proceeding to lung transplantation were discussed, which resulted in the final decision in favour of transplantation. This decision was based on the following considerations: (1) virus culture was negative and real-time RT-PCR Ct values were high; (2) it was more than 5 weeks since the start of the SARS-CoV-2 infection; (3) no alternative treatment options

were available; (4) the case was a single-organ failure in a young patient; (5) it was a pre-septic condition originating from the lungs; and (6) there were no other obvious barriers for long-term recovery. As the patient could not consent to the procedure, next-of-kin consent was obtained from her spouse. She was put on the waiting list on day 52 and was granted a lung allocation score of 49.3. Daily immunoabsorption therapy was initiated, with the aim of achieving desensitisation of the patient (ie, removal of preformed antibodies from the circulation) before transplantation (appendix p 4).

On day 58, a suitable donor organ became available and a sequential bilateral lung transplantation was performed. Intraoperatively, a central venoarterial ECMO circuit was installed and the venovenous ECMO was kept running in parallel with a reduced flow of 1 L/min. Without clear anatomical borders, only extrapleural mobilisation of the lungs was possible. The implantation was equally challenging because of the remarkably fragile tissue quality of the recipient's bronchus and vessels, most likely due to a spread of the infectious process (ie, inflammatory changes resulting from the previous infection) to these tissues. Meticulous haemostasis was performed; nevertheless, a total of 30 units of packed red blood cells and five units of platelets were required to establish coagulation. At

the end of the procedure, signs of incipient reperfusion oedema were observed, so the central venoarterial ECMO support was switched to prolonged peripheral femorofemoral venoarterial ECMO and venovenous ECMO was removed.¹⁰

The patient was transferred to the ICU in a stable condition and was put into prone position to relieve the lower lobes of the lungs. Reopening of the chest was indicated on postoperative day 1 for haematoma evacuation. Thereafter, the patient quickly recovered, the venoarterial ECMO system could be removed on postoperative day 3 and primary graft dysfunction grading at 72 h was 0.

Standard triple immunosuppression was initiated, including tacrolimus, mycophenolate mofetil, and steroids. As the patient was highly presensitised, six additional treatment cycles of immunoabsorption were done and antithymocyte globulin was administered. As expected, the crossmatch between donor and recipient was positive; however, in serial blood samples taken after transplantation, class II donor-specific antibodies were substantially reduced and class I donor-specific antibodies were completely absent (appendix p 3).

Similar to most recipients bridged to their transplant for a long time, the further postoperative course of the patient was characterised by slow recovery. From day 72 after the initial positive SARS-CoV-2 test (postoperative

day 14), the patient was regularly mobilised to sitting at the edge of the bed, and on day 83 (postoperative day 25), the patient was able to speak via a tracheal multifunction cannula. She was able to be transferred to a non-ICU ward on day 121 (postoperative day 63), was able to walk with some assistance, and was recovering from neuromuscular deconditioning. At this stage, no functional impairments related to the cerebral bleeding were apparent. Cellular analysis of bronchoalveolar lavage samples confirmed regular recovery with mainly viable cells, an increasing abundance of alveolar macrophages, and the presence of mature neutrophils (appendix p 2).

Notably, real-time RT-PCR for SARS-CoV-2 was performed regularly after the transplantation and remained positive in samples from nasopharyngeal swabs and bronchoalveolar lavage until postoperative day 10, but was negative thereafter. In addition, a second Vero cell culture from a bronchoalveolar lavage sample retrieved on postoperative day 7 was negative and thus confirmed absence of infectivity in the patient.

Pathological examination of the explanted lungs showed large zones of necrosis almost completely taking up both lower lobes and large areas of the upper lobes. A large proportion of alveoli were destroyed and replaced by granulation tissue, corresponding to massive diffuse alveolar damage. Throughout all lobes, remnants of substantial widespread thromboembolism were present (figure 1).

To our knowledge, available evidence for lung transplantation in COVID-19 is limited to two preliminary reports from China, suggesting that this treatment might be an option for SARS-CoV-2 PCR-negative patients.^{11,12} The case we present here extends the reports from China by showing that lung transplantation can be done in patients with positive RT-PCR results, provided that Vero cell cultures confirm non-infectivity. Of the cases reported so far through the scientific literature and the media, ours seems to represent the first successful lung transplantation of a patient with COVID-19 outside of China.

According to WHO guidelines, laboratory confirmation of SARS-CoV-2 is defined as positive RT-PCR of a nasal or pharyngeal swab.¹³ However, an increasing body of evidence shows that PCR positivity can persist for several days or even weeks beyond virus infectivity.¹⁴ A study by Bullard and colleagues⁹ showed that SARS-CoV-2 infectivity was restricted mainly to patients with a duration of symptoms shorter than 8 days and low RT-PCR Ct values (<24). Although Vero cell cultures are

Analyses for pre-existing antibodies showed high levels of class I and class II HLA antibodies, probably due to the previous administration of multiple blood products, including convalescent plasma.

not yet universally available, they are considered the gold standard to establish virus infectivity.

At day 144, the patient remained well. Despite the success of this case, it is important to emphasise that lung transplantation is an option for only a small proportion of patients with COVID-19. Many patients with COVID-19 who are admitted to the ICU are older than the acceptable age limit for the procedure or have other comorbidities that might preclude them from lung transplantation.

Furthermore, it has been shown that even patients with severe COVID-19-related ARDS have some potential to recover.¹⁵ As donor organs are a scarce resource, it is important to consider lung transplantation only for patients with irreversibly damaged lungs. In our case, a complete absence of pulmonary gas exchange after 5 weeks of venovenous ECMO, extensive signs of necrosis, and thrombotic occlusions of peripheral vessels on CT angiography, as well as highly abnormal bronchoalveolar lavage cytology, suggested that the patient was a good candidate for transplantation. This judgment was later confirmed by pathological examination of the explanted lungs.

The critical status of a patient with such extensive lung damage, the permanent risk of bacterial superinfection, and the imminent muscle loss are strong arguments to consider lung transplantation early, certainly before an already complex situation becomes completely unmanageable.

In our opinion, it is therefore highly unlikely that a strategy of rehabilitation on ECMO first and lung transplantation at a later point would have resulted in an acceptable clinical outcome. Furthermore, it is important to make full use of such short-lived opportunities for critically ill patients, and SARS-CoV-2 RT-PCR positivity alone should not exclude them from lung transplantation when it is the only remaining potentially successful therapy.

This Case Report shows that lung transplantation should be added to the armamentarium of therapies for patients with COVID-19-related ARDS. The criteria applied herein for patient selection and timing of lung transplantation need to be validated in future studies.

Contributors

CL, PJ, PS, WK, and KH drafted the report. MAH, GL, TK, KA, TS, ET, BZ, OR, and MK were involved in the treatment of the patient. SG, HP, RG, and SK acquired, analysed, and interpreted pathology specimens, radiology images, or cytology specimens. FT, AI, and RS analysed and interpreted virology data. GF interpreted donor-specific antibody tests. All authors were responsible for critical revision of the manuscript and approved the final version before submission.

Declaration of interests

We declare no competing interests.

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COVID-19: Risk Assessment & Mitigation Strategy

Lessons learned from Aster DM Healthcare Hospitals in India & GCC.





Dr A Malathi is Group Chief Medical & Quality Officer at Aster DM Healthcare

Aster DM Healthcare has been at the epicentre of managing COVID-19 pandemic in India and Gulf Cooperation Council countries ever since the pandemic hit in mid-March. This paper is a fascinating organisational case study and report about how Aster DM healthcare navigated the challenge of COVID - 19 Pandemic.

INTRODUCTION

The 2020 COVID-19 Pandemic has made society and the global economy volatile, uncertain, and ambiguous, even though high levels of preparedness have been developed for the situation. Late 2019, and early 2020, when the Coronavirus outbreak was limited to China, there was little expectation that it would grow to such pandemic proportions. No aspect of life, including business ventures, has been left untouched by this scourge. While the world stands still due to the COVID-19 pandemic, the impact that this disease has had on healthcare systems in various countries has been profound. Healthcare organizations, along with government functionaries from across the country, have delved into innovative ways to battle the disease, and have devised policies and protocols to ensure continuity of care and therapy for both COVID and non-COVID patients, within the ambit of safety for both patient and healthcare workers.

This paper provides a case study of how ASTER DM Healthcare handled the COVID-19 situation, to keep afloat both clinical and operational functions while ensuring the safety of healthcare workers. This was achieved by adopting new protocols based on updated scientific information and guidance from thought leaders across the Aster Group, which enabled the leadership team and staff at Aster to plan and respond swiftly to the daily dynamic uncertain environment created by the COVID-19 onslaught.

OBJECTIVES OF THE STUDY

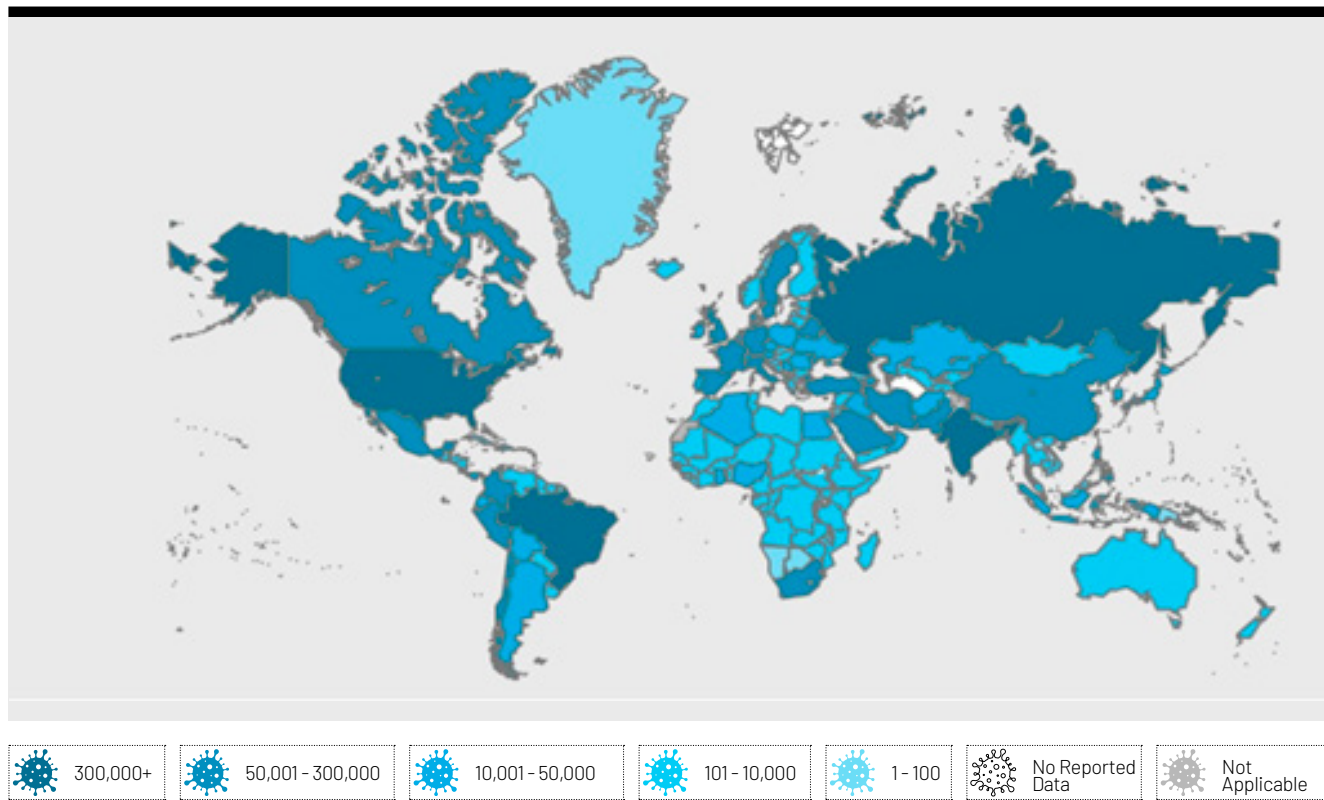
1. It provides an insight to the reader on how Aster DM worked towards establishing best practices within the healthcare scenario and act as a

foundation for action if the future again inflicts similar challenges.

2. Ensure continuity of clinical and operational functions, albeit within the ambit of safety and mitigation of the risk of cross-infection for patients and health care workers.
3. Create a base document that records the futuristic approach for handling emergency and elective cases with new protocols during this new “normal” COVID era.
4. Share the arduous journey which paved the way for new learnings, to make Aster DM battle-ready in these uncertain times.
5. Implementation of a top-down approach for clinical and nonclinical staff to stringently follow the new rules of engagement in the workplace, based on the three pillars of safety- hand hygiene, social/ physical distancing, and universal masking (along with adequate PPE).

IMPACT & COVID PREPAREDNESS

An outbreak of the respiratory disease was reported from Wuhan, a city of 11 million people in China, on 31st December 2019. The causative agent was discovered in January 2020 to be a novel enveloped β -coronavirus of the same sub genus as SARS-CoV-1 and has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) also called Coronavirus disease 2019 (COVID-19).² Novel Corona Virus (SARS CoV2 / COVID-19) is a highly contagious infection and has been declared as a pandemic by the World Health Organization. It is important to be vigilant about the spread of the disease and be able to provide the rapid implementation of outbreak control and management measures. The lack of a proven treatment and vaccine as well as the high



The widespread presence of Aster DM Healthcare in different geographies paved the way of learning in such a challenging scenario and helped in sharing the best practices.

vulnerability of hospital staff makes it imperative to have guidelines as to how we can protect healthcare workers.

Hospitals are complex and vulnerable institutions, dependent on crucial external support and supply lines. Under normal working conditions, many of our hospitals frequently operate at near-surge capacity. Consequently, even a modest rise in admission volume can overwhelm a hospital beyond its functional reserve. Well-established partnerships with local authorities, service providers (e.g. of water, power, and means of communication), supply vendors, transportation companies, and other organizations are required to ensure the continuity of essential services.

During the current outbreak of COVID-19, well-prepared health facilities are at the center of an effective response. The rapidly evolving outbreak requires all hospitals to be able to adapt to a swift increase in demands while continuing to ensure safe environments for health workers. All hospitals need to take precautions against potential interruptions of critical support services and shortages of equipment and supplies. This document aims to provide a Risk Assessment and mitigation strategy based on lessons learned from Aster DM Healthcare Hospitals in India & GCC.

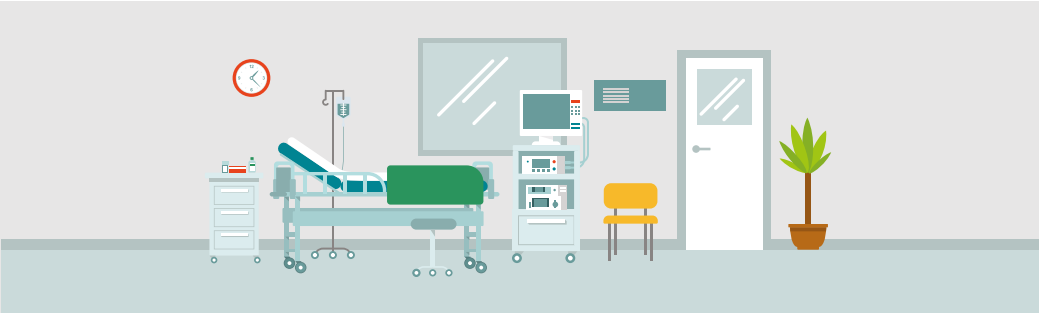
Also, a high rate of staff absenteeism can be expected. A shortage of critical equipment and supplies could limit access to needed care and have a direct impact on healthcare delivery. Panic could potentially jeopardize established working routines. Even for a well-prepared hospital, coping with the health consequences of a COVID-19 would be a complex challenge. Despite the difficult demands and obstacles foreseen, the proactive and systematic implementation of key generic and specific actions facilitated effective hospital-based management during a rapidly evolving pandemic.

RISK, MITIGATIONS & STRATEGIES

Well-prepared health facilities

Well-prepared health facilities is the key to saving the lives of COVID-19 patients. Preparations have been well done for global outbreaks and disasters in our system with our knowledge & experience from Kerala floods and the Nipah virus outbreak. On 30 January 2020, a public health emergency of international concern was declared by the World Health Organization (WHO). We activated our incident command centers across the group and carried out a rapid risk assessment. The overall objective was to strengthen the preventive action

Process Flowchart - Aster DM Command Center

	WHY	WHAT	ACTION STEPS			
PURPOSE AND CORE COMMITTEE	To provide immediate response to COVID19 Pandemic and identify responsibilities of individuals and departments to initiate action	Objectives: 1. To identify the level of risk and impact on organization/each Business vertical/ community 2. To initiate disaster management plan for the Business Unit hospitals to combat COVID 19 3. To respond & minimize the danger allow the most effective utilization of available resources 4. To provide support to the community and government	a → Review risk at each location and develop immediate and back up mitigation strategies according to situation. Identify high risk units provide immediate response to deal with COVID19 Pandemic. Initiate resource stockpiling and the identification of priority units for receipt of these	b → Identify resources –manpower, supplies, and infrastructure capability. Form Emergency task force at all units and initiate trainings on infection control and required specialized training in clinical management of COVID 19 patients, Coordinate technical aspects. Open alternate care sites if required working with health authorities	c → Ensuring preparedness/ implementation of safety standards/ protocols laid down by health authorities for COVID 19 surge. Support and handle staff queries to reduce/ avoid panic, Provide emotional and professional support	d Provide timely information to stakeholders Work alongside authorities. Support organization and community in convalescing from COVID 19
	3 LEVELS: EXCOM - CHQ Executive Council Vertical Executive Committee Unit Level Incident command center/ -Task Force HOD ID & CEO (India) part of the National Task force *India Unit CEO's part of the District COVID management task force Deputy Managing Director Member of CHQ Exe. Council appointed representative at National Level Task Force-DHA* constituted by Niti Ayog for sharing of best practices in management of COVID 19					
TIMELINE	Incident command centres activated by GCMO on 31 Jan 2020	Schedules: Unit Level: Daily Executive; Vertical Level Daily; CHQ- Council: Biweekly	Schedules: Unit Level Daily; Vertical Level Daily; CHQ-Executive Council: Bi-weekly/ Immediately on very urgent matters	Immediate action as per risk identification Unit Level: Daily; Vertical Level Daily; CHQ-Executive Council: Biweekly	Ongoing /Immediate Unit Level: Daily; Vertical Level Daily; CHQ-Executive Council: Biweekly	As per situation report. Unit Level: Daily; Vertical Level Daily; CHQ-Executive
ACCOUNTABILITY	Incident commanders at all levels	Incident commanders at all levels	All members of emergency and disaster management committee			

to reduce COVID-19 risk and enable Aster to take a timely and useful response. Priority measures were identified based on significant references like WHO, CDC, and national guidelines. An executive council was established to cascade our business units with effective strategic plans.

KEY MEASURES TAKEN TO COMBAT SPREAD

Clinical Excellence

As the COVID-19 situation is rapidly evolving, Aster focused on developing clinical guidelines for healthcare workers in concurrence with interna-

tional organizations like WHO, CDC etc. The clinical excellence was achieved by implementing updated guidelines which were constantly shared with healthcare providers in order to achieve the best patient outcomes. Our COVID dashboards helped us to monitor our outcomes and at the same time, providing insight into improvement strategies in patient care.

MANAGEMENT OF COVID CASES AT THE FIRST POINT OF CONTACT



THE EMERGENCY ROOM (ER)

On 30th January 2020, the WHO declared COVID-19 a public health emergency which soon evolved into a pandemic. From the early days of this disaster, Aster DM has been working tirelessly with the local authorities to prepare its response to the disease.

One of the major elements of the response was the set-up of more than 4 facilities with a total capacity of 800 plus beds which helped control the spread of the virus. Meanwhile the hospitals stopped their elective activities and focused almost entirely on the management of the suspected and confirmed cases.

The COVID response team in hospitals decided to dedicate the emergency departments to the management of suspected cases and the wards and ICUs were dedicated to the management of confirmed cases. As a consequence, the more severe cases were taken directly to the wards or the ICUs and the number of severe cases seen in the ERs remained

very low. The vast majority of the patients who attended the ER's were suspected cases that needed a confirmation or confirmed cases who required screening before isolation. Most of them were clinically well. Despite this organisation the ERs received a few severe cases and the level of response was exemplary. A few cases have been highlighted to showcase the quality of the emergency response:

Case Number 1

A 62-year-old male patient was admitted in one of the isolation hotels, having been referred directly by DHA (Dubai Health Authority). The patient did not have any identified risk factors other than being over the age of 60. He was not obese and had no co-morbidities identified at the time. He tested positive for COVID-19 after a period of persistent cough and fever. 12 hours after admission he was found to be hypoxic on room air and was promptly transferred to the ER. On arrival, he was found to be conscious and responsive, patent airway, breathing at a rate of 24 per minute, saturation on room air was 70% and only reached 85% with 10 liters of supplemental oxygen delivered via a non-rebreathing mask. His cardiovascular parameters were within normal limits and stable with a pulse of 71 bpm and a BP of 128/62. His GCS was 15 with no neurological deficit. An arterial blood gas showed a respiratory failure of type 1. A chest X-Ray showed a picture evocative of atypical pneumonia compatible with corona virus.

The patient was immediately referred to ICU for further investigations and management. The NIV was not started in the ER due to the speed at which the patient could be moved to a more appropriate environment given the risk of contamination of staff that is associated with the procedure.

The patient was successfully managed conservatively in ICU without intubation before being discharged home. This case highlights the excellent level of teamwork that was displayed throughout the COVID crisis. The coordination and communication between the different teams (hotel staff, ambulance team, ER and ICU staff) was excellent, and ensured permanent safety for the patient and the members of staff in spite of the challenging circumstances.

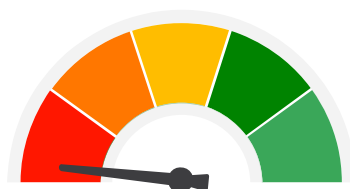
Case Number 2

A 67-year-old male patient was brought to the ER by national ambulance in cardiac arrest. The patient was a confirmed case of COVID who was

The probability, the severity of impact and system preparedness for each event were scored on a scale of 1-5 as per the average risk scores across all departments were in the range of 21 to 40. The six most consistently identified risks across departments and their total scores and actions are shown below.

Likelihood	CONSEQUENCES				
	1 - MINIMUM No injuries/ minimal financial loss	2 - MINOR First aid treatment/ medium financial loss	3 - MODERATE Medical treatment / high financial loss	4 - MAJOR Hospitalable / large financial loss	5 - FATAL Death / massive financial loss
5 - ALMOST CERTAIN Often occurs / once a week	5	10	15	20	25
4 - LIKELY Could easily happen / once a month	4	8	12	16	20
3 - POSSIBLE Could happen or known it to happen / once a year	3	6	9	12	15
2 - UNLIKELY Hasn't happened yet but could / once every 10 years	2	4	6	8	10
1 - RARE Conceivable but only on extreme circumstances / once in 100 years	1	2	3	4	5

 **Fatal (>15)**
 **High (10-15)**
 **Moderate (4-9)**
 **Minimum (1-3)**



 **HIGH 21 - >40**

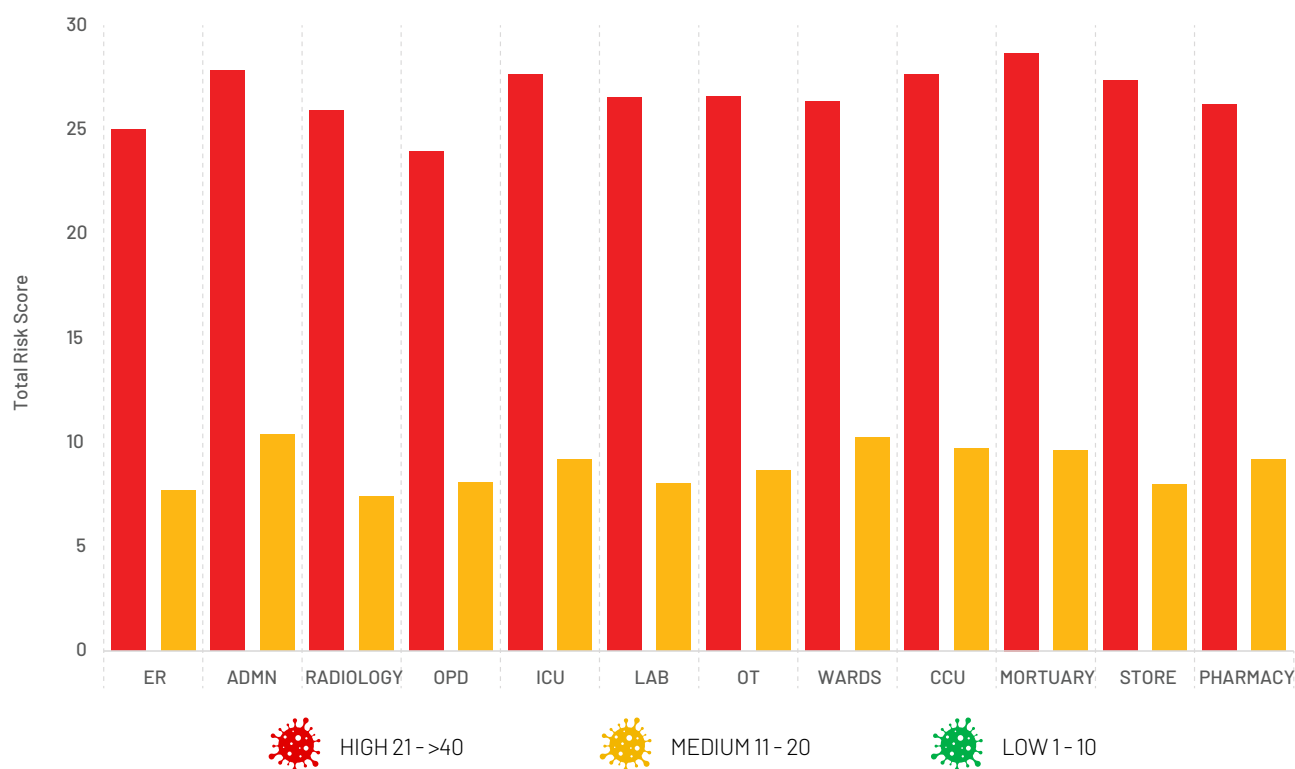


 **MEDIUM 11 - 20**

 **LOW 1 - 10**

PRE-IDENTIFIED RISK (32-40)	POST-RISK REDUCTION METHOD (12-16)
Inadequate critical care staff	Competency upgrading and up-skilling programs
Lack of staff education in COVID prevention measures	Education programs and awareness strategies
Improper use of PPE	Policy and protocols for the proper use of PPE
Transportation protocol	Transport measures to prevent spread and transmission
Work Culture	Work from Home
Fear of transmission of virus among staff and their families	Communication strategies to encourage reporting of concerns, psychological support

Department wise reduction in risk scores



The focused mitigation strategies were staff training, new or revised protocols, infrastructure, staffing, communication, audit, and monitoring. The percentage contribution of the focused strategy is depicted in the graph below:

in self isolation at home and was known to suffer from diabetes, hypertension and cardiac failure. The staff members were pre alerted and had enough time to get prepared and were wearing full PPE when the patient arrived. The patient presented a trismus which was probably an early sign of rigor mortis. He was managed following the ACLS protocol for 40 minutes with continuous CPR and adrenaline on alternate cycles, before he was declared dead in view of the lack of response to the resuscitative attempt.

Despite the poor outcome, this case highlighted the level of preparedness of the all the emergency staff members. The case was managed calmly and professionally in full respect of staff safety measures, by the means of PPE. There was no precipitation and every step of the ACLS protocol was followed without failure.

These two examples demonstrate that, after weeks of training and with the help of the infection control team, internal medicine and intensive care, the ERs have been able to safely manage critical cases in the most professional manner.

Despite the constantly growing feeling of anxiety, and despite some serious technical challenges posed by the nature of the infectious agent, the team has shown a real level of maturity in this unique crisis management.

MANAGEMENT OF CRITICAL CARE PATIENTS IN PANDEMIC

Beginning

Medcare Hospital partnered with DHA in March 2020 and we started preparing the critical care unit to accommodate and manage such cases by increasing the number of rooms with negative pressure.

As we strongly believe that prevention is most effective at the start, we immediately took measures to prevent and limit transmissions between the hospital staff, and protect the healthcare workers in accordance to the international and national COVID-19 precautions guidelines. This included the availability of PPE and proper use and disposal of the protective equipment. Continuous education and close communication with the infection control

team have been at the core of the initial phases of our plan of facing the pandemic.

We formulated and set up guidelines and protocols derived from the recommendations of surviving sepsis guideline 2020 - special edition for COVID, World Health Organization.

The learning phase

We soon started receiving cases of different nationalities. We have noticed that we have a considerably higher number of male patients compared with female patients, most of them between 30 and 60 years old. But these observations have to be taken in the context of Dubai's special demographic (higher number of male residents, most of them young or middle aged.)

Most of the patients presented with complaints of fever and some degree of difficulty in breathing. We observed that a significant number of patients presented with low levels of PaO₂ and SpO₂ without clinical signs, symptoms, or visible distress - silent hypoxia.

Most of our patients showed worsening of the symptoms in the second week of disease, many times after a few days of improvement, which can give a false sense that patient is starting the recovery phase. This second phase of the disease is when most of the critical care patients end up on ventilator. A small percentage of those in respiratory failure are improving on NIV, thus we chose to initially give a trial for most of our patients with noninvasive support if tolerated before going for intubation.

Once the patient had an ET tube in place we faced one of our biggest challenges, which was sudden ET tube blocks with large clot and necrotic tissues. Despite daily proper suctioning (closed and opened) on the ET tube, the high majority of patients required ET tube to be frequently changed due to acute blockage with clots (in some cases more than once per day). In our ICU all ventilated patients have been started on heparin nebulization and this therapy seems to offer some decrease in the need for change of ET tubes.

Although all specific ARDS ventilation recommendations have been used, we have soon realized that this is not the "classic" ARDS picture with stiff lung that we are facing, as there was not a requirement for high plateau pressures to obtain satisfactory tidal volumes (6-8 ml/kg), but despite the high volumes, patients remained severely hypoxic even at very high PEEP and hypercapnic, (situation associated more

with pulmonary embolism). Prone position offered some relief in patients with refractory hypoxia (it has to alternate with supine every 8 to 10 hours).

For the patient that required prolonged ventilation we opted for percutaneous tracheostomy which made it easier to deal with recurrent tube blockage, and difficult weaning mainly due to hypercapnia.

We have noticed that intensive chest physiotherapy is worsening the patient's ventilation, thus we opted for mild or no chest physiotherapy in the initial phases of the disease in critical patients and to return to usual physiotherapy in the recovery phases.

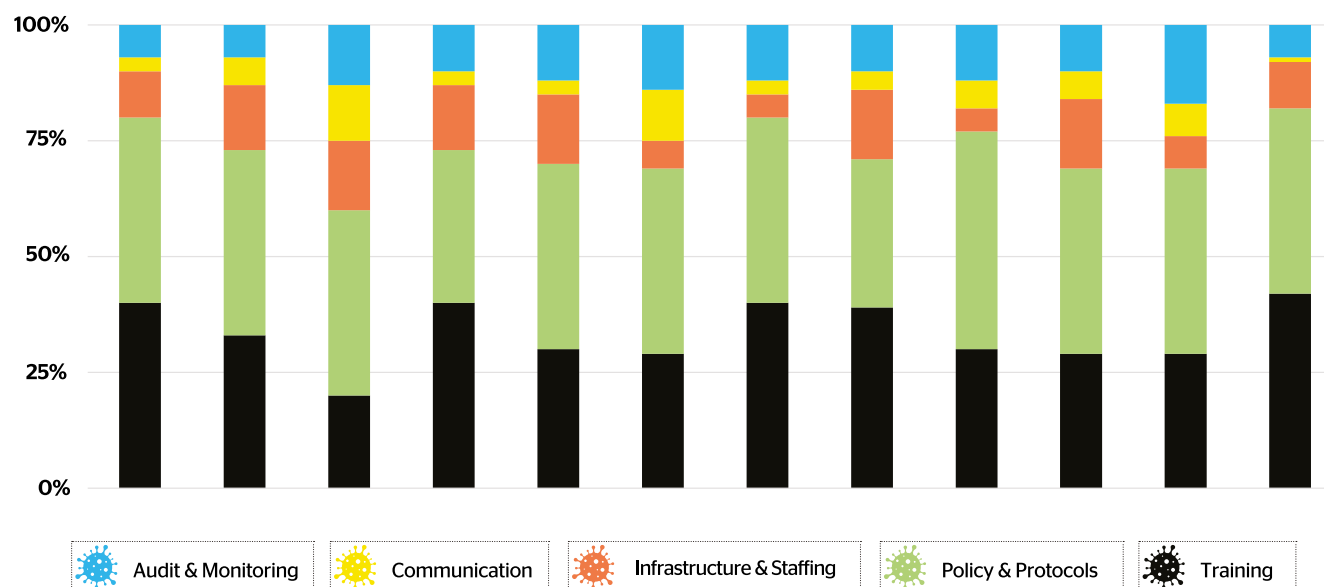
Though this masquerading virus was affecting the oxygenation and ventilation of the patient, it gave us more challenging complications such as thrombotic events like ACS ischemic stroke, acute tubular necrosis and pulmonary embolism. A considerable percentage of our patients were developing myocarditis and acute coronary syndrome pictures. Thus all our patients have been started on enoxaparin therapeutic dose and Aspirin. After this protocol had been put in place it was noticed that there was a decrease in the thrombotic complications. In one case in which Thromboembolism was required for acute MI, a significant improvement in ventilation was noticed, but unfortunately only for 24 hours after the therapy.

We have also noticed that all patients admitted in ICU have very high levels of D dimers, Ferritin, CRP. The D- dimers levels were found to be between 3000 and more than 30000, and it looks like there is a direct correlation between these lab levels and the course of the disease. Trombocytopenia have been also noticed, but only mild to moderate decrease of platelets levels. In one case in which thrombolization had been required for acute MI, an improvement in ventilation was also noted. Among dyselektrolytemias Phosphate levels have been found to be low in almost all critical COVID-19 patients.

OUTCOMES

It has been noticed that patients recovering from severe form of the disease are left with Chronic/ permanent lung damage. Most of the patients that have recovered from moderate/severe ARDS form of COVID 19, have been discharged with radiological images suggestive of lung fibrotic changes from mild to extensive. In one particular case, the changes were accompanied by the presence of emphysema and large bullae which complicated with spontaneous pneumothorax. There is a need to follow these

Department wise reduction in risk scores



The percentage contribution of the focused strategy is depicted in the graph above. Medium risks were further identified in some areas following the audits. The mitigation strategy focused on staff education. Also, methods to expedite the diagnosis and circumvent the delays in PCR test results were implemented.

patients in the future and assess their outcomes on a long term basis.

Managing the corona virus infected patient

- ♦ In accordance to the surviving sepsis guidelines, we started general management like any other septic patient. Although we were initially following the fluid restriction recommendations, we have soon decided to use the initial fluid resuscitation as per patient needs in hemodynamically unstable patients, using minimally invasive cardiac monitoring and assessing patient's fluid responsiveness, followed by deresuscitation when patient is out of the shock phase.
- ♦ Along with the specific support of functions, we included in our protocols virus specific management which included the use of antivirals as recommended by the national and international protocol. The anti-viral agents that were used included (lopinavir/ritonavir, favipiravir). Immunomodulatory drugs such as tocilizumab, have been also used in critical patients which showed some benefit.
- ♦ Managing the thrombotic complications of the corona virus was a challenge we faced every day. We used subcutaneous anti-coagulants (LMWH in the therapeutic dose). We used anti-platelets including (Aspirin and Plavix). We used NOACs

(rivaroxaban) in stable COVID-19 patients with mild pneumonitis.

- ♦ Facing the ET blocks, we used heparin nebulizations with which showed some decrease in the frequency of changing ET tubes.
- ♦ Early tracheostomy showed a better outcome in patients on long ventilator time due to refractory hypercapnia.
- ♦ We used prone position for the patients with severe ARDS with refractory hypoxia. Some improvement in the oxygenation have been noticed

CONCLUSIONS

There are still many unknown aspects of the infection with SARS-Cov2 virus. These major knowledge gaps make dealing with critical patients with COVID-19 a special and unprecedented challenge. There is a need to continuously adapt the current guidelines, as new managements with a strong evidence base and new therapeutic options are emerging.

*Disclaimer: The situation regarding COVID-19 is rapidly evolving and changes daily. Although timely policies should be implemented to facilitate objective decision-making, such directives will inevitably need to adapt to this fluid environment. This document content stands as on date. Visit the article page at www.theamj.org to access the full version of the Whitepaper along with the details of mitigations strategies implemented by the individual Aster hospitals in India and GCC.



100% Sensitivity in Blood Culture for Neonatal Sepsis: Myth or Reality?



Being a developing country and with its own limited resources, sepsis-related mortality and morbidity are perhaps the most prevalent in India. We often ascertain a number of “sepsis variant” diagnoses in our clinical practice. Definite sepsis, probable sepsis, early onset neonatal sepsis, late onset neonatal sepsis, suspect sepsis and even culture negative sepsis!

Neonatal sepsis remains a major problem in NICUs, as possibly the most commonly diagnosed/suspected and treated illness in NICUs around the world. Being a developing country and with its own limited resources, sepsis-related mortality and morbidity are perhaps the most prevalent in India. We often use a number of “sepsis variant” diagnoses in clinical practice- definite sepsis, probable sepsis, early onset neonatal sepsis, late onset neonatal sepsis, suspect sepsis and even culture negative sepsis!

One drawback of being “over familiar” with sepsis is that many of us tend to attribute each and every symptom and illness to sepsis in some way. We often resort to our own clinical acumen or gut instinct rather than using evidence-based methods to reach such a diagnosis. Many of us are hypocritical in that we take supporting lab investigations at face value only when the results favour our preferred diagnosis. If lab evidence of sepsis/ SIRS is lacking, we often fail to revise the diagnosis or treatment rather than using novel strategies or terms to reach a unequivocal diagnosis of sepsis (diagnosing culture negative sepsis, for example).

Though we all know that blood culture remains the “gold standard” for the diagnosis of neonatal sepsis, our approach to blood culture practices is far from ideal. We often do not send a proper blood culture, or do not trust a culture report.

There are many categories of neonatologists with regard to their approach towards blood culture!

1. **The pessimist:** altogether doubts the practical usefulness of blood culture in treatment of neonatal sepsis, and chooses not to send this particular investigation at all. They argue that the culture yield is too low to be helpful to them. The fact that culture is not a cheap investigation may also influence their conviction.
2. **The hypocrite:** sends the blood culture, often just because it is in their protocol or routine work up list. They have lost their trust in blood culture results a long time ago, and choose to treat neonates purely based on their clinical experience/ trust. They may accept a positive blood culture if it matches with their clinical diagnosis, but otherwise choose to ignore the report!
3. **The optimist:** sends blood cultures religiously, and although the yield is low, chooses to hope for the best and gets excited every time a positive report is available.

4. **The steadfast:** ensures a proper blood culture is sent in every suspected case of blood culture, and trusts the report fully. They show courage to take action based on the blood culture, whether the report is positive or negative.

Though in practice there is so much variation in the attitudes of neonatologists (as mentioned above) we all like to be the steadfast example in an ideal world. The question is whether all of us can alter/ improve our clinical practice to match such standards or not. There are a lot of valid questions that we have to answer and convince ourselves of before we have any scope in changing existing practices:

1. What is the supposed sensitivity of the blood culture in neonatal sepsis?
2. How can we improve the sensitivity of blood cultures?
3. How can we avoid false positive reports?
4. How early can I take action based on the culture report?
5. Should I need to step down treatment if the baby is clinically improving?

Contrary to popular belief, blood culture in neonatology is supposedly 100% sensitive!¹ That relies on at least 1ml of blood being inoculated, and the neonate having a bacteremia level of a minimum 4 CFU (colony forming units) per milliliter. Fortunately, or unfortunately, in a typical case of neonatal sepsis, the extent of bacteremia is > 100 CFU per milliliter.² The detection rates of modern blood culture methods are becoming even more accurate, retaining high sensitivity even when the bacteremia is low level, such as at 1-4 CFU/ml. Though it can be argued that, in the unusual case of a neonate with ultra-low bacteremia (that is < 1 CFU/ml), the sensitivity decreases significantly, such a situation is often clinically irrelevant. In all practical aspects, for a baby with ultralow bacteremia, the natural body defense mechanisms would be sufficient to clear the bacterial infection, and an inevitable dose of antibiotics (for 48 hours or so) should do the job.³

This naturally raises the question of “why are culture yields traditionally so low?”. The simple answer is that we are miserly with respect to the amount of blood we are inoculating! Believe it or not, we often end up submitting < 0.5 ml of blood for blood culture. Decreasing the amount of blood from 1 ml to 0.5 ml would decrease the sensitivity by as much as 40%. A 0.1 or 0.2 ml sample of blood sent for the purpose of blood culture almost makes the process a waste of time and resources. One of the perceived reasons behind not sending a 1 ml blood sample for

culture is the practical difficulty in bloodletting. Though 1 ml is a significant amount in very preterm babies, the clinical implications make it an absolute necessity. The problem can be partially solved by taking the first 1 ml of blood after accessing the IV cannula/ or during sampling for the culture, with all other investigations being given second priority. This means that, for an occasional baby, the RFT or PT/ INR etc. may have to be postponed. A clear written order in the case sheet mentioning this and the amount of blood needed is also found to be helpful.

Another condition that makes blood culture less sensitive is prior antibiotic use. Ensuring that blood culture samples are taken at first contact or before administering the first dose of antibiotics may be the only way around this problem. This problem is greatest in outpatient births and referred cases of neonates. However, even in those cases, ensuring a proper amount of blood for culture often greatly improves the situation.

False positives or contamination in blood culture can be easily avoided by ensuring proper aseptic precautions are taken during sampling. Proper use of skin disinfectants such as 2% chlorhexidine gluconate in 70% isopropyl alcohol (2% alcoholic chlorhexidine), or even 10% povidone iodine is mandatory. Creating a specific “cannulation set” is a rewarding and simple practice (a sterile tray with cotton swabs and other necessities for cannulation), as this ensures a sterile surface/field which significantly decreases the contamination risks.

Trusting blood culture reports and taking the necessary actions are steps which are as important as ensuring proper blood culture collection technique. This means that, once a positive culture is received

and sensitivity is available, we should downgrade antibiotics to the narrowest spectrum antibiotic clinically appropriate. This is necessary even if the baby's condition was very poor to begin with and this is currently improving on an empirically sensitive broad-spectrum antibiotic.

Trusting the blood culture if the report is sterile is often a more demanding process. There is plenty of evidence to show that it is safe to take action over a 48-hour blood culture report.^{4,5} A practical approach is to stop antibiotics if the blood culture is sterile and the baby is doing well after 48 hours. If the baby is still symptomatic at 48 hours (and you are still not able to rule out infection as a cause for the symptoms), it is wise to consider inflammatory markers (CRP, Procalcitonin etc) and to stop antibiotics if these fall within an acceptable range.

Preventing the unnecessary use of antibiotics is the need of the hour, and an essential step in providing quality care for sick neonates. Antibiotic usage in a culture negative vulnerable neonate has been shown to increase the incidence of necrotizing enterocolitis, bronchopulmonary dysplasia and death.⁶

Though a 100 percent theoretical sensitivity of blood culture in neonatal sepsis is difficult to achieve in routine clinical practice, we can definitely improve neonatal outcomes with the above-mentioned quality improvement initiatives. This is like targeting a zero incidence of health care associated infection (HAI) rate in the NICU: we won't succeed unless we try, we won't try if we don't believe, and if we don't believe then nothing will ever happen.

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Preventing the unnecessary use of antibiotics is the need of the hour, and an essential step in providing quality care for sick neonates.

Blood Clots: A Major Problem in Severe COVID-19

Out-of-control clotting can endanger some patients even after the virus has gone. Clinicians and researchers are trying to understand why it happens and how best to manage the problem.

In the early days of the New York COVID-19 outbreak, as March turned to April, hematologist Jeffrey Laurence was called to consult on the case of a 32-year-old bodybuilder. Nurses had noticed an odd rash on his buttocks, “as if you had kind of peeled away the skin layer and were seeing what blood vessels look like on his bottom,” recalls Laurence, who works at Weill Cornell Medicine in New York City. The vessels were outlined so clearly because the blood inside was coagulating, almost jelly-like.

Within a couple of weeks, Laurence observed several similar, striking cases — making some of the earliest observations that the blood-clotting process could go horribly awry in severe instances of COVID-19. Researchers and clinicians are working to understand why, and trying medications to tamp down the clotting or the intense immune responses that seem to underlie it. Ongoing clinical trials may help to provide clearer guidelines in the future, but with so much about this virus still unknown, for now they must guess at best treatments and doses.

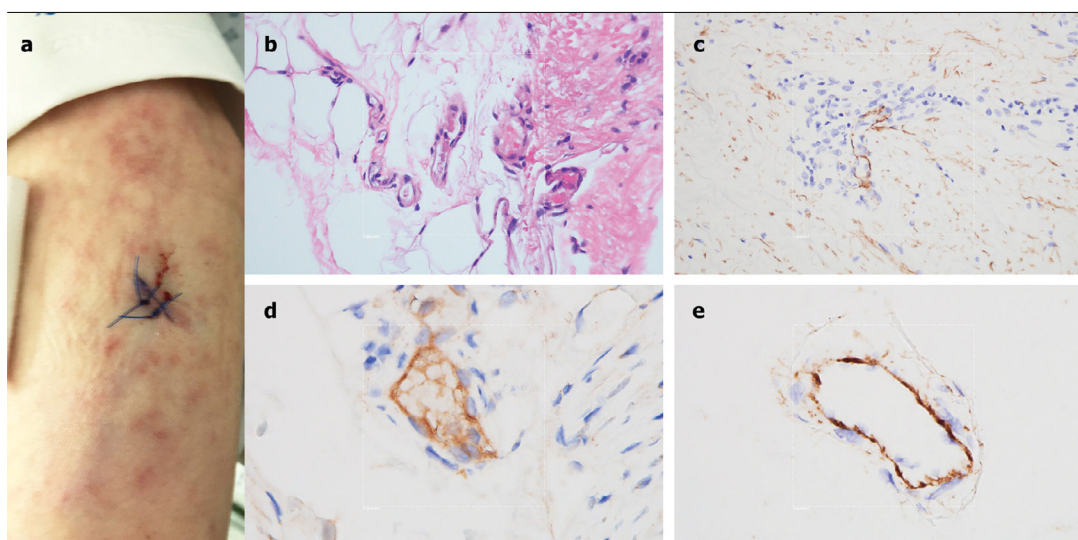
Clotting is normally a good thing. When a blood vessel is injured, cell fragments called platelets rush to plug the leak. Proteins in the blood called clotting factors switch from dormant to active states in a chain reaction, and

build a fibrous mesh. “It’s sort of a domino effect,” says Hanny Al-Samkari, a hematologist at Massachusetts General Hospital in Boston.

Clotting in uninjured blood vessels is a common occurrence in hospital patients, especially those in the intensive care unit. Being bedridden encourages clotting, especially in the legs and pelvis, and the clots may migrate to the lungs where they impede the organs’ ability to load the blood with oxygen. Depending on their location, clots can lead to problems such as breathing difficulties, heart attack, stroke and death.

Inflammation due to infection can also tip those clotting-factor dominoes. But as COVID-19 patients filled hospital wards, it became apparent that their clotting was more frequent, more widespread and more severe than in other infections. The clots filled needles used to draw blood, or the tubing connecting patients to medication drips and machines. “Everything was clotting,” Al-Samkari says.

The consequences can be devastating. In a July report in the journal *Blood*, Al-Samkari and colleagues found that nearly 10 percent of 400 people hospitalized for COVID-19 developed clots. In a February report by researchers in China, about 70 percent of people who died of COVID-19 had widespread clotting, while few



This image shows a skin rash on the arm of a COVID-19 patient. Tissue biopsies revealed the presence of clots inside tiny veins (b), as well as the presence of complement proteins in the skin and tiny blood vessels (c, d, e).

survivors did. And in a July article in the *New England Journal of Medicine*, autopsies revealed that the lungs of people who died of COVID-19 were nine times as likely to be speckled with tiny clots as those of people who died of influenza. Major risk factors for severe COVID-19 — such as diabetes, obesity and advanced age — are linked to worn-out blood vessels that make clotting more likely, says John Atkinson, an immunologist and rheumatologist at Washington University School of Medicine in St. Louis.

What Laurence finds downright “spooky” is that all this clotting happens in spite of the common US practice of prescribing blood thinners, such as heparin, to hospital patients to ward off clotting.

Bad blood

Why does clotting go overboard in some people with COVID-19? Theories abound. One possibility, Al-Samkari speculates, is that the virus activates one of the clotting factors and jump-starts the domino effect — but there’s no specific evidence that this is happening.

Another idea is that because SARS-CoV-2 infects and damages the cells lining blood vessels, it could expose the tissue underneath. That tissue makes proteins that promote clotting and normally perform a vital function, Al-Samkari says: If blood vessels are injured, the proteins get into the blood and induce clotting to plug any leak.

A third possibility is that clotting results from inflammation. And here, many experts are eyeing a set of proteins called the complement system. These proteins, known collectively as complement, attack invaders and call in other parts of the immune system to assist. They also can activate platelets and promote clotting.

Like the clotting cascade, the proteins of the complement system are activated in sequence, and scientists now know that SARS-CoV-2 can directly activate one of them, Laurence says. So can damaged body tissues, which build up during the virus’s attack.

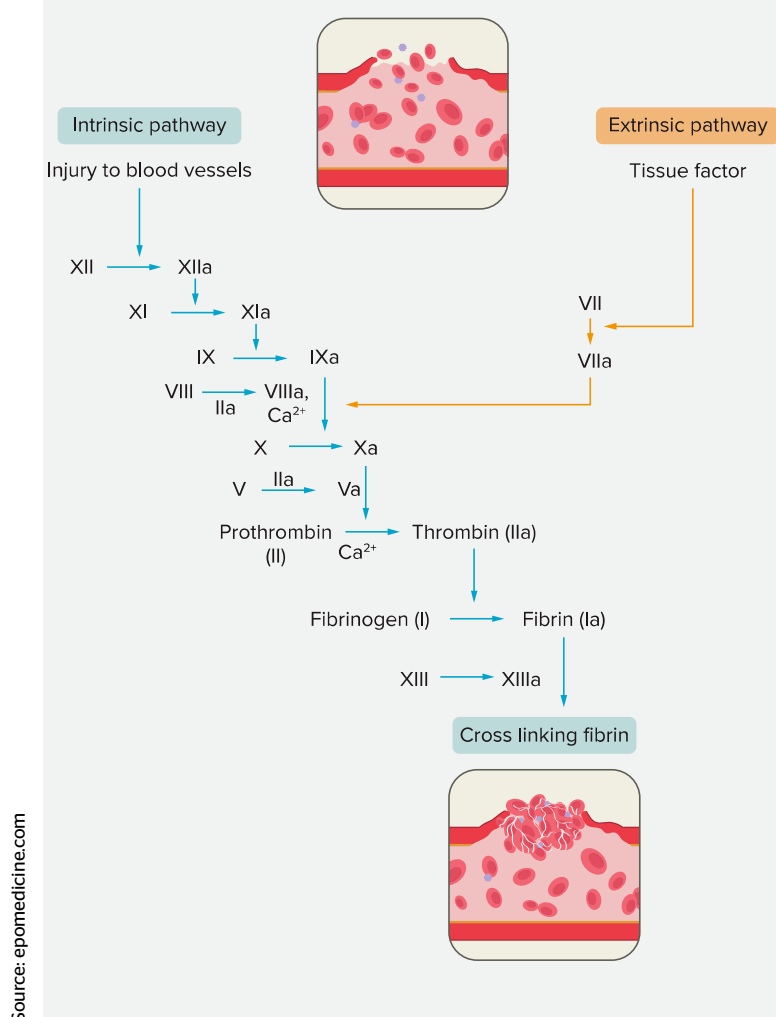
Clinicians have observed that the complement cascade appears to get out of hand in many people with severe COVID-19, says immunologist and complement expert Claudia Kemper of the National Heart, Lung, and Blood Institute, who coauthored an article about complement and immune cells in the *Annual Review of Immunology*. She and her colleagues found signs of complement activity in the lungs and livers of people who died from COVID-19, for example, and Laurence found several active complement proteins in the skin and blood vessels of his early COVID-19 clotting cases. “There is currently not super-super-hard evidence, but many complementologists think that this is a massive part of the disease,” Kemper says.

In another study of 11,000 people who had COVID-19, which has been posted online prior to review by other scientists, a New York team found that patients were more likely to become very ill and die if they had a history of clotting or bleeding, or if they had macular degeneration, which can indicate complement problems. The team also found that genes involved in complement and clotting responses were more active when the virus was present in patients’ nasal swabs.

Not only that, but the researchers also reported that people with certain variants of genes involved in the complement and clotting systems had a higher risk of severe COVID-19 disease.

In addition to complement, another immune element

Steps to clotting



A series of proteins activate each other in stepwise fashion to create a blood clot. External trauma to the blood vessel activates clotting by the faster extrinsic pathway, while the slower intrinsic pathway happens when there are problems within the vascular system.

may promote clotting in severe COVID-19 cases: an overreaction called a cytokine storm, in which the body releases an excess of inflammation-promoting cytokine molecules. "Your whole system gets revved up," Atkinson says. "When it's revved up, your clotting system gets revved up, because it senses danger."

Triple threat

As they treat their COVID-19 patients, physicians seek to hit the brakes on these clotting, complement and cytokine effects. "What you try to do is calm the

trigger," says Atkinson, who co-wrote an overview of abnormal complement control in macular degeneration and a childhood disorder for the Annual Review of Pathology: Mechanisms of Disease.

Early in the course of infection, that trigger is the virus itself, so doctors reach for antivirals such as remdesivir. But later on, says Laurence, the body's response is the biggest problem. "The virus, you might as well forget about it," he says. "You've got to control the clotting, you've got to control the inflammation, you've got to control the complement pathway — and that's easier said than done."

For clotting, there are blood thinners like heparin. Hematologists are hotly debating how much to use for COVID-19 patients, Al-Samkari says, because doctors must balance the risk of clotting with the danger of bleeding. Al-Samkari has most often observed bleeds into the digestive system for these patients, but they may also hemorrhage in the lungs, brain or spots where medical devices pierce the skin.

Many hospitals are discharging COVID-19 patients with a prescription for blood thinners in case the risk of clotting remains high at home, though there are currently no solid data to back up this practice, Al-Samkari says. More than a dozen clinical trials aim to identify the right course of action to manage clotting alongside COVID-19.

Al-Samkari stresses that there is no evidence that people with less severe COVID-19, who do not require hospitalization, should take blood thinners or aspirin to ward off clots.

For some patients, stifling inflammation may help. Steroids such as dexamethasone calm the immune system, and other medications specifically block cytokines or individual proteins in the clotting and complement cascades. Argatroban, for example, is a Food and Drug Administration-approved anticoagulant that interferes with thrombin, an element of the clotting cascade. And eculizumab, which blocks one of the complement proteins, is approved for certain inflammatory conditions.

Again, physicians await better guidance from trials. "Right now," says Al-Samkari, "we use clinical judgment as best we can, and just do our best."

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**“THE RECOGNITION
OF THE IMPACT OF
SOCIAL ISOLATION ON
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Precision Medicine



by **Dr Luis Lasalvia & Reto Merges**

Moving Towards Precision in Managing Pandemics: 5 Critical Domains for Success in Public Health

A thought leadership paper on how to “expand precision medicine” in public health

The challenge

The COVID-19 pandemic is an ongoing challenge to public health systems around the world. It has exposed the stark reality that many of these systems could be better prepared to make effective and coordinated responses to combat and contain the spread of a novel infectious disease.

COVID-19 has caused severe and immediate health and economic consequences. Millions have been infected and hundreds of thousands have died. At the same time, massive unemployment and supply chain challenges have pushed social safety nets to the breaking point. And the long-term physical and psychological effects of the pandemic will only become clear over time.

In the midst of this crisis, “infodemics” – rapidly spreading outbreaks of false, misleading, or unsafe information on the pandemic and its fallout – have left many people wondering who they can trust for reliable information on the pandemic. With the advent of online

channels and social media platforms, disinformation can spread rapidly and cause serious harm on top of the devastation inflicted by the disease itself.

Rapid progress has already been made on a number of fronts. Vaccine development efforts are proceeding at a record pace. Manufacturing concerns have responded by retooling plants and increasing capacity to produce personal protective equipment (PPE), ventilators, and other vital supplies. Hospital workflows have been radically adapted to the new situation and important diagnostic equipment has been provided at unprecedented speed under difficult circumstances. And control measures such as social distancing have significantly slowed the spread of the virus.

Both the successes and the shortcomings of the response to COVID-19 demonstrate the need for precise, coordinated, data-driven responses to infectious disease outbreaks in order to contain or even prevent the next pandemic.

The solutions

1. TESTING

Effective management of the pandemic, both on the individual case level and on the population level, starts with testing. Testing programs should be extensive and massive enough to quickly and accurately identify patients, so that community transmission can be reduced with control measures and care management.

There are two main testing categories for COVID-19: molecular testing detects active disease; antibody (or serological) testing detects patients' prior exposure to SARS-CoV-2, the virus that causes COVID-19.

Molecular testing (by a technique called polymerase chain reaction or PCR) detects viral RNA from a sample taken by a swab inside the nose. People with symptoms or at high risk to contract and spread COVID-19, like healthcare workers, should be considered for PCR testing. A positive PCR test has implications not only for the patient, but also for people who have had exposure to that patient.

It is vital that contacts of a patient with COVID-19 self-quarantine as soon as possible, ideally within 24 hours.

PCR testing has important limitations. The test technology and collection techniques are prone to potential errors. Thus, a negative molecular result does not necessarily preclude viral infection. Poor specimen quality, very early infection, improper handling, as well as technical reasons inherent to the test or even potential virus mutation can produce a false negative result. For these reasons, PCR test results must be combined with clinical observations, patient history, and epidemiologic information to guide treatment and quarantine decisions.

The other type of testing for COVID-19 is serologic (antibody) testing. Serologic testing is vital to gauge overall population exposure to the virus. This type of test also has significant limitations. For example, an apparently low false positive rate in a population where less than 1% of people have been exposed can mean a substantial absolute number of false positives.

Test quality is vital, and new tests require high accuracy, with close to 100% sensitivity and specificity and proper validation. Clearly, the need for precision and accuracy is an absolute requirement in both molecular and serologic testing.

Serologic testing has also been considered a factor in developing "immunity passports," government-backed certificates that indicate the bearer has immunity to the virus and can therefore return to work and other activities. However, there is currently no definitive evidence that antibodies produced during COVID-19

recovery confer prolonged immunity and protection from a second infection.¹ "We shouldn't jump to conclusions and use antibody test results as the sole basis for a return to work and other activities," said David Nash, MD, Founding Dean Emeritus, Jefferson College of Population Health at Thomas Jefferson University in Philadelphia, PA. "That could potentially lead to continued transmission if it turns out immunity is not conferred by prior exposure," he continued. We will need more time and studies to confirm the clinical and prognostic significance of the presence of antibodies, beyond the virus infection information they provide.

The key to effective use of both PCR and serologic testing is volume. Testing programs must be massive, coordinated, and well regulated. "Testing, more testing, and even more testing. That is the key to controlling the spread of this virus," according to Nash.

2. TRACING AND SURVEILLANCE

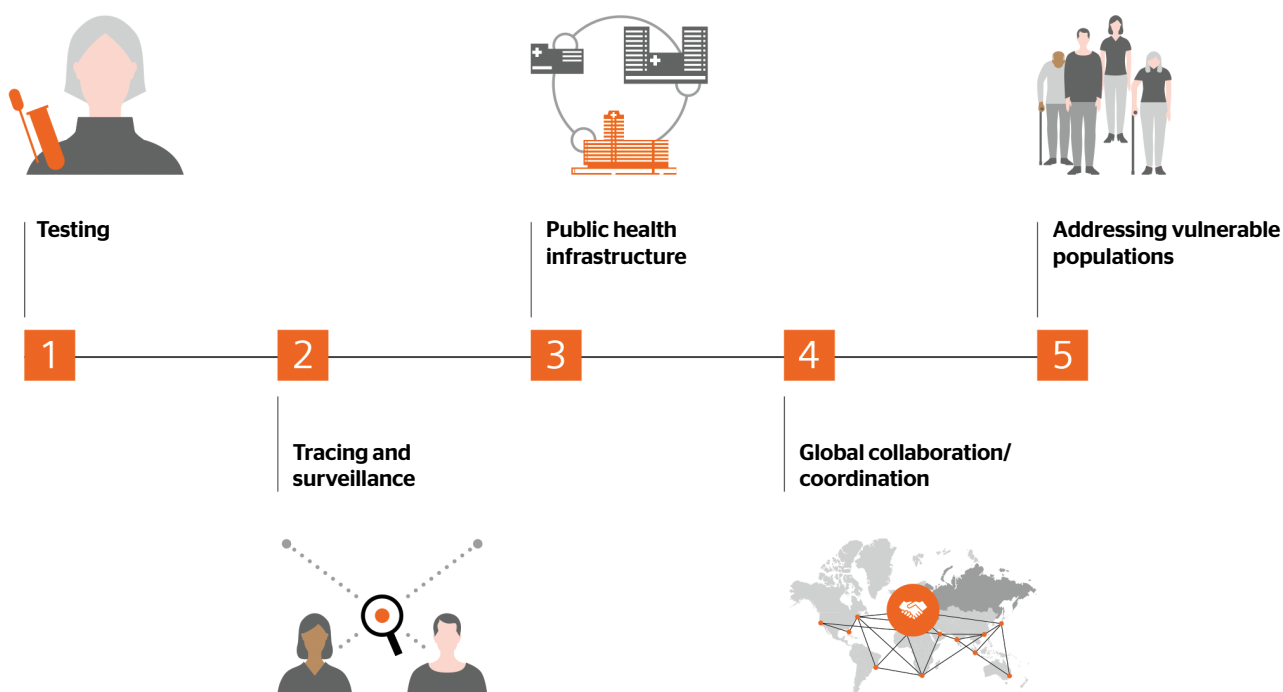
Contact tracing is a valuable tool to control outbreaks, and even more valuable when the prevalence of infection is relatively low. Effective contact tracing requires a veritable army of tracer personnel and can be enabled by properly used digital tools.

Contact tracing doesn't need to be 100% perfect but needs to be widespread to be highly effective. According to initial estimations referenced by MIT Technology Review, at least 50% of new cases need to be detected - and at least 50% of their contacts isolated - to reduce transmission by 10% or more. And 90% detection and 90% reach of contacts, with 100% testing, can reduce transmission by more than 45%.²

Achieving the results described above is a daunting challenge and quickly becomes unattainable as infection rates rise. In countries where there's high prevalence, relatively low testing rates, and a general distrust of guidelines by national agencies, contact tracing is unlikely to be effective on a national level.²

Yet it is important to create the infrastructure for wide spread contact tracing now. Contact tracing can help prevent localized outbreaks from becoming regional epidemics. In order for countries like the US to lift social distancing and other precautions and safely reengage in social and economic activity, informed policy guided by data gathered through extensive testing and contact tracing programs is a necessity. According to US CDC Director Robert Redfield, a "... substantial expansion of public health field workers" will be needed to undertake the aggressive contact tracing needed to allow social, recreational, and economic activity to resume safely.

The solutions



Technology, including smartphone apps, can certainly supplement human contact tracing. However it raises privacy concerns and requires wide uptake and public support to be effective. Such technology-based solutions may be viewed skeptically because of potential privacy risks and the specter of governmental surveillance. Conforming with data privacy regulations in many Western nations, like GDPR in Europe, further complicates technology-based pandemic surveillance efforts. Even in such circumstances, apps and other digital enablers might play an important role in syndromic surveillance, patient education (surveys/chatbots), and population morbidity aggregation.

Complementary, well coordinated digital and non-digital tracing strategies can work in tandem to prevent community transmission. New Zealand accomplished its favorable results by quickly interviewing each patient who tested positive in order to identify recent contacts. This approach was complemented by mobile device apps that help people track recent contacts, in order to rapidly identify and isolate those who may have been exposed to the virus. Similar approaches in other countries, like Uruguay, have produced positive results to date.

In addition to contact tracing, coordinated international surveillance and information sharing will be vital to managing this pandemic and any that may arise in the future.

3. PUBLIC HEALTH INFRASTRUCTURE

In order to respond more effectively to - or even prevent - future outbreaks of COVID-19 or other potential pandemics, many nations would benefit from upgrading their public health infrastructure. Pandemic preparedness has emerged as a key national security and economic imperative. According to one estimate, every month of partial economic shutdown reduces the US gross domestic product by 5%, leading to a loss of \$2 trillion and tens of millions of jobs in just the first couple of months of shutdown in the US.⁴

Contrast this impact with the estimated investments in public health that can reduce the impact of future outbreaks. The costs of contact tracing infrastructure and widespread molecular and serological testing have been estimated at roughly \$5 billion USD, or 0.3% of the initial loss to GDP.⁴

In addition, upgrading and standardizing healthcare IT infrastructure will allow real-time data sharing and will help mobilize resources needed to cope with a surge in cases. Real-time data is critical since outbreaks begin as local events. The prime objective in a local outbreak is to stop community transmission. Precision in early detection and mitigation can produce powerful results, as seen in New Zealand and other nations that generated a rapid, comprehensive, and data-driven initial response to COVID-19.

Tracking and increasing reserves of personal pro-

South Korea's COVID-19 success: Data-driven approach supported by public IT infrastructure

SARS, undertook aggressive measures to mitigate the risks of COVID-19. South Korea implemented a number of practices that, considering its high population density, proximity to the epicenter of the COVID-19 outbreak, and relatively open travel policies, appear to have been highly successful to date, as the country

has only reported 274 deaths as of June 8, 2020. These measures allowed Korea to flatten the COVID-19 curve without taking draconian measures. How did South Korea manage its COVID-19 response? The government focused on data generation, transparency, and sharing to support key decisions. South Korea

quickly rolled out innovative data-based methods like drive-thru and walk-thru screening centers, extensive free testing, quick diagnosis, tracking and tracing confirmed cases, the use of information technology to share data, and an effective public and private partnership for the implementation.³

Data Sources	Mobile phone carriers			Institutional records			Movement trackers		
Data Categories	Location data			Personal identification information	Immigration records	Prescription and medical records	CCTV footage	Credit/debit transactions	Transit pass records

South Korea leveraged its IT infrastructure to enable data-driven decision making based on multiple complementary data sources.

tective equipment, as well as other critical resources (hospital and ICU beds, ventilators), should align with the creation of plans to rapidly scale up production and distribution as needed.

A robust, data-driven strategy will enable a precise, timely response that can mitigate some of the clinical and economic impacts of infectious disease outbreaks.

Perhaps one of the most important learnings is that governments should invest in communication and patient education systems that provide their people with accurate, up-to-date information and combat the plague of misleading, fragmented, or false information that has left residents of some nations confused as to what they should be doing to protect themselves and others. This will require cooperation and commitment from across the socio-political spectrum in order to create and distribute the most accurate and helpful information available. Centralized guidelines should work in tandem with tailored regional and local efforts to support and inform the public about what to do during a pandemic.

4. GLOBAL COLLABORATION/COORDINATION

Viruses and other pathogens do not respect national borders. The ease and prevalence of global trade and travel means that a disease outbreak anywhere in the world can quickly become a pandemic everywhere in the world. This calls for an effective coordination at a global level, on top of national and regional efforts.

A critical element for success is a global infectious disease surveillance system established to provide early warning of, and support for, initial localized outbreaks that could broaden.

Lessons learned in earlier outbreaks led East Asian nations to take aggressive actions to stem the spread of COVID-19, leading to lower caseloads than those seen in many Western nations that were slower to adopt similar actions. This know-how needs to be shared in a collaborative manner, as well as information on the equipment and technology requirements to accomplish rapid testing, tracing, and quarantine. This collaboration can be strengthened by coordination between the public and private sectors for a timely, technology-driven, innovative, and coordinated response to future pandemics.

Having more scientists and analysts working on the problem and sharing information from a variety of contexts and social settings will enhance the effectiveness of local and global responses to future pandemics. "We're taking that data and giving it extra analytics firepower," said Beth Blauer, Executive Director of the Centers for Civic Impact.⁵

This global collaboration should respect the vast global diversity of cultures and regulations. For example, some measures may be viewed with suspicion where they run contrary to established social mores and political norms. Education and communication programs, along with culturally appropriate community outreach, can help build trust and increase participation in and success of infectious disease mitigation programs.

The full potential of international cooperation can only be reached if sensitive data are protected from both corruption and misuse by bad actors. Blockchain technology and other safeguards can help ensure data security and patient privacy.

Finally, wealthy nations should consider assisting or cooperating with lower-income countries to help

manage the spread of infectious diseases. Working closely with countries that don't have the resources of an industrialized nation is a priority in terms of both ethics and national self-interest.

5. ADDRESSING THE MOST VULNERABLE PATIENT POPULATIONS AND HIGH-RISK GROUPS

People around the world are not homogeneously exposed to the same morbidity/mortality risk, nor to the same risk of infection. Identifying the subpopulations that are most vulnerable provides a more tailored approach for addressing their specific needs.

We know that the elderly and people with chronic comorbidities are at greater risk of morbidity and mortality from COVID-19 than others. But there are other dynamics at play that put additional populations at risk.

Some people face an increased risk of contracting COVID-19 because of higher exposure. This is the case for essential workers, like healthcare workers and workforces in food industries. A clear roadmap to managing infectious disease outbreaks is emerging. Widespread, precise testing is a must.

When outbreaks are detected, rapid contact tracing coupled with isolation and other appropriate measures can lower infection rates substantially and prevent widespread infection. Immediate and substantial investments in health infrastructure will help countries cope with the current pandemic and prepare for future events. International cooperation can help identify and contain outbreaks, potentially preventing pandemics.

It is vitally important to identify groups that might face structurally higher risks of both exposure and mortality during outbreaks of infectious disease. Identifying subpopulations - including the elderly, minorities, immigrants, and LGBTQ people in the current pandemic - enables development of tailored prevention and treatment strategies: in other words, precision medicine at scale.

There are many other viruses with the potential to cause a pandemic with an impact equal to or even greater than the current pandemic. We don't know the answer to the question of when the next pandemic will happen. We do know how to mitigate this risk significantly. Now is the time to pursue improved public health infrastructure, national/regional coordination, technology-driven solutions, and pandemic preparedness on a global scale.

Conclusion

A comprehensive response to infectious disease outbreaks requires prompt and accurate identification of subpopulations that are disproportionately affected due to social determinants like income, education, access to care, and geography.

Racial and ethnic disparities play a role, due to economic conditions and unequal healthcare access. In the US, for example, African-Americans face an increased risk of hospitalization and death from COVID-19.⁶ This gap is correlated with a lack of access to healthcare and the high prevalence of asthma and other chronic conditions.

This situation may be even more dire for undocumented immigrants worldwide, who are less likely to seek care for fear of immigration action against them and their families. The LGBTQ community also faces a higher risk due to factors including income, comorbidities and access to healthcare.

Effective, tailored, trusted community outreach will be vital to assessing the impact on, and serving the needs of, vulnerable subpopulations during this and future pandemics. A data-driven precision medicine approach may even predict in advance which subpopulations may be more vulnerable and require additional healthcare infrastructure and support. Containing community transmission within these vulnerable groups is vital to effective pandemic management.

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Why Do You Feel Lonely?

Neuroscience is Starting to Find Answers

A neuroscientist's hunt for loneliness could help us better understand the costs of social isolation.

Long before the world had ever heard of COVID-19, Kay Tye set out to answer a question that has taken on new resonance in the age of social distancing: When people feel lonely, do they crave social interactions in the same way a hungry person craves food? And could she and her colleagues detect and measure this “hunger” in the neural circuits of the brain?

“Loneliness is a universal thing. If I were to ask people on the street, ‘Do you know what it means to be lonely?’ probably 99 or 100% of people would say yes,” explains Tye, a neuroscientist at the Salk Institute of Biological

Sciences. “It seems reasonable to argue that it should be a concept in neuroscience. It’s just that nobody ever found a way to test it and localize it to specific cells. That’s what we are trying to do.”

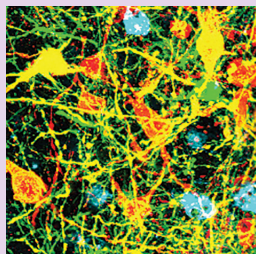
In recent years, a vast scientific literature has emerged linking loneliness to depression, anxiety, alcoholism, and drug abuse. There is even a growing body of epidemiological work showing that loneliness makes you more likely to fall ill: it seems to prompt the chronic release of hormones that suppress healthy immune function. Biochemical changes from loneliness can accelerate the spread of cancer, hasten heart disease and Alzheimer’s, or simply drain the most vital among us of the will to go on. The ability to measure and detect it could help identify those at risk and pave the way for new kinds of interventions.

In the months ahead, many are warning, we’re likely to see the mental-health impacts of COVID-19 play out on a global scale. Psychiatrists are already worried

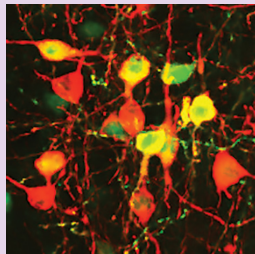


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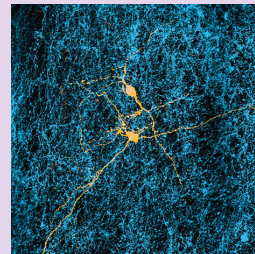
DRN neurons are shown here within the dopamine system and downstream circuitry.



Matthew Ungless/Imperial College London



Gillian Matthews/Kay Tye/MIT



Gillian Matthews/Kay Tye/Mit

about rising rates of suicide and drug overdoses in the US, and social isolation, along with anxiety and chronic stress, is one likely cause. “The recognition of the impact of social isolation on the rest of mental health is going to hit everyone really soon,” Tye says. “I think the impact on mental health will be pretty intense and pretty immediate.”

Yet quantifying, or even defining, loneliness is a difficult challenge. So difficult, in fact, that neuroscientists have long avoided the topic.

Loneliness, Tye says, is inherently subjective. It’s possible to spend the day completely isolated, in quiet contemplation, and feel invigorated. Or to stew in alienated misery surrounded by a crowd, in the heart of a big city, or accompanied by close friends and family. Or, to take a more contemporary example, to participate in a Zoom call with loved ones in another city and feel deeply connected—or even more lonely than when the call began.

This fuzziness might explain the curious results that came back when Tye, before publishing her first scientific paper on the neuroscience of loneliness in 2016, ran a search for other papers on the topic. Though she found studies on loneliness in the psychological literature, the number of papers that also contained the words “cells,” “neurons,” or “brain” was precisely zero.

Though the nature of loneliness has preoccupied some of the greatest minds in philosophy, literature, and art for millennia, neuroscientists have long assumed that questions about how it might work in the human brain would elude their data-driven labs. How do you quantify the experience? And where would you even begin to look in the brain for the changes brought about by such a subjective feeling?

Tye hopes to change that by building an entirely new field: one aimed at analyzing and understanding how our sensory perceptions, previous experiences,

genetic predispositions, and life situations combine with our environment to produce a concrete, measurable biological state called loneliness. And she wants to identify what that seemingly ineffable experience looks like when it is activated in the brain.

If Tye succeeds, it could lead to new tools for identifying and monitoring those at risk from illnesses worsened by loneliness. It could also yield better ways to handle what could be a looming public health crisis triggered by COVID-19.

FINDING THE LONELINESS NEURONS

Tye has homed in on specific populations of neurons in rodent brains that seem to be associated with a measurable need for social interaction—a hunger that can be manipulated by directly stimulating the neurons themselves. To pinpoint these neurons, Tye relied on a technique she developed while working as a postdoc in the Stanford University lab of Karl Deisseroth.

Deisseroth had pioneered optogenetics, a technique in which genetically engineered, light-sensitive proteins are implanted into brain cells; researchers can then turn individual neurons on or off simply by shining lights on them through fiber-optic cables. Though the technique is far too invasive to use in people—as well as an injection into the brain to deliver the proteins, it requires threading the fiber-optic cable through the skull and directly into the brain—it allows researchers to tweak neurons in live, freely moving rodents and then observe their behavior.

Tye began using optogenetics in rodents to trace the neural circuits involved in emotion, motivation, and social behaviors. She found that by activating a neuron and then identifying the other parts of the brain that responded to the signal the neuron gave out, she could trace the discrete circuits of cells that work together to perform specific functions. Tye meticulously traced the

connections out of the amygdala, an almond-shaped set of neurons thought to be the seat of fear and anxiety both in rodents and in humans.

Scientists have long known that stimulating the amygdala as a whole could cause an animal to cower in fear. But by following the maze of connections in and out of different parts of the amygdala, Tye was able to demonstrate that the brain's "fear circuit" was capable of imbuing sensory stimuli with far more nuance than previously understood. It seemed, in fact, to modulate courage too.

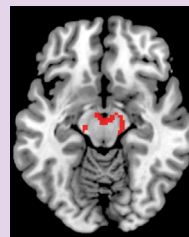
By the time Tye set up her lab at MIT's Picower Institute for Learning and Memory in 2012, she was following the neural connections of the amygdala to places like the prefrontal cortex, known as the brain's executive, and the hippocampus, the seat of episodic memory. The goal was to construct maps of the circuits across the brain that we rely on to understand the world, make meaning of our moment-to-moment experience, and respond to different situations.

She began studying loneliness largely by serendipity. While scouting for new postdocs, Tye came across the work of Gillian Matthews. As a graduate student at Imperial College London, Matthews had made an unexpected discovery when she separated the mice in her experiments from one another. Social isolation—the very fact of being alone—seemed to have changed brain cells called DRN neurons in ways that implied they might play a role in loneliness.

Tye immediately saw the possibilities. "Oh, my gosh—this is incredible!" she recalls thinking. That the signs of social isolation could be traced to a specific part of the brain made total sense to her. "But where is it and how would you find it? If this could be the region, I thought, that would be super interesting." In all her studies of neurons, says Tye, "I'd never seen anything about social isolation before. Ever."

Tye realized that if she and Matthews could construct a map of a loneliness circuit, they could answer in the lab precisely the kinds of questions she hoped to explore: How does the brain imbue social isolation with meaning? How and when does the objective experience of not being around people, in other words, become the subjective experience of loneliness? The first step was to better understand the role the DRN neurons played in this mental state.

One of the first things Tye and Matthews noticed was that when they stimulated these neurons, the animals were more likely to seek social interaction with other mice. In a later experiment, they showed that animals, when given the choice, actively avoided areas of their



Tomova and Saxe used fMRI scans to measure the brain's response to food and social interaction after periods of fasting and isolation. The scan on the right shows activity in the midbrain associated with rewards.

cages that, when entered, triggered the activation of the neurons. This suggested that their quest for social interaction was driven more by a desire to avoid pain than to generate pleasure—an experience that mimicked the "aversive" experience of loneliness.

In a follow-up experiment, the researchers put some of the mice in solitary confinement for 24 hours and then reintroduced them to social groups. As one would expect, the animals sought out and spent an unusual amount of time interacting with other animals, as if they'd been "lonely." Then Tye and Matthews isolated the same mice again, this time using optogenetics to silence the DRN neurons after the period in solitary. This time, the animals lost the desire for social contact. It was as if the social isolation had not been registered in their brains.

Scientists have long known that the brain harbors the biological equivalent of a car's fuel gauge—a complex homeostatic system that allows our gray matter to track the state of our basic biological needs, like those for food, water, and sleep. The purpose of the system is to drive us toward behaviors aimed at maintaining or restoring our natural state of balance.

Tye and Matthews seemed to have found the equivalent of a homeostatic regulator for the basic social-contact needs of rodents. The next question: What do these findings mean for people?

HUNGRY FOR A SMILE

To answer that question, Tye is working with researchers in the lab of Rebecca Saxe, a professor of cognitive neuroscience at MIT, who specializes in the study of human social cognition and emotion.

The human experiments are far harder to design because the brain surgery required for optogenetics is

not an option. But it's possible to expose lonely people to pictures of friendly people offering social cues—like a smile—and then monitor and record changes in blood flow to different parts of the brain using fMRI imaging. And, thanks to previous experiments, scientists have a good idea of where in the brain to look—an area analogous to the one Matthews and Tye studied in mice.

Last year, Livia Tomova, a postdoc who has been overseeing the research in Saxe's lab, recruited 40 volunteers who self-identified as having large social networks and very low levels of loneliness. Tomova exiled her subjects to a room in the lab and forbade any human contact for 10 hours. For comparison, Tomova asked the same participants to come back for a second 10-hour session that contained plenty of social interaction, but no food.

At the end of each session, the subjects were asked to climb into the fMRI scanner and were exposed to different images: some showed people offering nonverbal social cues, and others contained pictures of food.

Unlike Tye and Matthews, Tomova was unable to home in on individual neurons. But she was able to track changes in blood flow within larger areas of the scan, known as voxels; each voxel displayed the changing activity of discrete populations of several thousand neurons. Tomova focused in on areas of the midbrain known to be rich in the neurons associated with producing and processing the neurotransmitter dopamine.

These areas have already been linked in other experiments to the sensation of “wanting” or “craving” something. They're areas that light up in response to images of food when a person is hungry, or to drug-related images in people with addiction. Would they do the same in lonely people shown pictures of a smile?

The answer was clear: after the social isolation, the subjects' brain scans showed far more activity in the midbrain when they were shown the pictures of social cues. When the subjects were hungry but had not been socially isolated, they exhibited a similarly robust reaction to the food cues, but not to the social ones.

“Whether it's the drive for social contact or the drive for other things like food, it seems to be represented in a very similar way,” says Tomova.

THE PANDEMIC EXPERIMENT

Understanding how the hunger for social contact is produced in the brain might allow a deeper understanding of the role social isolation plays in some illnesses.

Objectively measuring loneliness in the brain, as opposed to asking people how they feel, could provide

some clarity on the connection between depression and loneliness, for example. Which comes first—does depression cause loneliness, or does loneliness cause depression? And might social intervention applied at the right time help fight depression?

Insights into the circuitry of loneliness in the brain might also shed some light on addiction, which isolated animals are more prone to, according to some research. The evidence appears particularly strong in adolescent animals, which seem to be even more sensitive to the effects of social isolation than older or younger ones. Humans between the ages of 16 and 24 are the most likely to report feeling lonely, and this is also the age when many mental-health disorders first begin to manifest. Is there a connection?

But the most obvious current need may be in response to the social isolation prompted by the covid pandemic. Some internet surveys report no overall increase in loneliness since the pandemic began, but what about people at most risk of mental-health problems? When they are isolated, at what point does it begin to endanger their psychological and physical well-being? And what types of interventions might protect them from that danger? Once we can measure loneliness, we can begin to find out, making it far easier to design targeted interventions.

“A vital question for future research is how much, and what kinds of positive social interaction are sufficient to fulfill this basic need and thus eliminate the neural craving response,” Tomova and Tye wrote in a preprint of their forthcoming paper, posted at the end of March. The pandemic “emphasized the need for a better understanding of human social needs and the neural mechanism underlying social motivation,” they wrote. “The current study provides a first step in that direction.”

That, in the typically understated language of science, signals the birth of a whole new field of research—not something you often get to witness, let alone be part of.

“It's just so exciting to me, because these are all concepts that we've heard about a million times in psychology, and for the very first time, we actually have cells in the brain that we can link to the system,” Tye says. “And once you have one cell, you can trace backwards, you can trace forwards; you can figure out what's upstream; you can figure out what all the neurons that are upstream are doing, and what messengers are being sent,” says Tye. “Now you can find the whole circuit; you know where to start.”

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As the patient had diffuse proliferative glomerulonephritis, with massive proteinuria and renal failure, he was started on Prednisolone 60mg/day (1.5 mg/kg/day). Renal functions improved gradually after initiation of steroids.

Acute Post-streptococcal Glomerulonephritis and Acute Rheumatic Fever, Co-existing in the Same Patient

Post streptococcal glomerulonephritis and rheumatic fever have different epidemiology and immunological features; their concurrent development in the same patient is very rare.

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Abstract: A 15-year-old male presented with acute glomerulonephritis, preceded by a history of sore throat and fever. He had features of acute rheumatic fever and echocardiographic evidence of severe mitral regurgitation and aortic regurgitation. He had proteinuria, haematuria and renal failure; renal biopsy showed diffuse exudative endocapillary proliferative glomerulonephritis. Simultaneous occurrence of acute glomerulonephritis and rheumatic fever in the same patient is very rare. He responded to treatment with steroids and his renal functions recovered over three months.

INTRODUCTION

Acute post-streptococcal glomerulonephritis (APSGN) and acute rheumatic fever (RF) are both well-recognized non suppurative sequelae of group A beta hemolytic streptococcus infections.¹ The serotypes of group A Streptococci can be divided into those with rheumatogenic and nephritogenic potential.² Post-streptococcal glomerulonephritis and rheumatic fever have different epidemiology and immunological features; their concurrent development in the same patient is very rare,³ because of their different pathophysiologic mechanisms.^{1,4}

CASE REPORT

A 15-year-old male presented with history of fever of three weeks duration, associated with a sore throat. Twenty days after the onset of fever, he noticed puffiness of the face followed by progressive worsening of oedema involving the rest of the body. He had bilateral

Summary of electrographic findings in the patient

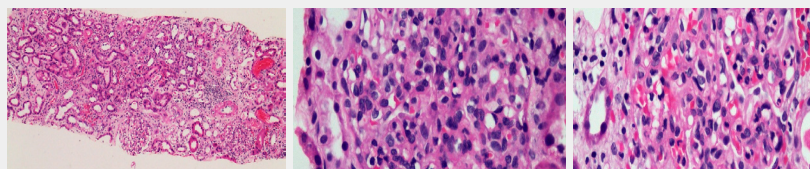
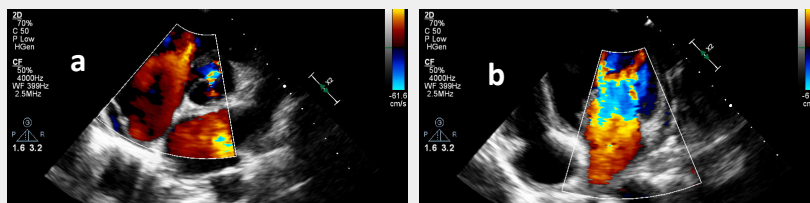


Figure 1a: Renal biopsy showing enlarged glomeruli, interstitial edema, interstitial inflammation and RBC casts in the tubular lumina (H&E, 20X), **1b & c:** showing diffuse endocapillary proliferation with mononuclear and neutrophilic exudate (H&E, 40X)



Figures 2a, 2b: Valvular thickening of aortic leaflets with moderate aortic regurgitation and moderate mitral valve regurgitation seen on echocardiogram

pedal oedema and abdominal distension, associated with dark-coloured urine and reduced urine output. He had arthralgia involving both knee joints. Urine examination showed numerous RBCs and proteinuria; Serum creatinine was 1.8mg/dl. There was a weight gain of 8 kg.

On admission to our center, the patient was febrile, and blood pressure was 130/88 mm Hg corresponding to the 95th centile). He had pallor, facial and pedal oedema. He had gradual worsening of dyspnoea and tachypnoea, and a grade 3/6 pansystolic murmur in the mitral area radiating to the axilla.

Investigations revealed Haemoglobin: 9.9 g/dl, WBC count: 8100 /cu mm, Platelet count: 242000/cu mm, ESR: 44mm at 1 hour, CRP: 103.5mg/dl, serum creatinine: 1.77mg/dl and serum albumin: 2.8 g/dl. Urine analysis showed albumin 2+ and microscopic haematuria. Urine protein (24hr) was 6.1 g. The patient had elevated ASO titres (>800) and hypocomplementemia (serum C3:45 mg/dl). A chest X-ray showed bilateral blunting of the costophrenic angles, suggestive of bilateral pleural effusion. An electrocardiogram showed a prolonged PR interval (0.32 seconds). Renal failure worsened rapidly; serum creatinine increased to 6.9 mg/dl over 7 days. In view of this, a renal biopsy was done after initiation of dialysis. Blood and urine cultures were sterile, and a throat swab showed no growth.

The renal histology showed features of diffuse exudative proliferative glomerulonephritis with neutrophilic exudates (Figs 1A, 1B, 1C). Immunofluorescence revealed granular capillary wall staining for IgG (3+) and C3 (2+). There were no crescents. The picture was consistent with post-infectious glomerulonephritis.

A 2D echocardiogram (figs 2A, 2B) showed dilated left atrium and left ventricle, right coronary cusp pro-

lapse and severe aortic regurgitation. The aortic valve annulus was 2.2 cm. The anterior mitral leaflet was thickened, and there was severe eccentric mitral regurgitation with chordal rupture (mitral annulus 3.4cm). A trans-oesophageal echocardiogram confirmed the findings. As he had one major and two minor criteria of modified Jones criteria for rheumatic fever, he was diagnosed to have acute rheumatic fever. Infective endocarditis was ruled out, as repeated blood cultures were sterile and there was no evidence of vegetations from the echocardiogram.

As the patient had diffuse proliferative glomerulonephritis, with massive proteinuria and renal failure, he was started on Prednisolone 60mg/day (1.5 mg/kg/day). Renal functions improved gradually after initiation of steroids. He was treated with oral Furosemide and antihypertensives. Benzathine Penicillin (1.2 MIU injection intramuscularly) was advised every 3 weeks. He improved remarkably on treatment with steroids. The aortic regurgitation (AR) improved from severe AR to mild AR over ten days; however moderate mitral regurgitation persisted. At the time of discharge, serum creatinine was 2.9 mg/dl. On follow-up at three months, serum creatinine was 1.1mg%,

and ESR 15mm/hr. Urine analysis showed 5 RBCs/hpf and no albuminuria. A 2D echocardiogram showed persistence of mild mitral and aortic regurgitation. Steroids were tapered and stopped within three months.

DISCUSSION

APSGN can affect individuals of any age, but typically occurs usually between the ages of 5 and 15 years⁵; males are affected twice as often as females. Post-infectious glomerulonephritis is associated with a previous skin or throat infection by a group A streptococcus (*Streptococcus pyogenes*), or occasionally group C or G streptococci. Pyoderma associated APSGN occurs more frequently in summer. A review estimated that over 470,000 cases of APSGN occur annually worldwide. 97% of these cases are in less developed countries, with an annual incidence that ranges from 9.5 to 28.5 per 100,000 individuals⁷. Studies from India have reported that APSGN constitutes about 6 to 8% of all renal biopsy specimens.

Rheumatic fever can occur at any age, although most cases occur in children aged 5 to 15 years⁷. There are about 233,000 deaths worldwide attributable to rheumatic fever or rheumatic heart disease each year⁷.

The mean incidence of RF is 19 per 100,000 school-aged children worldwide¹⁰. Rheumatic fever occurs more frequently in winter months.

Two antigens have been implicated as potential causes of APSGN: the glycolytic enzyme identified as glyceraldehyde-3-phosphate dehydrogenase, and streptococcal proteinase exotoxin B (SPEB, zymogen), both of which activate the alternate pathway of the complement system⁸. APSGN occurs due to the antibody-mediated response to bacterial infection, typically with a nephritogenic strain of *Streptococcus pyogenes*, which results in glomerular deposition and/or in-situ formation of immune complexes; a glomerular inflammatory response ensues with leukocyte infiltration and complement activation⁶. Nephritogenic strains associated with the development of APSGN include M types 1, 4, 12, 15 (causing throat infection and ASPGN) and 2, 42, 49, 55, 57, 60 (causing skin infection and ASPGN).⁹

A streptococcal strain capable of causing a well-documented pharyngitis is almost always capable of causing rheumatic fever¹¹. Many M types are associated with RF, including 1, 3, 5, 6, 11, 12, 14, 17, 18, 19, 24, 27, 29, 30, 32, and 4112. The lack of specific rheumatogenic strains may explain the relatively high risk of recurrent disease with new streptococcal infections, in contrast to poststreptococcal glomerulonephritis, in which only a few "nephritogenic" strains appear to be capable of inducing the disease, and hence recurrent disease is uncommon.

Acute rheumatic fever is caused by the mechanism of molecular mimicry. M protein and the hyaluronate capsule cause inflammation by inducing cross-reacting autoantibodies against human tissue proteins, stimulated by cell-mediated immunity in genetically predisposed patients. Early recognition of acute rheumatic fever is very

important, because of the possibility of developing rheumatic heart disease if not treated appropriately.

Co-existent acute rheumatic fever and post streptococcal glomerulonephritis were observed in our patient. PSGN and RF rarely coincide, as has been previously described.^{1,3} Simultaneous occurrence of APSGN and acute RF was first reported in 1981. Since then, seventeen cases have been reported. Most of the cases had acute RF preceding, or after the event of APSGN. Only six out of seventeen patients had simultaneous occurrence of acute RF and APSGN, as seen in our case¹³. The explanation for the co-occurrence might be that certain strains have both nephritogenic and rheumatogenic potential (e.g. M types 1 and 12), which can result in the occurrence of both conditions.³ Although some serotypes are both rheumatogenic and nephritogenic, it cannot be said with certainty whether a single pharyngeal infection resulted in both APSGN and acute RF in this case; however the possibility of a single infection causing both PSGN and rheumatic fever cannot be ruled out. We could not isolate the organism on throat swab culture.

Mitral insufficiency is frequently seen in patients with concurrent acute RF and APSGN, however only 2 cases of aortic insufficiency have been reported so far with these conditions. Our patient had both mitral and aortic insufficiency¹.

In patients associated with acute RF, focal and mesangial proliferative glomerulonephritis has been reported; diffuse exudative proliferative glomerulonephritis which is typical of APSGN is rare; our patient had diffuse proliferative GN³.

CONCLUSION

Co-existence of RF and APSGN in the same patient is very rare. Awareness of infection risk and prevention strategies

at the grass roots level is essential to lessen the burden of post-infectious glomerulonephritis in our country.

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Case Report

Polymerase Gamma: A True Story of Men Against a Gene

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INTRODUCTION

Mitochondria play an important role in the generation of adenosine triphosphate via the electron-transport chain through oxidative phosphorylation. Mitochondrial dysfunction often leads to disorders that present with various neurologic, hepatic and muscular symptoms¹. Mitochondrial disorders are infrequently diagnosed in India, mainly because of the lack of advanced diagnostic facilities and molecular studies. However, with the increasing availability and feasibility of genetic testing, it has now become possible to confirm these diagnoses – to guide the future management of affected children, as well as for accurate counselling and prenatal diagnosis in future pregnancies in their families².

Mutations in the polymerase gamma gene (*POLG*), which codes the DNA polymerase enzyme in mitochondria, are associated with a clinical continuum of heterogeneous syndromes, ranging from infantile-onset epilepsies and liver failure to late-onset ophthalmoplegia and muscle weakness. Alpers disease, or progressive neuronal degeneration of childhood, which first received attention from Alpers in 1931 and was further described with its hepatic manifestation by Huttenlocher and Harding^{3,4}, is a rare mitochondrial disease characterized by its classic triad of refractory seizures, psychomotor regression, and hepatopathy⁵. Alpers Syndrome is one of the most severe phenotypes of polymerase gene mutation, and death usually occurs before 10 years of age.

CASE REPORT

A 7-year-old boy initially presented to the Emergency department with generalised tonic-clonic movement of his limbs. He had generalised clumsiness which had lasted

for two years, and had difficult vision in bright lights. The developmental milestones were otherwise normal. He had no prior hospital admission. The patient was the third child of a non-consanguineous married couple. The birth history and perinatal history had been unremarkable, and his weight and height were between the third and fiftieth centiles.

The child was initially treated with benzodiazepines, phenytoin and levetiracetam. His EEG showed continuous generalised epileptiform discharges, hence midazolam infusion was started. A CT scan and MRI were normal (Fig 1), as was the CSF. In view of the super refractory status epilepticus and not being able to control the electrographic seizure activity, a general anaesthetic agent, isoflurane, was initiated. Burst suppression was achieved after 2 hours of initiation of isoflurane, this was then gradually tapered over a period of 48 hours. Other anticonvulsants Phenytoin, levetiracetam and valproate were optimised. Concurrent infections were treated accordingly. The child was discharged after a 4 week of hospital stay, and remained under regular follow up.

Two months later, the child was readmitted for repeated bouts of vomiting and lethargy. On examination, he had mild ptosis and external ophthalmoplegia, hypotonia of all 4 limbs and the liver was slightly enlarged. An EEG showed occipital spikes. The initial laboratory findings suggested acute liver failure, with AST and ALT levels of 244 IU/L and 168 IU/L, total and direct bilirubin of 4.4 mg/dL and 3.3 mg/dL, and ammonia of 98 µg/dL respectively. An initial blood gas analysis test, with normal pH of 7.37 and bicarbonate of 25.8 mmol/L, was not suggestive of definite metabolic acidosis, although the lactate level was slightly elevated to 5.4 mmol/L. The prothrombin time was initially 2.5(INR),

and over the course of time the INR gradually increased, along with the liver enzymes. An MRI Brain did not show any significant changes.

Drug levels were requested, to rule out any drug-induced cause for liver dysfunction. The serum phenytoin and serum valproate levels were normal. Ammonia reduction measures including sodium benzoate and carnitine were started. Plasmapheresis was initiated, in order to eliminate the valproate metabolites in the blood that can cause liver dysfunction. The serum lactate levels were progressively increasing. Numerous viral and autoimmune evaluations were performed that all returned as normal, and there were no remarkable findings in an imaging study. The lactate-to-pyruvate ratio was 20, and urine sent for GCMS suggested the possibility of lactic acidosis due to a mitochondrial disorder.

MR Spectroscopy (Figs 2, 3) did not show any elevated levels of lactate, and tandem mass spectroscopy results were normal. Therefore, a whole-exome sequencing analysis was sent for further evaluation. Meanwhile, the patient's mental status became drowsy with hyperammonemia, and he had become progressively jaundiced. He had multiple episodes of seizures in the form of myoclonic jerks and focal seizures, and had persistent ptosis and external ophthalmoplegia. An EEG showed generalised slowing. A liver transplant was not performed in view of the mitochondrial etiology and neurological involvement. The child died a few weeks later because of progressive liver failure. Two weeks postmortem, his genetic results showed he was positive for a polymerase gene mutation.

DISCUSSION

Alpers-Huttenlocher syndrome is a rare autosomal recessive disorder, caused by mutation in the polymerase gamma gene. The most common age of onset is between 2 and 4 years, with a range of 3 months to 8 years. Infants and children with Alpers-Huttenlocher syndrome are healthy until disease onset, although some have identified non-specific developmental delays. The age of onset is influenced, in part, by specific mutations within the polymerase gamma gene, other genes, and environmental factors such as intercurrent viral infections and certain medications like valproic acid. The classic clinical triad is developmental regression, hepatopathy and refractory seizures (Table 2).

Thus, the diagnostic criteria for Alpers-Huttenlocher syndrome were met in this patient; the classic clinical triad of refractory seizures, liver failure and developmental regression; elevated blood and CSF lactate; and an electroencephalogram showing multifocal spike-and-wave discharges. In addition, the diagnosis was confirmed

Table 2. Diagnostic criteria for Alpers-Huttenlocher syndrome⁶

1. Clinical triad of refractory seizures, psychomotor regression and hepatopathy
2. In the absence of hepatopathy or additional findings, the diagnosis can only be confirmed by polymerase-gamma gene sequencing, liver biopsy, or postmortem examination
3. Additional clinical findings (at least two of the following 11 findings must be present):
 - 1.) Cranial proton magnetic resonance spectroscopy indicating reduced N-acetyl aspartate, normal creatine, and elevated lactate
 - 2.) Elevated cerebrospinal fluid protein (>100 mg/dL)
 - 3.) Cerebral volume loss (central more than cortical, with ventriculomegaly) on repeated magnetic resonance imaging or computed tomography
 - 4.) At least one electroencephalogram revealing multifocal paroxysmal activity with high-amplitude δ slowing (200-1000 μ V) and spikes/polyspikes (10-100 μ V, 12-25 Hz)
 - 5.) Cortical blindness or optic atrophy
 - 6.) Abnormal visual-evoked potentials and normal electroretinogram findings
 - 7.) Quantitative mitochondrial DNA depletion in skeletal muscle or liver (35% of the mean)
 - 8.) Deficiency in polymerase- γ enzymatic activity ($\leq 10\%$) in skeletal muscle or liver
 - 9.) Elevated blood or cerebrospinal fluid lactate (3 mM) on at least one occasion in the absence of acute liver failure
 - 10.) Isolated complex IV or a combination of complex I, III, and IV electron transport defects ($\leq 20\%$ of normal) upon liver respiratory chain testing
 - 11.) A sibling confirmed as manifesting Alpers-Huttenlocher syndrome

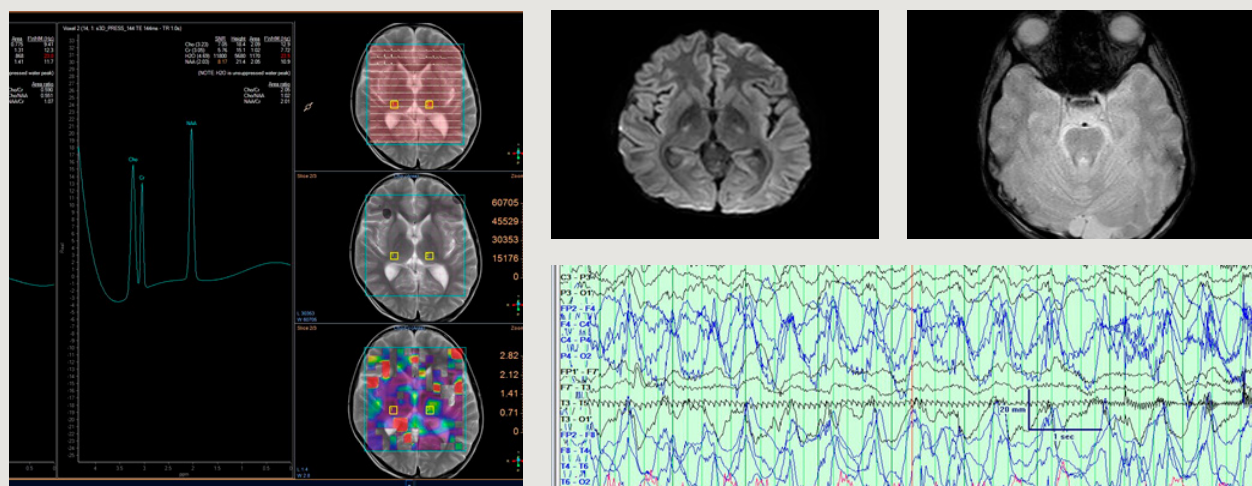
via genetic analysis, which revealed polymerase-gamma (*POLG*) gene mutations.

The *POLG* gene encodes the mitochondrial DNA replicase protein, which is essential for maintaining the integrity of mitochondrial DNA. There are over 50 known mutations associated with Alpers-Huttenlocher syndrome and over 200 mutations of the *POLG* gene.

Alpers-Huttenlocher syndrome primarily affects organs that require large amounts of energy, and which are prone to oxidative damage, which include: the brain, peripheral nervous system, liver, and gastrointestinal tract.

Seizures are the most dramatic central nervous system of the syndrome. In about 50% of patients, seizures are the heralding symptom. Once seizures appear, the tempo of the disease becomes rapidly progressive, and death usually occurs within 4 years of disease onset. In other cases, disease progression is usually slower. The etiology for the variation in disease progression is unknown⁷.

Figures 1, 2, 3 & 4



In a situation in which a patient is placed on valproate, liver dysfunction usually begins within 2–3 months, but may be delayed by up to 6 months. Liver dysfunction is usually heralded by hypoglycaemia, decreased albumin synthesis, reduced synthesis of coagulation factors, and mild transaminase elevation. Early recognition of liver dysfunction may stop the progression to failure^{8,9}.

The first association of the use of valproic acid and rapid onset of liver disease in a child with Alpers-Huttenlocher syndrome soon led to the understanding that the clinical variables associated with valproate-induced liver failure were in fact the clinical features of Alpers-Huttenlocher syndrome. Therefore, valproic acid (and divalproex sodium) have likely altered the natural history of Alpers-Huttenlocher syndrome, and may have given the impression of a universally rapidly progressive disease⁸. Now that it is possible to rapidly identify patients with Alpers-Huttenlocher syndrome, and it is widely accepted that valproate is contraindicated in this disorder, an analysis of seizure frequency, duration, and medication use (without valproic acid exposure) needs to be performed in order to understand the natural history of disease progression without this variable.

Treatment of patients with Alpers-Huttenlocher syndrome is limited to supportive care. Family education should be addressed as soon as the family is able to absorb the diagnosis. The holistic perspective of care should be palliative even if death is not imminent. This illness progresses to a fatal encephalopathy or liver failure, and varying levels of treatment can be addressed openly with the family. Supportive care will include the placement of a gastrostomy feeding tube for medication, hydration, and/or nutrition¹⁰.

SUMMARY

Awareness of mitochondrial disorders is essential, as there are no specific pointers other than raised lactate in

concurrency with organ-specific dysfunction. An index of suspicion should be raised whenever any child is noted to have the constellation of symptoms of the hepato-cerebral or myopathic form, or even in cases of isolated liver disease. It is important to recognize Alpers-Huttenlocher syndrome to avoid administering medications that can predispose a patient to liver failure, particularly since liver transplantation is not appropriate in such a patient.

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Monochorionic Twin Pregnancy Complicated by Selective Intrauterine Growth Restriction with Co-existent Twin-to-twin Transfusion Syndrome

Management of growth restriction in monochorionic twin pregnancies represents a challenge and more so when it is co-existent with twin to twin transfusion syndrome.

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Key words

Monochorionic twin, twin to twin transfusion syndrome, selective intra uterine restriction.

Conflict of interest

There are no conflicts of interest to report and no external funding sources.

INTRODUCTION

Monochorionic twin pregnancies, by virtue of vascular anastomoses, are at risk of unique complications. These include Twin-To-Twin Transfusion Syndrome (TTTS), Selective Intrauterine Growth Restriction (sIUGR), and Twin Reverse Arterial Perfusion (TRAP) sequence. Vascular anastomoses are present in every monochorionic placenta; these represent a state of imbalance in the shunting of blood, or an abnormality in the nature of anastomosing vessels, which forms the basis for these unique clinical entities. The extreme circumstances of these complications eventually lead to single foetal demise in such twins. The intra-uterine demise of one fetus results in the acute transfer of intravascular volume from the co-twin to the dying twin (rescue transfusion), resulting in exsanguination with accompanying hypotension, anaemia, death and ischaemic cerebrovascular insults to the co-twin. The demise of one foetus in a monochorionic gestation is associated with co-foetal demise in 12–25% of cases, and a risk of neurological abnormalities in 18–25% of surviving infants.¹

Umbilical artery Doppler flow is the parameter which best reflects the difference in growth restriction between monochorionic and dichorionic twins; Changes in flow within the umbilical artery are closely related to clinical changes and outcomes. Foetuses with positive diastolic flow have a benign prognosis, whilst foetuses with intermittent absent or reversed diastolic flow have a high risk

of intra-uterine foetal demise, and consequently ischaemic damage, especially parenchymal brain damage, to the normally growing twin. Under such circumstances, selective termination of one foetus optimizes the chances of survival of the co-twin. Selective foetal reduction is known to improve the perinatal outcome in the extreme situations caused by this complication of monochorionicity.^{2,3} Interventional procedures such as intra-cardiac injection of cardio toxic agents like potassium chloride cannot be carried out in monochorionic pregnancies, because of the risk of a drug being transferred to the co-twin via the anastomosing vessels. Selective termination in monochorionic pregnancies instead requires ablation of the blood flow in the umbilical cord, to prevent acute intra-foetal transfusion.

We present here a case of TTTS with sIUGR, for which growth restriction typing was completed according to the classification criteria proposed by Gratacos et al.⁴ TTTS was classified based on the Quintero system.⁵

CASE

A 39-year-old gravida 2, para 1, living 1 (previous LSCS) patient was referred to the foetal medicine unit of MWCH, for a second opinion on a monochorionic diamniotic twin pregnancy with TTTS at 20 weeks of gestation. Her blood group was rhesus A positive. All recent menstrual cycles were regular and there was no significant medical, surgical and family history. The patient had conceived naturally. At a scan at 12 weeks of gestation, a diagnosis of

monochorionic diamniotic twin pregnancy was made. The fetuses were concordant for liquor growth and aneuploidy markers. The first trimester screen was negative for aneuploidies, with all biochemical parameters within the normal limits.

On referral, Monochorionicity was confirmed through the ultrasound findings of a single placenta, a thin intervening membrane and lack of a lambda sign. A detail target scan with Doppler study and foetal echo was carried out. Our findings were a monochorionic twin pregnancy at a gestational age of 20 weeks and 3 days, with an anterior common placenta (gestational age was assigned as per the last menstrual period). The twins were discordant for liquor, bladder, growth and Doppler flow. Twin A had no measurable liquor pocket, suggestive of anhydramnios, and the single deepest pocket of liquor for twin B was 8.7cm. The bladder was absent for twin A and distended for twin B. Estimated foetal weights were 225 g and 356 g for twin A and B respectively. The weight discordancy between the fetuses was 37%.

Twin B was structurally normal for the period of gestation. The anatomical survey was limited for twin A due to anhydramnios. The Doppler study of twin A showed an intermittent absent diastolic flow pattern in the umbilical artery (type 3 Gratacos), with normal flow in the Ductus venosus and middle cerebral artery. Twin B gave normal Doppler results, and was haemodynamically stable. The CHOP (Children's Hospital of Philadelphia cardiovascular score in twin to twin transfusion syndrome) score was 0.

A final diagnosis was made, of a monochorionic twin pregnancy, discordant for bladder, liquor, growth and Doppler, with features suggestive of twin to twin transfusion syndrome stage 2 with selective intra uterine growth restriction of twin A type 3. The couple was counseled accordingly. All abnormal findings were confirmed with repeated sittings and multiple measurements (especially the absence of a bladder and the Doppler findings for twin A). The Doppler study was performed following the guidelines (ISUOG practise guidelines 2013).

The family was briefed on the findings, their implications and the consequences in the setting of monochorionicity. The benefits and risks of conservative management versus intervention, and in particular in intervention the option of laser ablation of placental vessels versus selective foetal reduction, were all discussed in length. The family opted for selective foetal reduction.

A selective foetal reduction was conducted, via radiofrequency ablation. After in-house monitoring for 48 hours post-procedure, the pregnancy was followed up with Doppler and growth study fortnightly for two months. Twin B was haemodynamically stable throughout, and maintained an estimated foetal weight of between 30 – 33 % until 30 weeks. At 33 weeks, we observed a slight drop in the biometry parameters (estimated foetal weight 22%) and the liquor volume. Steroids were administered to prompt lung maturity. At 34.3 weeks the liquor further reduced (AFI < 5 cm), and a suboptimal CTG reading was recorded, following which the patient was posted for an elective LSCS. A female baby weighing 2.120 kg was delivered with a good APGAR score.

The baby was observed in the NICU and was started on feeds the second day. A brain USG was normal and all screenings tests (new-born metabolic and hearing screen tests) were also normal.

DISCUSSION

The management of growth restriction in monochorionic twin pregnancies represents a challenge, and even moreso when it is co-existent with TTTS. Classification of sIUGR into types, based on the characteristics of umbilical artery diastolic flow in the IUGR twin, permits differentiation clinically, and is helpful in prognosticating, counselling and clinical decision-making.⁴ sIUGR type 1 has normal diastolic flow, and relatively good outcomes. Type 2 is defined by persistently absent/reverse end-diastolic flow and is associated with a high risk of intrauterine demise of the IUGR twin, and/or very preterm delivery. Type 3 is defined by the presence of intermittent absent/reverse end-diastolic flow (iAREDF), and is associated with a 10-20% risk of unexpected foetal demise of the smaller twin and a 10-20% risk of neurological injury in the larger twin.³

This case had type 3 sIUGR with TTTS stage 2. The determinants of grading the severity of sIUGR (GA <22 weeks or discordancy > 35% or AREDF or DV PI >p95) were all hostile to expectant management. Left to its natural evolution, with these findings at as early as 20 weeks, the outcomes would certainly have been adverse. Delivery would have been indicated if the gestation was greater than 26 weeks.⁶ Expectant management may be associated with the very preterm birth of both twins, and the inherent morbidity associated with prematurity.⁷

In monochorionic pregnancies, selective foetal termination can be considered in an attempt to salvage at least one foetus, especially when the entire pregnancy is at threat. However, the final decision among therapy options will be influenced by the severity of growth restriction, the preferences of parents, and technical issues.

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Tracheal Stenting for Post-Tubercular Tracheal Stenosis in a Patient on ECMO Support

Tracheal head and neck squamous cell cancer recurrence without metastases may be related to physical displacement of cancer cells.

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Key Words

endobronchial tuberculosis, endobronchial stent, silicone stent, ECMO.

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Written informed consent for the paper to be published (including images, case history and data) was obtained from the patient/guardian for publication of this paper, including the accompanying images.

ABSTRACT

Endobronchial tuberculosis (EBTB) is defined as tuberculous infection of the tracheobronchial tree with microbial and histopathological evidence. It is seen in 10-40% of patients with active pulmonary tuberculosis. More than 90% of the patients with EBTB have some degree of airway stenosis. Balloon dilatation and self-expanding stent insertion is an effective treatment for bronchial stenosis. Use of endobronchial stents should only be considered in lesions of proximal location when other dilatational methods have failed. Here, we report the use of emergency bedside extracorporeal membrane oxygenation (ECMO) as a salvage manoeuvre in a case of distal tracheal obstruction of a patient receiving treatment for EBTB, and tracheal stenting using silicone stents in a patient on ECMO support.

INTRODUCTION

Critical Narrowing of the upper airway, including the trachea, is a life-threatening emergency. Initial management will depend on the degree of obstruction, the level of obstruction, and the specific cause. Endotracheal intubation, emergency tracheostomy or cricothyroidotomy can be life-saving when an obstruction is at the level of the vocal cords or above. Total occlusion of the upper airway will rapidly lead to death unless such an obstruction is relieved. Stenotic lesions may require repeated dilatations.¹ Jaiswal et al describe a case of tracheal stenosis following treatment for tuberculosis, in which the patient underwent serial dilatations. In order to maintain tracheal patency, stenting was also undertaken.² Historically, extracorporeal membrane oxygenation (ECMO) has been used primarily in cases of cardiac or respiratory failure. Over the last decade, ECMO has found increased utility in the form of short-term support in hypoxic patients undergoing upper airway surgery and complex tracheal operations. In this paper, we elucidate how ECMO helped as a rescue procedure for a patient who was inadequately ventilated. We discuss different types of tracheal stents and their complications.

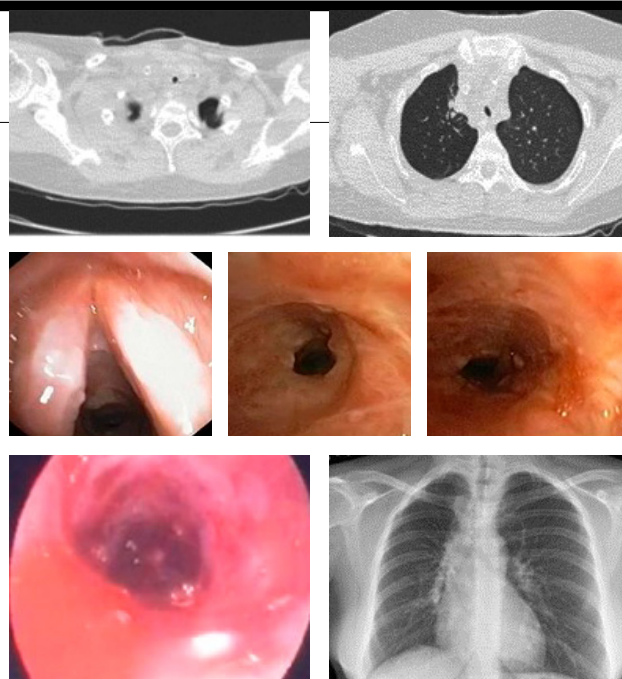
CASE PRESENTATION

A case of 25 year old female, who is a staff nurse by profession, presented with a 5 month history of cough and hoarseness of voice, and a 1 week history of breathing difficulty and stridor. She had associated loss of appetite and weight loss. On examination of the chest, breath sounds were reduced on the right mammary area, with reduced VR. Blood investigations showed leucocytosis with neutrophilia and thrombocytosis. A chest x-ray showed right side mid zone homogenous opacity. A CT thorax showed right upper lobe collapse consolidation, and mucosal irregularity of the tracheae, with secretions plugging the right upper lobe bronchus (figure 1) and mediastinal adenopathy. Bronchoscopy showed tracheal stenosis below the vocal cords, extending up to the carina (figure 2). A scope could be just passed. The right main bronchus was pin-pointed. The mucosa appeared irregular, friable and edematous. The left sided bronchial tree was normal. A biopsy was taken from the sloughed area, which showed multiple necrotising granulomas.

ZN stain showed acid fast bacilli. Analysis with GENEXPERT detected *Mycobacterium tuberculosis* with no rifampicin resistance detected. The patient was started on antitubercular therapy, having been diagnosed as a case of endobronchial tuberculosis. In view of the critical airway stenosis, it was decided to give a short course of steroids. The patient improved clinically with medical treatment, and hence was discharged. She was advised to continue ATT and the steroid was tapered off.

Following 2 months of ATT, the patient again presented with stridor and breathing difficulty. Bronchoscopy revealed mid tracheal stenosis, which was relieved using a tracheal knife and balloon dilatation. However, one month later, she presented with acute onset of stridor. At that time, she was tachypnoeic and had desaturation of up to 85%. She was admitted to the ICU. There, she developed respiratory acidosis, and after repeated attempts, she was intubated with a size 5 ET tube under bronchoscope guidance. As she was not adequately ventilated, even with a paediatric ET tube, it was decided to conduct emergency veno-venous ECMO (VV-ECMO) for temporary respiratory support until tracheal stent placement. Under local anaesthesia, after heparinization, 22Fr and 20 Fr Edwards cannula were placed through the right femoral vein and right internal jugular veins respectively. After cannula positions were confirmed by USG, VV-ECMO was established.

The following day, on VV-ECMO support, the patient underwent rigid bronchoscopy. The trachea showed long segment stenosis. We dilated the trachea along the full length, coring out the fibrotic parts of the trachea using the rigid tube. Repeated dilatation was performed using a dilator through the rigid tube. Under the guidance of fluoroscopy, we stented the trachea with a size 14 silicon stent (9 cm long), with the help of a rigid bronchoscope with size 16 barrel. Later, a CT Thorax was taken, which showed the silicone stent in situ (figure 3). The patient was reintubated and, after 2 days, once the glottic



edema had reduced, she was extubated. The next day she was weaned off from ECMO and underwent frequent surveillance bronchoscopies to assist with secretion clearance and assess for airway patency (figure 3). The patient was advised to continue ATT for 9 months.

After 4 months of tracheal stenting, a bronchoscopy revealed granulation tissue beneath the tracheal stent, and a severely compromised right main bronchus lumen. As there was critical narrowing of the right main bronchus, it was decided to undergo Y-stenting of the trachea and main bronchus. The patient was electively put on VV-ECMO. Under rigid bronchoscope guidance, the previous tracheal stent was removed, balloon dilatation of the right main bronchus was completed and a silicone Y-stent was successfully deployed. Post-procedure, ECMO was decannulated and the patient extubated and discharged with a tapering dose of steroids.

DISCUSSION

Tuberculous infection of the tracheobronchial tree is known as endobronchial tuberculosis (EBTB). In patients with active pulmonary tuberculosis, EBTB frequency ranges from 10–50%.³⁻⁶ It can occur with or without parenchymal involvement and is more common in young adults and females.⁵⁻⁶ EBTB is a distinct form of tuberculosis which continues to remain a diagnostic challenge, even in high TB prevalence countries. The chest X-ray in EBTB can appear normal, and diagnostic confirmation can only be achieved bronchoscopically. Bronchoscopy is pivotal to the diagnosis of EBTB. Endobronchial lesions have been categorised as actively caseating, oedematous-hyperaemic, fibrostenotic, tumorous, granular, ulcerative and non-specific bronchitic.⁷ Tracheal stenosis is not a frequent complication of Endobronchial TB. In many cases it will respond to anti-

tuberculous drugs together with steroids, to suppress the inflammation; however, additional measures are sometimes needed.

Dilatation seems an effective and safe treatment. Of 59 patients in one series, 83% reported a substantial improvement in symptoms.⁸ Complications were few, but recurrence was common. 80% of patients had a primary relapse of airway stenosis and 43% had a secondary relapse. Recurrence is the usual reason for stent insertion. Since retrieval of metallic stents can be difficult, non-metallic stents are preferred for the management of benign disease; they can be left in situ for long periods. There are 4 categories of airway stents⁹- silicone stents, balloon dilated metal stents, self-expanding metal stents (SEMS) and covered SEMS. The silicone Dumon stent (Novatech, Boston Medical, Massachusetts, USA) is widely popular and is often used to treat benign tracheal stenosis. Complications include stent migration (17%), granuloma formation (6%) and mucostasis (6%).^{10,11} We used a silicone stent for our patient, but she developed granuloma formation beneath the stent and maintained a recurrent cough, which prompted us to complete serial bronchoscopy and clearance.

To the best of our knowledge this is the first case reported from India on airway stenting completed while a patient was on ECMO. This patient's long segment tracheal stenosis made oxygenation and ventilation impossible, prohibitively limiting the duration of each tracheobronchial intervention. Given the complexity of the necessary airway intervention and the time constraints imposed by the patient's poor respiratory status, VV-ECMO was used without complication to support the patient during tracheobronchial intervention. The first case of non-cardiac surgical application of extracorporeal circulation was reported by Woods et al. in 1961.¹² They used extracorporeal circulation for resection of the carina and both main stem bronchi for bronchial adenoma.

Kim et al have described application of a veno-venous type extracorporeal membrane oxygenator (ECMO) in high-risk tracheal procedures in six cases, including five patients with tracheal stenosis.¹³ During ECMO perfusion, the surgeons could concentrate on the procedure without worrying about patients' oxygenation. However, ECMO also has its own risks, such as thromboembolism and bleeding due to anticoagulation. In our case, ECMO was established safely without complication. While conventional ventilation is sufficient for the vast majority of patients undergoing tracheobronchial intervention, a subset of patients cannot maintain respiratory function during intervention and can be safely bridged with ECMO support.

CONCLUSION

In patients with endobronchial tuberculosis, tracheal stenosis is a dreaded complication which should be always kept in mind while starting treatment. Diagnostic confusion can occur as the symptoms can simulate major pulmonary disorders

such as bronchial asthma and lung cancer. Antituberculosis chemotherapy remains the mainstay of treatment. The role of corticosteroids is controversial, and even with timely treatment, some patients eventually progress to tracheobronchial stenosis. Bronchoscopic-guided balloon dilatation can be done as a single procedure, or may require repeated staged events, and cryotherapy may help. Stents, preferably silicone stents, may be inserted to maintain airway patency. Should these measures fail, surgical options including bronchoplasty can be explored to help patients with debilitating stenosis. Other treatment options include sleeve resection, carinal resection, reconstruction of the bronchus or trachea and end-to-end anastomosis. This case highlights the use of ECMO as a salvage procedure and as an adjunct to the optimal management of a difficult airway when the patient cannot be adequately ventilated through an ET tube and when there is complete stenosis of the central airway.

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Regulars

Next Driver of Growth?

COVID-19 offers a unique opportunity for radically reforming India's healthcare system.

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Book Review

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In Richard Selzer's fictional story "Whither Thou Goest," a widow searches for the man who received her late husband's heart. The liver, kidney and corneas were in other people, but she needed to be with the heart. When she and the stranger ultimately connect, it's as if she's recovered lost love.





Next Driver of Growth?

COVID-19 offers a unique opportunity for radically reforming India's healthcare system.

The ongoing pandemic has given us a unique opportunity to transform India's health system, which needs to be prioritised and escalated through infrastructure, investment and manpower. By undertaking radical reforms, India will not only be able to save lives and protect households slipping into poverty due to catastrophic illnesses but also significantly boost economic growth.

The Indian healthcare story has achieved notable successes. We are the pharmacy of the world; doctors and nurses from India have excelled and distinguished themselves across the US and Europe; private hospitals provide healthcare to almost 70% of India and have been a key driver of medical tourism.

Yet, the Indian healthcare system suffers from major weaknesses. The government (Centre and states together) spends a mere 1.13% of GDP on health. Almost 62% of healthcare spending is met through out-of-pocket expenditure by households. And as much as 98% of healthcare facilities in India are provided by those who employ fewer than 10 people. This has led to a highly complex and fragmented delivery of health services. Individual health records are all manual and with such a large number of individual transactions, there are huge challenges of market failures and governance.

What does India need to do to create a vibrant, dynamic and progressive 21st century health system?

First, it's been observed that countries with strong primary healthcare systems have better health outcomes, lower inequalities and much lower costs of care. We need to strengthen



primary healthcare in India. The creation of 1,50,000 health and wellness centres by 2022 by transforming existing sub-centres and primary health centres under the Ayushman Bharat Scheme is a major move in this direction.

Currently, the primary healthcare service is largely focussed on hospital based curative services, which fail to provide a continuum of care. The healthcare system is fragmented with focus on disease-centric programmes rather than integration of programmes. We need to design integrated and comprehensive ways of delivering primary healthcare. This is the critical paradigm shift that India needs. There's also a need to strengthen district and subdistrict hospitals to provide high quality referral cases.

Second, there's endemic shortage of qualified doctors across the country, especially in rural

areas. India's current doctor population ratio of 0.7:1000 is significantly lower than the global average of 1.72:1000 and the WHO norms of 1:1000. It's imperative to address this imbalance urgently on account of the crisis precipitated by COVID-19.

At the core of this is augmenting the number of medical seats in the country. Current norms for undergraduate and PG faculty for PG courses must be radically relaxed. We also need to rationalise the high capital costs required for land, building equipment for establishment of medical colleges. The cost of producing a doctor is the highest in India and currently, over Rs 250 crore capital expenditure is required for establishing a 150 seat college. This is just too high and existing norms need to be modified.

Third, we need widespread opening of medical schools across districts throughout the country. This will provide an opportunity to local students to acquire medical education within their district and state, thereby encouraging them to continue in their district serving the needs of the local population. There are 22 times more engineers than doctors in India. As a result, self-styled doctors without formal training provide up to 75% of primary care visits.

We need widespread opening of medical schools across districts throughout the country. This will provide an opportunity to local students to acquire medical education within their district and state, thereby encouraging them to continue in their district serving the needs of the local population.

Fourth, there's been a major surge in non-communicable diseases. There's also an increasing demand for mental health and palliative care services. A vast segment of our population goes below the poverty line on account of these diseases. Fifth, we need to undertake reskilling of human resources and utilise them fully. For instance, nurses in the UK, Thailand and African countries are increasingly taking doctors' role at the primary level. There have been commendable examples, such as Chhattisgarh's three-year community medical course. India also needs to develop bridge courses for dental and Ayush doctors and utilise them as community doctors. The measures initiated by the government for reforming the Medical Council of India need to be extended to the Dental and Nursing Council of India.

Sixth, substantial funding has to be earmarked for health research, with focus on developing novel diagnostics, drug molecules, therapies, morbidities and surveillance for diseases. We must create an enabling environment so that products are designed, developed, validated and technologies converted into products. A good example is the dengue ELISA test and the COVID-19 ELISA tests developed by ICMR.

Lastly, we need to harness the power of digital health as a critical enabler for transforming the health system. India must use technology to leapfrog and become a model for digital health adoption. This would require a unique identity for patients and putting order into patient flows, doctor workflows, care plans, medication and diagnostic results, all of which generate data. A national health stack will facilitate collection of comprehensive healthcare data across the country. This will enable everyone in the health sector to be linked digitally. Data produced can provide valuable information, which can be analysed to improve the health system. This will fuel mobile technologies, telemedicine application, use of AI and cloud-based solutions.

India's health sector can emerge as its biggest driver of growth and employment in pharmaceuticals, bio-pharma, hospitals, doctors, nurses and medical equipment. It has a huge multiplier impact on the economy and on the lives of its citizens. For this, it needs key policy reforms with a major emphasis on primary healthcare.

A cardiologist on matters of the heart

Being a cardiologist, Sandeep Jauhar beautifully weaves his own experiences with the defining discoveries of the past to tell the story of our most vital organ.

In Richard Selzer's fictional story "Whither Thou Goest," a widow searches for the man who received her late husband's heart. The liver, kidney and corneas were in other people, but she needed to be with the heart. When she and the stranger ultimately connect, it's as if she's recovered lost love. I, on the other hand, always considered the heart a pump, much the way a doctor explained it to Sandeep Jauhar during his cardiology fellowship. "In the end," the doctor said, "cardiology is mostly a problem of plumbing."

Jauhar quickly learned otherwise. His gripping new book, "Heart: A History," had me nearly as enthralled with this pulsating body part as he seems to be. The tone — a physician excited about his specialty — takes a sharp turn from his first two memoirs. The first, "Intern," was filled with uncertainty; the second, "Doctored," with disillusionment.

Jauhar hooks the reader of "Heart" in the first few pages by describing his own health scare — an exam showed obstruction in the main artery feeding his heart. We don't hear more about his condition again until the final chapter, when a further assessment reveals premature ventricular contractions, "a mostly

benign condition in which my heart flutters or does a sort of flip-flop when an extra, unexpected beat comes in." Sandwiched between his own heart tests is his journey to understand this organ that has mystified and frightened him ever since he was a child and heard about his grandfather's sudden death from a heart attack.

Most chapters launch with a riveting scene: a patient in the thick of getting a heart transplant, say, or having open-heart surgery. You feel as if you're watching an episode of a medical television drama. Before we find out what happens, Jauhar takes us back in time to explain the discoveries that made all of these advances possible.

That's where the stories get particularly strange and captivating. We read about Werner Forssmann, who attempted one of the first cardiac catheterizations in 1929. He did it on himself. Forssmann threaded a thin tube through his arm until it pierced his right atrium. Colleagues called him a quack. Almost 30 years later, he won the Nobel Prize in Physiology or Medicine.

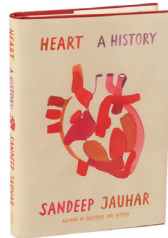
We go into an operating room where a young girl is having open-heart surgery, tethered to a heart-lung machine. Then we

learn that the concept for this machine began with one doctor's brazen idea of connecting a patient to another person's blood supply. He was inspired by the way a fetus feeds off its mother. Six of seven cases ended with a death.

Eventually, the heart-lung machine replaced the volunteers. The machine got off to a rough start too: 17 of the first 18 patients died. As one of the mid-20th-century researchers remarked, "You don't venture into the wilderness expecting to find a paved road."

Being a cardiologist, Sandeep Jauhar beautifully weaves his own experiences with the defining discoveries of the past to tell the story of our most vital organ. Amid gripping scenes from the operating theatre, Jauhar tells stories about the patients he has treated. And he relates the moving tale of his family's own history of heart problems, from his grandfather's sudden death in India — an event that sparked his lifelong obsession with the heart — to the first ominous signs of his own mortality.

He also confronts the limits of medical technology and argues that future progress will be determined more by how we choose to live than by any device we invent.



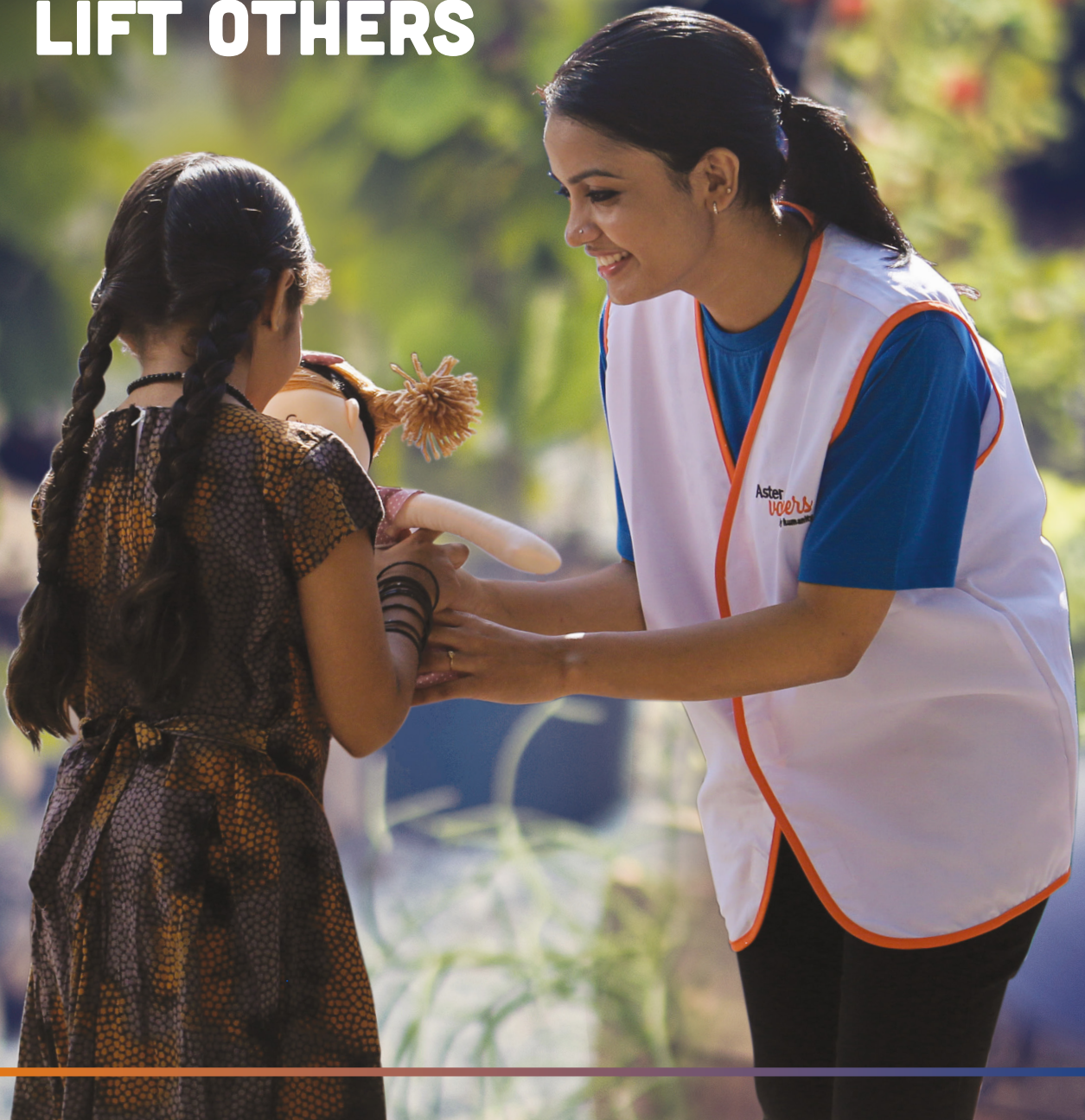
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