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Researchers find new potential treatment for prion diseases

A new study in Nucleic Acids Research, published by Oxford University Press, suggests a possible effective treatment strategy for patients suffering from prion disease.

Prion disease is a rapidly fatal and currently untreatable neurodegenerative disease. While prion disease is quite rare, it typically causes rapid neurodegeneration. About 300 cases of prion diseases are reported each year in the United States. The most common form of prion disease that affects humans is Creutzfeldt-Jakob disease. Bovine spongiform encephalopathy, popularly known as Mad Cow Disease, is another prion disease. Prion diseases are caused by disrupting the structure of a normal human prion protein, producing toxic clumps in the brain. Because prion protein is central to disease, reducing levels of prion protein in patients is a promising therapeutic approach.

Senior author Sonia Vallabh learned that she carried a mutant form of the prion protein gene prior to switching careers to become a patient-scientist and advocate for treatment. She and her coworkers had previously observed that antisense oligonucleotides that reduce levels of prion protein can extend the survival of animals infected with misfolded prions. While these initial data were promising, many critical questions remained before therapeutic development could be possible.

Research teams led by Vallabh at the Broad Institute of Harvard and MIT, Holly Kordasiewicz at Ionis Pharmaceuticals, and Deb Cabin at McLaughlin Research Institute, report the results of preclinical studies of an antisense therapy against prion disease. In this new work, using an expanded set of prion protein -targeting antisense oligonucleotides, the authors have laid the basis for full scale clinical development. This research shows that, across multiple treatment paradigms, reducing levels of prion protein in prion-infected lab animals significantly extends their survival.

Researchers here showed that reducing levels of prion protein can triple the survival of prion-infected animals. Even reducing prion protein levels by a small amount, which should be easier to achieve clinically, resulted in significant survival benefits.

Reduction of prion protein is effective across prion strains and across a battery of different treatment timepoints. The researchers show that reducing prion protein is effective before any symptoms are seen. They also demonstrate, for the first time, that a single dose of a prion protein -lowering treatment can reverse markers of disease even after toxic clumps have formed in the brain.

"While there are still many steps ahead," said Vallabh, "these data give us optimism that by aiming straight at the genetic heart of prion disease, genetically targeted drugs designed to lower prion protein levels in the brain may prove effective in the clinic."

The article, "Prion Protein Lowering is a Disease-modifying Therapy Across Prion Strains, Stages, and Endpoints" is available to the public on August 10th.

To request a copy of the study, please contact: Daniel Luzer daniel.luzer@oup.com

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The Mammalian Brain Starts Eating Itself When It Doesn't Get Enough Sleep

Researchers have found that persistently poor sleep causes the brain to clear a significant amount of neurons and synaptic connections

Bec Crew

The need for sleep goes far beyond simply replenishing our energy levels every 12 hours. Our brains actually change states when we sleep to clear away the toxic byproducts of neural activity left behind during the day.

Weirdly enough, research on mice has revealed the same process starts to occur in brains that are chronically sleep-deprived too - except it's kicked into hyperdrive.

Researchers have found that persistently poor sleep causes the brain to clear a significant amount of neurons and synaptic connections, and recovering sleep might not be able to reverse the damage.

In 2017, a team led by neuroscientist Michele Bellesi from the Marche Polytechnic University in Italy examined the mammalian brain's response to poor sleeping habits, and found a bizarre similarity between the well-rested and sleepless mice.

Like the cells elsewhere in your body, the neurons in your brain are being constantly refreshed by two different types of glial cell - support cells that are often called the glue of the nervous system.

The microglial cells are responsible for clearing out old and worn out cells via a process called phagocytosis - meaning "to devour" in Greek.

The astrocytes' job is to prune unnecessary synapses (connections) in the brain to refresh and reshape its wiring.

We've known that this process occurs when we sleep to clear away the neurological wear and tear of the day, but now it appears that the same thing happens when we start to lose sleep.

But rather than being a good thing, the brain goes overboard with the clearing, and starts to harm itself instead.

Think of it like the garbage being cleared out while you're asleep, versus someone coming into your house after several sleepless nights and indiscriminately tossing out your television, fridge, and family dog.

"We show for the first time that portions of synapses are literally eaten by astrocytes because of sleep loss," Bellesi told Andy Coghlan at *New Scientist.*

To figure this out, the researchers imaged the brains of four groups of mice:

- ***one group was left to sleep for 6 to 8 hours (well-rested)***
- ***another was periodically woken up from sleep (spontaneously awake)***
- ***a third group was kept awake for an extra 8 hours (sleep-deprived)***
- ***and a final group was kept awake for five days straight (chronically sleep-deprived).***

When the researchers compared the activity of the astrocytes across the four groups, they identified it in 5.7 percent of the synapses in the well-rested mouse brains, and 7.3 of the spontaneously awake mouse brains.

In the sleep-deprived and chronically sleep-deprived mice, they noticed something different: the astrocytes had increased their activity to actually eating parts of the synapses like microglial cells eat waste - a process known as astrocytic phagocytosis.

In the sleep-deprived mouse brains, the astrocytes were found to be active across 8.4 percent of the synapses, and in the chronically sleep-deprived mice, a whopping 13.5 percent of their synapses showed astrocyte activity.

As Bellesi told *New Scientist*, most of the synapses that were getting eaten in the two groups of sleep-deprived mice were the largest ones, which tend to be the oldest and most heavily used - "like old pieces of furniture" - which is probably a good thing.

But when the team checked the activity of the microglial cells across the four groups, they found that it had also ramped up in the chronically sleep-deprived group.

And that's a worry, because unbridled microglial activity has been linked to brain diseases like Alzheimer's and other forms of neurodegeneration.

"We find that astrocytic phagocytosis, mainly of presynaptic elements in large synapses, occurs after both acute and chronic sleep loss, but not after spontaneous wake, suggesting that it may promote the housekeeping and recycling of worn components of heavily used, strong synapses," the researchers report.

"By contrast, only chronic sleep loss activates microglia cells and promotes their phagocytic activity ... suggesting that extended sleep disruption may prime microglia and perhaps predispose the brain to other forms of insult."

Many questions remain, such as if this process is replicated in human brains, and if catching up on sleep can reverse the damage.

But the fact that Alzheimer's deaths have increased by an incredible 50 percent since 1999, together with the struggle that many of us have in getting a good night's sleep, means this is something we need to get to the bottom of - and fast.

https://bit.ly/30VPyAj

Got someone with coronavirus at home? Here's how to keep the rest of the household infection-free

Although some positive signs suggest Victoria's second wave may be slowing, we continue to see large numbers of COVID-19 cases recorded every day.

Thea van de Mortel *

Most people who test positive for COVID-19 won't need hospital care and will self-isolate at home. But is it then inevitable the rest of the household will catch it? It shouldn't be, if you follow a few important infection prevention steps.

First, how does the virus spread?

We understand SARS-CoV-2, the coronavirus that causes COVID-19, spreads to others primarily in two ways:

- ***an uninfected person breathes in infectious droplets released when an infected person breathes, talks, coughs or sneezes***
- ***an uninfected person touches a surface contaminated with these droplets and then touches their mouth, nose, eyes or food. Viral particles can remain infectious on surfaces for extended periods.***

There's also mounting evidence SARS-CoV-2 can spread via the airborne route: smaller "aerosolised" particles that linger in the air.

Living in close quarters with someone with COVID-19 means thinking about ways to prevent each of these modes of transmission.

Isolation and ventilation

Ideally, the COVID-positive person should have their own room and bathroom to minimise contact with others. If a dedicated room isn't available, they should maintain as much distance as possible from other members of the household.

It's especially important for anyone in the household who is at higher risk — such as elderly family members or people with compromised immune systems — to keep their distance from the infected person. Additionally, the better the ventilation, the lower the risk of transmission. Weather permitting, open windows to encourage air exchange.

It's also a good idea to keep the door to the infected person's room closed to minimise the movement of contaminated air into the rest of the house.

Personal hygiene

Everyone in the household — but the COVID-19 patient especially — should practise good respiratory hygiene (covering coughs and sneezes and disposing of used tissues).

Hand hygiene becomes even more important. Everyone in the household should wash their hands frequently, particularly before eating or after handling potentially contaminated objects. Use soap and water for at least 20 seconds or a sanitiser with at least 60% alcohol.

The World Health Organisation recommends the infected person wear a mask as much as possible to reduce the number of infectious particles in the air and lower the risk of transmission.

Caregivers may also choose to wear a mask when entering the infected person's room. They should wear gloves if they're going to come into contact with body fluids such as vomit, faeces or saliva.

All contaminated waste — such as used tissues, masks and gloves — should be put into a dedicated bin. The bin should have a lid and be lined. Wear gloves when emptying the bin.

Sharing isn't caring

To prevent possible spread via contaminated objects, avoid sharing sheets, towels, toothbrushes, cups and glasses, eating utensils or equipment such as mobile phones with a COVID-positive person.

If others need to use or handle utensils the COVID-positive person has used, wear gloves when handling them, wash them with hot water and detergent or put them through a hot cycle in the dishwasher. Objects you can't wash can be wiped down with disinfectant.

Handle used linen and clothing carefully to avoid the possibility of shaking virus particles into the air. In hospital settings, nurses make beds without flapping the sheets around to minimise the transfer of pathogens. Put used linen directly into the washing machine and wash and dry it at the highest possible temperature setting. If you don't have a clothes dryer, hang laundry in the sun. Evidence suggests sunlight can inactivate viruses.

Up your cleaning game

You should clean surfaces such as benchtops and tables daily with hot soapy water followed by a disinfectant. Pay particular attention to cleaning frequently touched shared surfaces, such as door and cupboard handles, light switches, toilets, sinks and taps.

If the bathroom is shared, the COVID-positive person should clean and disinfect the bathroom after using it if they're well enough to do so. There is some evidence SARS-CoV-2 can be present in faecal matter.

Caring for someone with COVID-19

If you're looking after a family member or housemate with COVID-19, ensure they have nutritious food to eat and fluids to drink. Staying well hydrated is important when a person has a fever, to replace fluids lost due to sweating.

People with a virus often feel fatigued as a result of their body's immune response, so it's important they get plenty of rest.

While fever is nature's way of fighting off an infection — our immune cells work better when we have a fever — if needed, anti-pyretic drugs such as paracetamol can make the person more comfortable. It's important to monitor how the person is feeling, and seek medical help if they deteriorate.

Finally, members of the household should keep an eye out for and get tested if they develop any COVID-19 symptoms, such as cough or fever.

Professor, Nursing and Deputy Head (Learning & Teaching), School of Nursing and Midwifery, Griffith University

Disclosure statement

Thea van de Mortel teaches into the Griffith University Master of Infection Prevention and Control program.

https://bit.ly/31VY5T0

Agtech to the rescue in a pandemic: adapting plant labs for human testing

Marshalling the research equipment and expertise of the many agtech labs around the world could help combat pandemics

Just as redeploying a fleet of small British fishing boats helped during the Battle of Dunkirk, marshalling the research equipment and expertise of the many agtech labs around the world could help combat pandemics, say the authors of a just-published article in *Nature Biotechnology*.

Sophisticated agtech labs and equipment used for crop and animal breeding, seed testing, and monitoring of plant and animal diseases could easily be adapted for diagnostic testing and tracing in a human pandemic or epidemic, the article states.

"If there is anything this current pandemic has shown us, it is that we need to mobilize efforts on a large scale to ramp up diagnostics," said lead author Steven Webb, chief executive officer of the Global Institute for Food Security (GIFS) at the University of Saskatchewan (USask).

"We must mobilize 'large ships' to fight pandemics by exploiting and adapting the screening capacity of high-throughput plant breeding laboratories which can rapidly analyze hundreds of thousands of samples."

The authors urge a national or international effort to co-ordinate rapid redeployment of digital agriculture infrastructure for pandemic preparedness. This approach would relieve the pressure on limited testing tools in the health sector and speed up the ability to respond with treatment and measures to contain the spread and occurrence of disease.

"Agtech has the infrastructure and capacity to support this need through its versatile equipment that can be used for very large-scale and automated applications including genetic testing and sequencing, virus detection, protein analysis, and gene expression," Webb said.

For instance, automated analysis of new plant varieties could be quickly switched to the automated detection of viral RNA or proteins, as well as detection of neutralizing antibodies, in humans. Selection of the fittest plant cultivars for breeding could be replaced by confirmation of patient diagnose of infectious diseases.

"As an example, the Omics and Precision Agriculture Laboratory (OPAL) at GIFS combines the digital data analysis of plant genes and traits with the latest precision agriculture technologies, and can provide a complete profile and data analysis of 3,000 plant samples per day," said Webb.

"Appropriate quality control measures would guide OPAL's switch from plant sample testing and analysis to human sample diagnostics during a pandemic, complying with regulation and using processes personnel are trained to employ."

GIFS has already lent equipment to enable expanded testing of COVID-19 blood samples and has donated materials and supplies to the Saskatchewan Health Authority.

The article notes that pandemics also affect animals and plants, with severe consequences for human food security, the economy, the environment, and society. For instance, the Great Famine in Ireland caused by the potato blight in the 1800s led to one million deaths and the spread of the blight in Europe claimed another 100,000 lives.

The article stresses the need to be able to adapt available agtech infrastructure from 'peacetime' applications to emergency use for diagnostic testing. This requires development of contingency protocols at national and international levels.

"There needs to be comprehensive quality control, standardizing the process and outcomes of this high-capacity testing of pandemic diagnostic samples," Webb said.

As well, there's a need to invest in agricultural technologies that can easily be adapted for medical use during pandemics.

"We need to be proactive to fight the next one. A proactive approach on all fronts will ensure the world is more prepared with the infrastructure and resources needed to respond to a pandemic," said Webb.

Other collaborators on the paper include: Richard Twyman, director of Scientific Management Consultancy TRM Ltd. in the United Kingdom, and Maurice Moloney, founder and management partner of AgritecKnowledge LLC, an international consultancy network for agricultural technologies, also in the United Kingdom.

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Tel Aviv University scientists reduce metastatic spread following tumor removal surgery

Study performed in colorectal cancer patients could lead to decrease in metastatic risk

A research group from Tel Aviv University (TAU) successfully reduced metastatic spread following tumor removal surgery in colorectal cancer patients. Using a short medication treatment around the time of the surgery, the researchers were able to reduce body stress responses and physiological inflammation during this critical period, preventing the development of metastases in the years following the surgery.

The study, which was published in the journal *Cancer* on June 13, was led by Prof. Shamgar Ben-Eliyahu from TAU's School of Psychological Sciences and Sagol School of Neuroscience and Prof. Oded Zmora from Shamir (Assaf Harofeh) Medical Center.

During the three-year-long study, researchers monitored 34 patients who received treatment surrounding a colorectal tumor removal surgery. During the pre- and post-surgical period, patients were administered two safe and known drugs: Propranolol (Deralin), an anti-anxiety and blood pressure reducing drug; and Etodolac (Etopan), an anti-inflammatory analgesic. The drugs were administered to the patients for 20 days -- from five days before surgery to two weeks after. Half of the patients received a placebo treatment as a control group.

The results were highly promising. While only 12.5% (2 out of 16) of patients receiving the drug treatment exhibited metastatic disease, the rate of metastases development was found to be 33% (6 out of 18 patients) in the control group, the known rate of metastasis for colorectal cancer patients. Prof. Ben-Eliyahu says that he is highly satisfied with these data, but also states that "despite the impressive results, this treatment must be examined again, in a much larger number of patients, in order to test whether it is, in fact, life-saving."

According to Prof. Ben-Eliyahu, the study of molecular markers in the cancerous tissue excised from the patients showed that the treatment with the medications led to a reduction in the metastatic potential of the tumor and potentially the residual cancer cells. In addition, the drugs triggered some beneficial alterations in the number and type of infiltrating tumor leukocytes (patients' white blood cells), markers that iindicate a reduced chance of disease recurrence.

"When the body is in a state of stress, whether physiological (from surgery) or psychological, this causes a release of high amounts of two types of hormones, prostaglandins and catecholamines," Prof. Ben-Eliyahu explains. "These hormones suppress the activity of the immune cells, indirectly promoting the development of cancer metastases. In addition, these hormones also directly promote the acquisition of metastatic traits in cancer tissue. Our study shows that inexpensive, accessible medication treatment could be used in order to reduce body stress responses and inflammation associated with surgery, which affects the tumor, significantly reducing the risk of metastases that might be detected months or years after surgery."

Following the success of the initial research, Prof. Ben-Eliyahu and Prof. Zmora are encouraging Israeli colorectal and pancreatic cancer patients to apply for participation in a large-scale clinical study now starting across Israel.

https://bit.ly/3aFYyqp

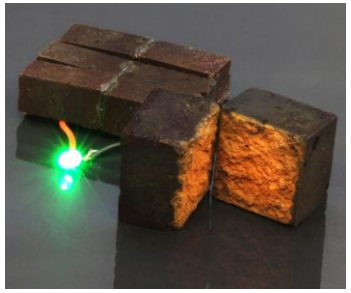
Storing energy in red bricks

Imagine plugging in to your brick house.

Red bricks -- some of the world's cheapest and most familiar building materials -- can be converted into energy storage units that

can be charged to hold electricity, like a battery, according to new research from Washington University in St. Louis.

Brick has been used in walls and buildings for thousands of years, but rarely has been found fit for any other use. Now, chemists in Arts & Sciences have developed a method to make or modify "smart bricks" that can store energy until required for powering devices. A proof-of-concept published Aug. 11 in *Nature Communications* shows a brick directly powering a green LED light.



Red brick device developed by chemists at Washington University in St. Louis lights up a green light-emitting diode. The photo shows the core-shell architecture of a nanofibrillar PEDOT-coated brick electrode. **D'Arcy laboratory, Department of Chemistry, Washington University in St. Louis**

"Our method works with regular brick or recycled bricks, and we can make our own bricks as well," said Julio D'Arcy, assistant professor of chemistry. "As a matter of fact, the work that we have published in *Nature Communications* stems from bricks that we bought at Home Depot right here in Brentwood (Missouri); each brick was 65 cents."

Walls and buildings made of bricks already occupy large amounts of space, which could be better utilized if given an additional purpose for electrical storage. While some architects and designers have recognized the humble brick's ability to absorb and store the sun's heat, this is the first time anyone has tried using bricks as anything more than thermal mass for heating and cooling.

D'Arcy and colleagues, including Washington University graduate student Hongmin Wang, first author of the new study, showed how to convert red bricks into a type of energy storage device called a supercapacitor.

"In this work, we have developed a coating of the conducting polymer PEDOT, which is comprised of nanofibers that penetrate the inner porous network of a brick; a polymer coating remains trapped in a brick and serves as an ion sponge that stores and conducts electricity," D'Arcy said.

The red pigment in bricks -- iron oxide, or rust -- is essential for triggering the polymerisation reaction. The authors' calculations suggest that walls made of these energy-storing bricks could store a substantial amount of energy.

"PEDOT-coated bricks are ideal building blocks that can provide power to emergency lighting," D'Arcy said. "We envision that this could be a reality when you connect our bricks with solar cells -- this could take 50 bricks in close proximity to the load. These 50 bricks would enable powering emergency lighting for five hours.

"Advantageously, a brick wall serving as a supercapacitor can be recharged hundreds of thousands of times within an hour. If you connect a couple of bricks, microelectronics sensors would be easily powered."

https://nyti.ms/2PU75CN

When Bugs Crawl Up the Food Chain

We usually think of insects as meals for vertebrates such as frogs. But arthropods may turn the tables more often than you think.

By Cara Giaimo

Epomis beetle larvae look delicious to frogs. They're snack-size, like little protein packs. If a frog is nearby, a larva will even wiggle its antennae and mandibles alluringly.

But when the frog makes its move, the beetle turns the tables. It jumps onto the amphibian's head and bites down. Then it drinks its would-be predator's fluids out like a froggy Capri Sun.

We tend to think of food chains moving in one direction: Bigger eats smaller. But nature is often not so neat. All around the world,

and maybe even in your backyard, arthropods are bodying vertebrates and gobbling them up.

Jose Valdez, soon to be a postdoctoral researcher at the German Centre for Integrative Biodiversity Research, identified hundreds of examples of this phenomenon in the scientific literature, which he detailed in a review published in July in Global Ecology and Biogeography. He and others who study the topic think that once the initial gasp of shock is past, it's important to understand what eats what.

Dr. Valdez became interested in these role reversals during his doctoral research, after watching a gang of water beetles devour a rare tadpole. The larvae were known predators, whereas the adults were widely considered to be scavengers. But Dr. Valdez developed a hunch, borne out by further research, that they were actively hunting vertebrates, too.

He got a similar feeling when, while reading the news or surfing YouTube, he saw other bugs punching above their weight: a huntsman spider savoring a pygmy possum, a praying mantis chewing off a gecko's face.

"Maybe this is not so rare," Dr. Valdez remembered thinking.

Dr. Valdez found 1,300 similar examples, which he gathered into a searchable database. The entries cover 89 countries and involve many types of arthropod predator: storied vertebrate-hunters like scorpions and spiders, along with less well-documented cases such as dragonflies and centipedes.

It is a formidable catalog of invertebrate vengeance: A spider snares a songbird in its web, giant water bugs wrestle snakes into submission, fire ants team up to overrun a baby alligator. "Every time I would read a new one I was like, 'Oh my goodness,'" Dr. Valdez said.

There are few full-fledged studies on the topic; Dr. Valdez built on the work of Martin Nyffeler, a conservation biologist at the University of Basel in Switzerland who has documented spiders eating everything from fish to bats. Another large contribution came from a 1982 literature review by Sharon McCormick and Gary Polis. Many of the matchups that Dr. Valdez added to his database were originally described in brief observational notes by scientists who hadn't set out to study the subject.

After witnessing his water beetle-tadpole smackdown, Dr. Valdez, too, had written it up as a note. But treating these instances as one-offs might be obscuring a larger ecological significance, he said: "We should see what kind of effect this is having on food webs."

There could also be conservation implications, said Dr. Valdez. He points to the case of the Devils Hole pupfish. Scientists had trouble breeding the rare species in a lab to save them until they realized that diving beetles — accidentally imported from the pupfish's habitat — were eating many of the larvae.

It is difficult to investigate what arthropods eat, said Eric Nordberg, a wildlife ecologist at James Cook University in Queensland who has also studied the topic but was not involved with the new paper. If you want to learn more about what a vertebrate eats, "you can flush the stomach contents or look at preserved specimens," he said. But invertebrates lack stomachs, so "you need to be in the right place at the right time."

These moments of serendipity are becoming increasingly common, said Gil Wizen, one of the entomologists who discovered the unique behavior of the Epomis beetles. He credited the prevalence of smartphones, as well as scientists and the public becoming "more alert to these interactions," he said.

Even with the new database, however, he didn't think scientists have seen it all. "Without doubt there are more arthropods out there hunting vertebrates," he said. "Nature is more fluid than we think."

https://bit.ly/311rQ5D

Right under your nose: A more convenient way to diagnose Alzheimer's disease

Certain proteins in nasal discharge can indicate the onset and progression of Alzheimer's, providing an avenue for early detection

The Republic of Korea, like other countries with a rapidly ageing population, is facing increasing numbers of patients with dementia, of which Alzheimer's disease (AD) is the most representative type. Unfortunately, AD has no complete cure yet; but, some treatments have been proven to delay its progression. Of course, this means that timely diagnosis while the symptoms are still mild is essential to maximize a patient's quality of life.

However, currently available technologies for diagnosing AD are limited because they involve expensive machinery and invasive or inconvenient procedures. Now, in a recent study published in *Scientific Reports*, scientists from Daegu Gyeongbuk Institute of Science and Technology, Korea, hint at a novel way of diagnosing AD in a much simpler way --collecting and analyzing specific proteins in nasal discharge samples.

Professor Cheil Moon, who led the study, explains how they came up with the idea: "In 2017, we found that olfactory dysfunction occurred in the early stages of AD in mice and suggested that the cause of the symptoms was induced by soluble species of amyloid-β (Aβ) oligomer accumulations in the peripheral olfactory system. We hypothesized that soluble Aβ oligomers could be detectable in nasal discharge and that they may be a useful parameter to monitor disease progression." To test their hypothesis, they gathered and compared nasal discharge samples from 39 patients with AD and 21 people from an age-matched control group.

They found that the levels of two particular Aβ oligomers (the aggregated forms of Aβ implicated as characteristic of Alzheimer's) were consistently higher in patients from the AD group. What's more, the levels of the "soluble" form of this protein could be used to not only separate healthy subjects from patients with AD, but also predict the onset and progression of AD over a three-year period.

Although further research will be required to better understand the link between Aβ oligomers in nasal discharge and the cognitive impairments related to AD, the results are certainly promising. Prof Moon remarks, "Routine nasal discharge screenings would be a better option to screen for AD because of its various advantages, such as its relatively low cost and non-invasive nature. The results of our study introduce a novel and simple approach to assess AD progression."

This new diagnostic technique will hopefully help in simpler and faster detection of Alzheimer's and improving the disease outcome, thus bringing much needed relief to millions suffering from the Alzheimer's worldwide.

Reference

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Chloroquine Linked to Serious Psychiatric Side Effects

Chloroquine may be associated with serious psychiatric side effects, even in patients with no family or personal history of psychiatric disorders, a new review suggests.

Batya Swift Yasgur, MA, LSW

In a letter to the editor published online July 28 in *The Journal of Clinical Psychiatry*, the authors summarize data from several studies published as far back as 1993 and as recently as May 2020.

"In addition to previously reported side effects, chloroquine could also induce psychiatric side effects which are polymorphic and can persist even after stopping the drug," lead author Florence Gressier, MD, PhD, CESP, Inserm, Department of Psychiatry, Le Kremlin Bicêtre, France, told *Medscape Medical News*.

"In COVID-19 patients who may still be [undergoing treatment] with chloroquine, close psychiatric assessment and monitoring should be performed," she said.

Heated Controversy

Chloroquine and hydroxychloroquine have been at the center of heated controversy for their potential role in preventing or treating COVID-19.

Following findings of a small French study that suggested efficacy in lowering the viral load in patients with COVID-19, President Donald Trump expressed optimism regarding the role of hydroxychloroquine in treating COVID-19, calling it a "game changer."

Other studies, however, have called into question both the efficacy and the safety of hydroxychloroquine in treating COVID-19. On June 15, the US Food and Drug Administration (FDA) revoked the emergency use authorization it had given in March to chloroquine and hydroxychloroquine for the treatment of COVID-19.

Nevertheless, hydroxychloroquine continues to be prescribed for COVID-19. For example, an article that appeared in *Click2Houston* on June 15 quoted the chief medical officer of Houston's United Memorial Center as saying he plans to continue prescribing hydroxychloroquine for patients with COVID-19 until he finds a better alternative.

As discussed in a Medscape expert commentary, a group of physicians who held a "white coat summit" in front of the US Supreme Court building promoted the use of hydroxychloroquine for the treatment of COVID-19. The video of their summit was retweeted by President Trump and garnered millions of views before it was taken down by Twitter, Facebook, and YouTube.

Sudden Onset

For the new review, "we wanted to alert the public and practitioners on the potentially psychiatric risks induced by chloroquine, as it could be taken as self-medication or potentially still prescribed," Gressier said.

"We think the format of the letter to the editor allows information to be provided in a concise and clear manner," she added.

According to the FDA's Adverse Event Reporting System database, 12% of reported adverse events (520 of 4336) following the use of chloroquine that occurred between the fourth quarter of 2012 and the fourth quarter of 2019 were neuropsychiatric. These events included amnesia, delirium, hallucinations, depression, and loss of consciousness, the authors write.

They acknowledge that the incidence of psychiatric adverse effects associated with the use of chloroquine is "unclear in the absence of high-quality, randomized placebo-controlled trials of its safety." Nevertheless, they point out that there have been reports of insomnia and depression when the drug was used as prophylaxis against malaria.

Moreover, some case series or case reports describe symptoms such as depression, anxiety, agitation, violent outburst, suicidal ideation, and psychosis in patients who have been treated with chloroquine for malaria, lupus erythematosus, and rheumatoid arthritis.

"In contrast to many other psychoses, chloroquine psychosis may be more affective and include prominent visual hallucinations, symptoms of derealization, and disorders of thought, with preserved insight," the authors write.

They note that the frequency of symptoms does not appear to be connected to the cumulative dose or the duration of treatment, and the onset of psychosis or other adverse effects is usually "sudden."

In addition, they warn that the drug's psychiatric effects may go unnoticed, especially because COVID-19 itself has been associated with neuropsychiatric symptoms, making it hard to distinguish between symptoms caused by the illness and those caused by the drug.

Although the psychiatric symptoms typically occur early after treatment initiation, some "subtle" symptoms might persist after stopping the drug, possibly owing to its "extremely long" half-life, the authors state.

Gressier noted that practicing clinicians should look up reports about self-medication with chloroquine "and warn their patients about the risk induced by chloroquine."

Safe but "Not Benign"

Nilanjana Bose, MD, MBA, a rheumatologist at the Rheumatology Center of Houston, Texas, said she uses hydroxychloroquine "all the time" in clinical practice to treat patients with rheumatic conditions.

"I cannot comment on whether it [hydroxychloroquine or chloroquine] is a potential prophylactic or treatment for COVID-19, but I can say that, from a safety point of view, as a rheumatologist who uses hydroxychloroquine at a dose of 400 mg/day, I do not think we need to worry about serious [psychiatric] side effects," Bose told *Medscape Medical News* when asked to comment.

Because clinicians are trying all types of possible treatments for COVD-19, "if this medication has possible efficacy, it is a great medicine from a rheumatologic perspective and is safe," she added.

Nevertheless, the drug is "not benign, and regular side effects will be there, and of course, higher doses will cause more side effects," said Bose, who was not involved in authoring the letter.

She counsels patients about potential psychiatric side effects of hydroxychloroquine because some of her patients have complained about irritability, worsening anxiety and depression, and difficulty sleeping.

Be Wary

Also commenting on the letter for *Medscape Medical News*, James "Jimmy" Potash, MD, MPH, Henry Phipps professor of psychiatry and behavioral sciences, Johns Hopkins Medicine, Baltimore, Maryland, said the "take-home message of this letter is that serious psychiatric effects, psychotic illness in particular," can occur in individuals who take chloroquine and hydroxychloroquine.

In addition, "these are potentially very concerning side effects that psychiatrists should be aware of," noted Potash, who is also the department director and psychiatrist-in-chief at Johns Hopkins.

He said that one of his patients who had been "completely psychiatrically healthy" took chloroquine prophylactically prior to traveling overseas. After she began taking the drug, she had an episode of mania that resolved once she discontinued the medication and received treatment for the mania.

"If you add potential psychiatric side effects to the other side effects that can result from these medications, that adds up to a pretty important reason to be wary of taking them, particularly for the indication of COVID-19, where the level of evidence that it helps in any way is still quite weak," Potash said.

Remington Nevin, MD, MPH, DrPH, executive director at the Quinism Foundation, White River Junction, Vermont, and faculty associate in the Department of Mental Health at the Johns Hopkins Bloomberg School of Public Health, agreed.

"The authors of this letter are to be commended for their efforts in raising awareness of the potentially lasting and disabling psychiatric effects of chloroquine and hydroxychloroquine, which, as with similar effects from other synthetic quinoline antimalarials, have occasionally been overlooked or misattributed to other conditions," Nevin told *Medscape Medical News*.

"I have proposed that the chronic neuropsychiatric effects of this class of drug are best considered not as side effects but as signs and symptoms of a disorder known as chronic quinoline encephalopathy caused by poisoning of the central nervous system," he said.

Gressier and the other letter authors, Bose, and Potash have reported no relevant financial relationships. Nevin reviewed the letter to the editor and serves as the executive director of the Quinism Foundation, a nonprofit organization that supports and promotes education and research on disorders caused by poisoning by quinoline drugs. He has also been retained as a consultant and expert witness in legal cases involving claims of adverse effects from quinoline antimalarial drugs.

J Clin Psychiatry. Published online July 28, 2020. Full text

https://bit.ly/2Y7S4S9

Malaria discovery could expedite antiviral treatment for COVID-19

New research into malaria suggests targeting enzymes from the human host, rather than from the pathogen itself, could offer effective treatment for a range of infectious diseases, including COVID-19.

The study, conducted by an international team and led by RMIT University's Professor Christian Doerig, outlines a strategy that could save years of drug discovery research and millions of dollars in drug development by repurposing existing treatments designed for other diseases such as cancer.

The approach shows so much promise it has received government funding for its potential application in the fight against COVID-19.

The study, published in *Nature Communications*, demonstrated that the parasites that cause malaria are heavily dependent on enzymes in red blood cells where the parasites hide and proliferate.

It also revealed that drugs developed for cancer, and which inactivate these human enzymes, known as protein kinases, are highly effective in killing the parasite and represent an alternative to drugs that target the parasite itself.

Lead author, RMIT's Dr Jack Adderley, said the analysis revealed which of the host cell enzymes were activated during infection, revealing novel points of reliance of the parasite on its human host.

"This approach has the potential to considerably reduce the cost and accelerate the deployment of new and urgently needed antimalarials," he said.

"These host enzymes are in many instances the same as those activated in cancer cells, so we can now jump on the back of existing cancer drug discovery and look to repurpose a drug that is already available or close to completion of the drug development process."

As well as enabling the repurposing of drugs, the approach is likely to reduce the emergence of drug resistance, as the pathogen cannot escape by simply mutating the target of the drug, as is the case for most currently available antimalarials.

Doerig, Associate Dean for the Biomedical Sciences Cluster at RMIT and senior author of the paper, said the findings were exciting, as drug resistance is one of the biggest challenges in modern healthcare, not only in the case of malaria, but with most infectious agents, including a large number of highly pathogenic bacterial species.

"We are at risk of returning to the pre-antibiotic era if we don't solve this resistance problem, which constitutes a clear and present

danger for global public health. We need innovative ways to address this issue," he said.

"By targeting the host and not the pathogen itself, we remove the possibility for the pathogen to rapidly become resistant by mutating the target of the drug, as the target is made by the human host, not the pathogen."

Doerig's team will now collaborate with the Peter Doherty Institute for Infection and Immunity (Doherty Institute) to investigate potential COVID-19 treatments using this approach, supported by funding from the Victorian Medical Research Acceleration Fund in partnership with the Bio Capital Impact Fund (BCIF).

Co-investigator on the grant, Royal Melbourne Hospital's Dr Julian Druce, from the Victorian Infectious Diseases Reference Laboratory (VIDRL) at the Doherty Institute, was part of the team that were first to grow and share the virus that causes COVID-19, and said the research was an important contribution to efforts to defeat the pandemic.

Royal Melbourne Hospital's Professor Peter Revill, Senior Medical Scientist at the Doherty Institute and a leader on Hepatitis B research, said the approach developed by the RMIT team was truly exciting.

"This has proven successful for other human pathogens including malaria and Hepatitis C virus, and there are now very real prospects to use it to discover novel drug targets for Hepatitis B and COVID-19," he said.

The paper is the outcome of an RMIT-led international collaboration with researchers from Monash University in Melbourne, Dr Danny Wilson (University of Adelaide's Malaria Biology Laboratory Head and Burnet Institute), Dr Jean-Philippe Semblat (from French Government agency Inserm, Paris) and Prof Oliver Billker (Umeå University, Sweden and Sanger Centre, UK).

The paper, 'Analysis of erythrocyte signalling pathways during Plasmodium falciparum infection identifies targets for host-directed antimalarial intervention' and is published in Nature Communications (DOI:10.1038/s41467-020-17829-7).

https://lat.ms/2PZiql4

San Quentin's coronavirus outbreak shows why 'herd immunity' could mean disaster

Any effort to achieve herd immunity before a vaccine is available would come with enormous costs in terms of illness and death

By Rong-Gong Lin II, Kim Christensen

San Francisco — For critics of aggressive stay-at-home orders, the solution seems clear: Reopen the economy and enough people will eventually become infected by the novel coronavirus to achieve "herd immunity" even before a vaccine is available.

The idea is that eventually, a sufficient percentage of the population will have survived COVID-19 and become immune, which in turn protects the rest of the uninfected population by interrupting the spread of the virus.

But the disastrous situation unfolding at San Quentin State Prison over the last two months has become the latest of several cautionary tales that show how any effort to achieve herd immunity before a vaccine is available would come with enormous costs in terms of illness and death.

COVID-19 spread unchecked across California's oldest prison in ways that stunned public health experts, despite efforts to control the disease. As of Monday, there had been more than 2,200 cases and 25 deaths, among a population of more than 3,260 people. On Sunday, a guard became one of the latest to die.

That means more than two-thirds of the prison's population has been infected, said Dr. George Rutherford, epidemiologist and infectious diseases expert at UC San Francisco.

And though new cases have slowed, they are still occurring — with 60 reported in the last two weeks — suggesting herd immunity has not yet been achieved.

San Quentin's death toll translates to a mortality rate of about 767 people dying out of every 100,000 persons.

If that same rate occurred across California, that would translate to a staggering 300,000 deaths statewide — many times larger than California's cumulative death toll of more than 10,400. Nationally, that would be equivalent to 2.5 million deaths; the current cumulative U.S. death toll is more than 163,000.

"You couldn't help but get it — you're staying in a place with no ventilation," Michael Kirkpatrick, 62, told The Times a week after he was freed. Kirkpatrick was released from San Quentin on July 13 after his parole on a burglary conviction was expedited because of the outbreak. He tested positive for the virus and has since recovered.

Kirkpatrick said his cellmate was infected, along with most of the rest of the inmates in the 50 or so cells on his tier.

"They put a little white piece of paper on the door of everyone who was positive," Kirkpatrick said. "On our wing, there were, like, maybe five cells that didn't have that piece of paper on them."

San Quentin is an imperfect setting to help understand when herd immunity might be achieved. Prisons are crowded settings that will promote coronavirus transmission more so than among people in other settings, like those who live in single-family homes.

But the San Quentin experience — as well as other data — does show that, in the absence of a vaccine, "in order to get to something that approaches herd immunity, we're going to have to get something well on the far side of 50% of people infected," Rutherford said. "Which comes with a resultant large cost in mortality and severe morbidity.

"If you believe the San Quentin stuff, you got to get up to way-up-there before you start seeing slowing of transmission," Rutherford said.

Dr. Anthony Fauci, the U.S. government's top infectious diseases expert, last week guessed it will probably require 50% to 75% of a population to be immune before achieving herd immunity — a goal that should be achieved not just through infected people recovering but also through vaccination.

California has a long way to go before the vast majority of residents have been infected.

In May, only about 2% of L.A. County residents had test results indicating presence of the antibodies to the coronavirus, indicating previous exposure to the virus. That means 98% of L.A. County's residents as of late spring were still susceptible to infection.

The prevalence of past coronavirus infection in the Bay Area was even less, with just 1% having evidence of it in late April, according to the U.S. Centers for Disease Control and Prevention.

Sweden famously pursued a herd immunity strategy when it decided not to impose a severe lockdown.

But now, Sweden has among the highest mortality rates among European countries, and has a worse rate than that of the United States.

Sweden has reported 5,763 deaths — a mortality rate of 57 deaths for every 100,000 residents, according to Johns Hopkins University. The United States is reporting a mortality rate of 50 deaths for every 100,000 residents.

Sweden's neighbors, by contrast, report far fewer deaths. Denmark has a mortality rate of 11 deaths per 100,000 residents; Norway's is five deaths per 100,000 residents.

And Sweden appears to be nowhere near herd immunity, with only 7% of the population testing positive for antibodies to the coronavirus, "leaving them far from reaching natural herd immunity in the population," according to a commentary by two virologists in Switzerland, published in the journal Lancet. "Most of the population appears to have remained unexposed to [the coronavirus], even in areas with widespread virus circulation.

"In light of these findings, any proposed approach to achieve herd immunity through natural infection is not only highly unethical, but

also unachievable," the commentary said, written by Isabella Eckerle and Benjamin Meyer.

The CDC estimates that perhaps only 23% of New York City's population has had past infection with the coronavirus. New York City could easily fall into a second wave of severe coronavirus pandemic conditions, Rutherford said.

Other data show how it's possible for far larger proportions of the population to get infected.

Among three slums in Mumbai, India, 57% of people tested have been exposed to the coronavirus, according to the BBC, citing a survey conducted by government officials. On a cruise ship with 217 passengers that left Argentina in March bound for Antartica, 59% tested positive for the virus, according to a study published in the journal Thorax.

Even nations that have previously been seen as hard hit still have plenty of susceptible people to fuel a second wave of disease.

Spain was hard hit in its first surge of the pandemic, having an experience as bad as Italy and New York City, Rutherford said. But a study in the journal Lancet said only about 5% of the population had antibody test results indicating past exposure to the virus.

Recently, Spain began experiencing a second wave of cases.

What all of this means is that a vaccine is going to be essential to controlling the pandemic.

Though officials and experts are expressing cautious optimism that California as a whole appears to be heading out of the current surge of disease, they are already warning the public to expect new surges of cases in the coming months — perhaps when disease levels fall low enough that more schools can begin to reopen.

Gov. Gavin Newsom last week said he's anticipating a new wave of disease in the fall — and is hoping that coronavirus disease transmission falls before the flu season hits. Newsom's Health and Human Services Agency secretary, Dr. Mark Ghaly, also spoke last week about second and third waves of disease.

In the last global pandemic comparable to this one, in 1918-19, there were three distinct waves of flu in the U.S., with levels of disease falling back down to the baseline level after the first wave hit.

But Rutherford warned that it's possible that California may be unable to get its disease down to a similar baseline level, given how the disease is extraordinarily widespread.

"I think it's almost impossible for us to return to baseline given how many people are infected and how broadly distributed the infection is," Rutherford said. "So we'll see it go ... down a little bit before it starts to go back up again," rising whenever officials think it's OK to allow adolescents to return to school.

"This is not going to be controlled without vaccine. Make no mistake about it," Rutherford said. "The solution is immunization."

Fauci, at a forum Wednesday hosted by the Harvard T.H. Chan School of Public Health, said he thinks officials will know by the end of this year or the beginning of next year, based on initial data from early studies, "whether we have a safe and effective vaccine. I'm cautiously optimistic that we will be successful."

Fauci's optimistic timeline is based on the assumption that everything will go right, said Dr. Joel Ernst, chief of UC San Francisco's division of experimental medicine.

But it's also plausible that we might not get an answer about a safe and effective vaccine until 2022, Ernst said, citing a more pessimistic timeframe offered by the scientists who designed the clinical trials for the vaccine. "That's very conservative," he said.

"It's difficult to predict exactly what date things will be ready," Ernst said.

It will also take time to figure out a way to start immunizing Americans. There won't be enough vaccines to inoculate everyone

in the nation immediately. “There will be a period of time when vaccines are proven to be safe and effective that you’re not going to have 300 million doses right away. So you’re gonna have to prioritize who gets it first,” Fauci said.

In contrast to President Trump saying the coronavirus will simply “go away,” some officials in California are bracing the public to face the reality that the coronavirus will be with us for the foreseeable future.

We need to get “everyone in shifting their mind-set to a long game,” said Santa Clara County health officer Dr. Sara Cody. “We have to be changing our behavior for a very, very long time.”

“If we see that the cases are rising and they’re rising fast, then we may need to put more stricter controls into place, as we did back in March,” Cody said.

Dr. Christina Ghaly, L.A. County’s director of health services, said the virus is just as capable of spreading now as it was several weeks ago. “And it will continue to spread if we give it a chance to do so.”

Lin reported from San Francisco, Christensen from Southern California.

Rong-Gong Lin II is a metro reporter based in San Francisco who specializes in covering statewide earthquake safety issues and the COVID-19 pandemic. The Bay Area native is a graduate of UC Berkeley and started at the Los Angeles Times in 2004.

Kim Christensen is a Pulitzer Prize-winning investigative reporter who joined the Los Angeles Times in 2005.

https://bit.ly/2E5r4eX

Breast screening women in their forties saves lives

Breast screening women aged 40-49 reduces breast cancer mortality, with minimal increased overdiagnosis, according to a study led by Queen Mary University of London that looked at data from 160,000 women.

Breast screening women aged 40-49 reduces breast cancer mortality, with minimal increased overdiagnosis, according to a study led by Queen Mary University of London that looked at data from 160,000 women.

The UK, along with many other countries, has a breast cancer screening programme offering mammography to women aged 50-70 years every 3 years. However, uncertainty currently exists over whether to start screening at a younger age, including whether it might lead to overdiagnosis of breast cancer.

Between 1990 and 1997, the UK Breast Screening Age Trial randomised more than 160,000 UK women aged 39-41 to receive either annual mammography, or the usual NHS breast screening which commences at age 50. The primary outcome was mortality from breast cancers diagnosed prior to first NHS breast screen.

In a new analysis, published in *The Lancet Oncology* which presents the 23-year follow-up results of the trial, it was found that screening women aged 40-49 led to a substantial and significant 25 per cent reduction in breast cancer mortality in the first ten years. The total years of life saved from breast cancer in the intervention group was estimated as 620, corresponding to 11.5 years saved per 1,000 women invited to earlier screening.

The results also suggest at worst modest overdiagnosis in this age group, and that any overdiagnosed cancers would otherwise be diagnosed at NHS screening from 50 years of age. Therefore, screening in the age group of 40-49 years does not appear to add to overdiagnosed cases from screening at age 50 years and older.

Lead researcher Professor Stephen Duffy from Queen Mary University of London said: "This is a very long term follow-up of a study which confirms that screening in women under 50 can save lives. The benefit is seen mostly in the first ten years, but the reduction in mortality persists in the long term at about one life saved per thousand women screened.

"We now screen more thoroughly and with better equipment than in the 1990's when most of the screening in this trial took place, so the benefits may be greater than we've seen in this study."

The researchers say that more research is needed to clarify whether progress in early detection technology and treatment of breast cancer might modify the screening-related reduction in mortality in the 40-49 age group. They also did not consider the cost-effectiveness of lowering the screening age.

The study was funded by the National Institute for Health Research Health Technology Assessment programme, and included researchers from King's College London, University of Nottingham, University of Dundee and Tel Aviv University.

Research paper: 'Effect of mammographic screening from the age of 40 years on breast cancer mortality (UK Age Trial): final results of a randomised, controlled trial'. Stephen W Duffy, Daniel Vulkan, Howard Cuckle, Dharmishta Parmar, Shama Sheikh, Robert A Smith, Andrew Evans, Oleg Blyuss, Louise Johns, Ian O Ellis, Jonathan Myles, Peter D Sasieni, Sue M Moss. The Lancet Oncology 2020.

Available here after the embargo lifts:
http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(20)30398-3/fulltext

https://bit.ly/30YzKNk

Preliminary study of 300+ COVID-19 patients suggests convalescent plasma therapy effective

American Journal of Pathology publishes efficacy results from Houston Methodist clinical trial

Houston - A preliminary analysis of an ongoing study of more than 300 COVID-19 patients treated with convalescent plasma therapy at Houston Methodist suggests the treatment is safe and effective. The results, which appear now in The *American Journal of Pathology*, represents one of the first peer-reviewed publications in the country assessing efficacy of convalescent plasma.

From March 28, when Houston Methodist became the first academic medical center in the nation to infuse critically ill COVID-19 patients with plasma donated from recovered patients, research physicians have used the treatment on 350 patients. The study tracked severely ill COVID-19 patients admitted to Houston Methodist's system of eight hospitals from March 28 through July 6. These latest results from Houston Methodist that now measured medical effectiveness offer valuable scientific evidence that transfusing critically ill COVID-19 patients with high antibody plasma early in their illness - within 72 hours after hospitalization proving most effective - reduced the mortality rate.

The study, titled "Treatment of COVID-19 Patients with Convalescent Plasma Reveals a Signal of Significantly Decreased Mortality," was led by principal investigator Eric Salazar, M.D., Ph.D., assistant professor of Pathology and Genomic Medicine with the Houston Methodist Hospital and Research Institute and corresponding author James M. Musser, M.D., Ph.D., chair of the Department of Pathology and Genomic Medicine at Houston Methodist.

"Our studies to date show the treatment is safe and, in a promising number of patients, effective," Musser said. "While convalescent plasma therapy remains experimental and we have more research to do and data to collect, we now have more evidence than ever that this century-old plasma therapy has merit, is safe and can help reduce the death rate from this virus."

The research team found that those treated early in their illness with donated plasma that has the highest concentration of anti-COVID-19 antibodies are more likely to survive and recover than similar patients who were not treated with convalescent plasma. Patients with a history of severe reactions to blood transfusions, those with underlying uncompensated and untreatable end-stage disease and patients with fluid overload or other conditions that would increase the risk of plasma transfusion were excluded.

The patients were tracked for 28 days after plasma transfusion and compared to a control group of similar COVID-19 patients who did not receive convalescent plasma. An observational propensity score-matched analysis was used to balance the characteristics of participants and allow for an objective interpretation of the results at this stage.

Several studies have measured safety, showing that the more than 34,000 COVID-19 patients in the U.S. who have received plasma transfusions for COVID-19 experienced minimal adverse effects.

In addition to Musser and Salazar, other collaborators from Houston Methodist on this study were Paul A. Christensen, Edward A. Graviss, Duc T. Nguyen, Brian Castillo, Jian Chen, Bevin Valdez Lopez, Todd N. Eagar, Xin Yi, Picheng Zhao, John Rogers, Ahmed Shehabeldin, David Joseph, Christopher Leveque, Randall J. Olsen, David W. Bernard, and Jimmy Gollihar of the US Army Research Laboratory-South, University of Texas Austin.

This study was supported by funding from the Fondren Foundation, Houston Methodist Hospital, Houston Methodist Research Institute and Houston Methodist Infectious Diseases Research Fund.

For more information: Treatment of COVID-19 Patients with Convalescent Plasma Reveals a Signal of Significantly Decreased Mortality. The American Journal of Pathology. (online/in press Aug. 11, 2020) E. Salazar, P.A. Christensen, E.A. Graviss, D.T. Nguyen, B. Castillo, J. Chen, B.V. Lopez, T.N. Eagar, X. Yi, P. Zhao, J. Rogers, A. Shehabeldin, D. Joseph, C. Leveque, R.J. Olsen, D.W. Bernard, J. Gollihar and J.M. Musser. DOI: https://doi.org/10.1016/j.ajpath.2020.08.001 [This article appears in advance of The American Journal of Pathology, volume 190, Issue 11 (November 2020) published by Elsevier.]

https://bit.ly/3q8x4kE

Gilead Urged to Explore Remdesivir Relative as COVID-19 Drug

Citizen advocates push the pharmaceutical company to examine a compound that has been used to treat certain coronavirus infections in cats.

Catherine Offord

Gilead Sciences, the maker of remdesivir, is under pressure from citizen advocates to launch clinical trials on COVID-19 patients of another of its compounds—one that advocates claim could be cheaper, easier to make, and more effective at treating the novel coronavirus.

Remdesivir is currently the only medication to have emergency use authorization from the US Food and Drug Administration (FDA) for hospitalized COVID-19 patients. In a letter posted last week (August 4), the Washington-based advocacy organization Public Citizen urged the company to focus on GS-441524, a compound that is chemically similar to remdesivir and has been used to treat cats infected with a different, feline-specific coronavirus.

The letter presses Gilead and government health agencies to "either work collaboratively to promptly pursue the development of the experimental antiviral drug GS-441524 . . . as a treatment for [COVID-19] or publicly provide evidence why it is not scientifically or medically feasible to develop this drug in parallel with its close analogue, remdesivir."

The organization isn't the first to highlight the possibility of repurposing drugs used to treat feline coronavirus. An in vitro study posted as a preprint in May by researchers in Canada suggested that another drug used to treat viral infections in cats, GC376, could inhibit an enzyme that SARS-CoV-2 needs in order to replicate. The company with the license for that compound, California-based Anivive Lifesciences, is reportedly planning clinical trials, according to *Science News*.

Neither compound has received FDA approval in cats with feline coronavirus infections, let alone in people with SARS-CoV-2 infections. Gilead tells the *Chicago Tribune* that the company is working on preclinical studies with GS-441524, which, unlike remdesivir, had not been formally tested in people prior to the pandemic. Remdesivir had gone through rapid clinical trials during the West African Ebola epidemic of 2013 to 2016.

Derek Lowe, a drug discovery scientist and author of *In the Pipeline*, a well-known blog about the pharma industry, tells *The Guardian* that remdesivir and other antivirals such as GS-441524 will become less important to the public health response to COVID-19 as efforts to find other treatments and prophylaxes progress. "Monoclonal antibodies and vaccines are, to my eyes (and not just mine) the answer to this pandemic," he says.

https://bit.ly/3kPczwC

A Vaccine Against a Widespread Common Cold Type Just Passed Promising Clinical Trials

Could actually reach the market in just a few years

Carly Cassella

A vaccine designed to prevent one of the most widespread common cold types has just delivered promising results in the latest set of clinical trials, and the developers now think it could actually reach the market in just a few years.

The cold, known as respiratory syncytial virus (RSV), is so common, more than 90 percent of kids contract it by the age of two.

In fact, this dangerous and sometimes deadly infection is the leading cause of serious lower respiratory diseases in children worldwide, and we still don't have a working vaccine to prevent it.

While Bavarian Nordic, the German company that owns this particular vaccine - known as MVA-BN-RSV - hopes it will become available in 2024, the medicine still has to pass a third clinical trial before the US Food and Drug Administration (FDA) would approve it for general use.

The first two clinical trials of a vaccine are usually limited to examining its safety and optimal dosage. The results of these phases might also give some indication of effectiveness, but the size and breadth of such trials are usually not enough to determine immunity.

So far, it appears as though a single dose of this new vaccine safely induces a broad immune response to RSV in most of the 420 adults over the age of 55 that were enrolled in the study.

In this randomised, placebo-controlled trial, the immune response from T cells, which hunt and destroy infections, and antibodies, which recognise foreign invaders, persisted for at least six months.

When followed up with a booster shot at 12 months, there was an even better immune response.

Those who received either one or both doses showed higher antibody levels at 56 weeks compared to the placebo group, "thus demonstrating persistence of MVA-BN-RSV induced immune responses for up to one year."

However, after a single, high dose of the vaccine, the T cell response had pretty much maxed out.

"Peak T cell responses following the booster vaccination were lower than peak responses following the initial vaccination, suggesting that activation of T cells may be regulated by pre-existing levels of antigen-specific T cells," the researchers write in a study summarising the results.

"This is consistent with the observation that a second vaccination did not induce further T cell responses."

In other words, if a bunch of T cells are already around, then a booster shot isn't going to induce a further response.

It's an interesting explanation, but more research will be needed to confirm those results and figure out the mechanism of action; given the challenges RSV keeps presenting for vaccine development, it's clear we're not quite there yet.

Not only is RSV good at hiding from the immune system, its presence does not induce long-lasting immunity, like chicken pox or measles might, which means we can keep on getting sick with the same thing over and over again, even as adults.

While usually mild cold and flu symptoms occur, older people and those with weakened immune systems are particularly vulnerable to RSV.

A vaccine could potentially stop 33 million serious respiratory infections a year, saving the lives of nearly 60,000 children annually. That would be a huge deal, and while there's reason to be hopeful, it's important not to get ahead of ourselves. There are many almost-vaccines out there, on the brink of hitting the market in the next five years.

The third clinical trial is set to start in 2021 and will include more than 12,000 adults. Hopefully that will be enough to answer some of these remaining questions.

Given "the broad immune response" already elicited by the vaccine, experts at Bavarian Nordic think there is more than enough promise here to merit a phase 3 efficacy trial. Watch this space.

The study was published in *The Journal of Infectious Diseases*.

https://bit.ly/3ay70ya

Early spread of COVID-19 appears far greater than initially reported

Patients with undiagnosed flu symptoms who actually had COVID-19 last winter were among thousands of undetected early cases of the disease at the beginning of this year.

In a new paper in The Lancet's open-access journal *EClinicalMedicine,* epidemiological researchers from The University of Texas at Austin estimated COVID-19 to be far more widespread in Wuhan, China, and Seattle, Washington, weeks ahead of lockdown measures in each city.

In the U.S., about a third of the estimated undiagnosed cases were among children. The researchers also concluded that the first case of COVID-19 in Seattle may have arrived as far back as Christmas or New Year's Day.

Lauren Ancel Meyers, a professor of integrative biology and statistics and data sciences who leads the UT Austin COVID-19 Modeling Consortium, worked with her team of researchers to extrapolate the extent of the COVID-19 epidemic in Wuhan and Seattle based on retested throat swabs taken from patients who were suffering from influenza-like illnesses during January in Wuhan and during late February and early March in Seattle. When the samples were analyzed later in each city, most turned out to be flu, but some turned out to be positive for SARS-CoV-2, the virus that causes COVID-19.

"Even before we realized that COVID-19 was spreading, the data imply that there was at least one case of COVID-19 for every two cases of flu," Meyers said. "Since we knew how widespread flu was at that time, we could reasonably determine the prevalence of COVID-19."

When the Chinese government locked down Wuhan on Jan. 22, there were 422 known cases. But, extrapolating the throat-swab data across the city using a new epidemiological model, Meyers and her team found that there could have been more than 12,000 undetected symptomatic cases of COVID-19. On March 9, the week when Seattle schools closed due to the virus, researchers estimate that more than 9,000 people with flu-like symptoms had COVID-19 and that about a third of that total were children. The data do not imply that health authorities were aware of these infections, rather that they may have gone unseen during the early and uncertain stages of the pandemic.

"Given that COVID-19 appears to be overwhelmingly mild in children, our high estimate for symptomatic pediatric cases in Seattle suggests that there may have been thousands more mild cases at the time," wrote Zhanwei Du, a postdoctoral researcher in Meyers' lab and first author on the study.

According to several other studies, about half of COVID-19 cases are asymptomatic, leading researchers to believe that there may have been thousands more infected people in Wuhan and Seattle before each city's respective lockdown measures went into effect.

"We can go back and piece together the history of this pandemic using a combination of investigative techniques and modeling," Meyers said. "This helps us understand how the pandemic spread so quickly around the globe and provides insight into what we may see in the coming weeks and months."

The new technique for estimating the amount of unseen COVID-19 based on the ratio of influenza cases to COVID-19 cases has also

been used to determine how many children were actually infected in each city and the pace of the early pandemic in the U.S., Meyers said.

The finding in the new paper is consistent with work that Meyers and her team have done on the virus's early spread. Using travel data, she and her team estimated how far the virus had spread and concluded that there were as many as 12,000 cases of COVID-19 in Wuhan before the lockdown.

In addition to Meyers and Du, graduate students Emily Javan and Ciara Nugent at The University of Texas at Austin and professor Benjamin J. Cowling of the University of Hong Kong contributed to the research. The research was funded by the National Institutes of Health.

https://wb.md/2E2vQKd

Can ED Visits Predict Thunderstorms?

Study finds that emergency department (ED) visits for respiratory complaints spiked before a thunderstorm

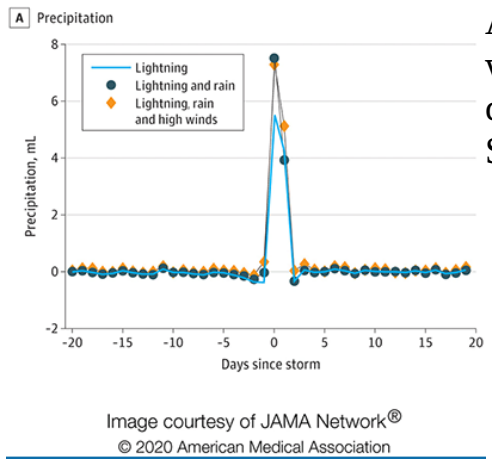
F. Perry Wilson, MD, MSCE

This transcript has been edited for clarity.

Welcome to *Impact Factor*, your weekly dose of commentary on a new medical study. I'm Dr F. Perry Wilson from the Yale School of Medicine.

I had a friend once who claimed that it was his special ability to be able to tell exactly when it would start raining. He'd look up at the sky and say, "In 90 minutes, it will be raining." This is not the most useful of talents in the age of meteorology. Nevertheless, I thought of him as I read this study, appearing in *JAMA Internal Medicine*, which found that emergency department (ED) visits for respiratory complaints spiked *before* a thunderstorm.

This was a large study. Researchers led by Anupam Jena of Harvard used the Medicare fee-for-service database to capture beneficiaries' ED visits for a respiratory ailment from 1999 to 2012. They then combined this data with US National Oceanic and Atmospheric Administration weather data covering all 3127 counties in the continental United States.



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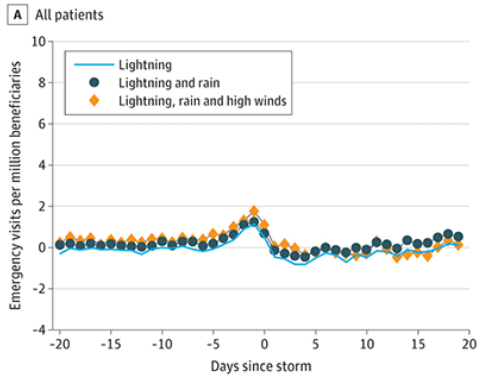
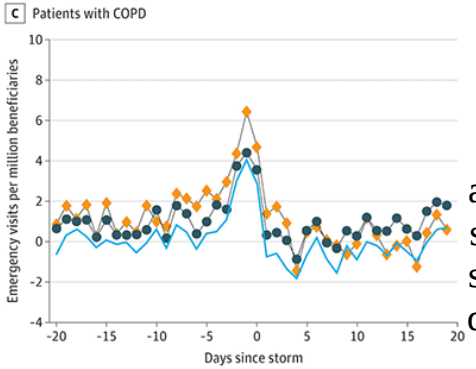
They used the weather data to find days when counties had thunderstorms, defined in this case by high winds, lightning, and precipitation. With that storm as "Time 0," they could look back and forward in time to see how ED visits stacked up. You can see that, as expected, precipitation spikes on a day that there is a thunderstorm. That's proof of concept.

Now look at ED visits for respiratory complaints.

The relationship is actually pretty striking. You can see here a bump in ED visits for respiratory complaints occurring about a day before the storm. The spike is even more evident among those with preexisting COPD.





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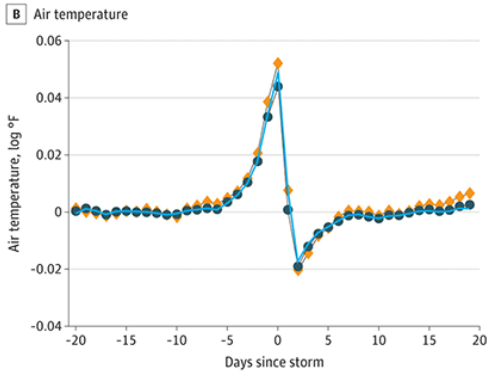
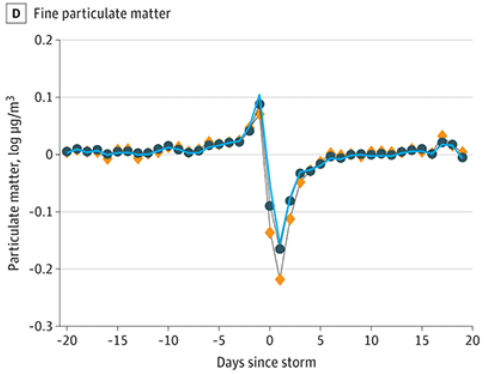
This is actually a bit surprising. Prior research has found an increase in admissions *after* storms, attributed to soaked pollen particles rupturing and spreading throughout the air after the downpour. Here, we see the opposite.

What's going on? Are lungs like my

friend, with the uncanny ability to detect rain in the near future? Looking at other environmental factors, you can see that two things anticipate a thunderstorm: an increase in air temperature and an increase in particulate matter in the air. Maybe it's not the storm at all, then; it's these presages of the storm.





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Hotter temperatures have been shown to be associated with COPD admissions, as have higher amounts of particulate matter, so either or both of these could be contributing. I'd have liked to see some adjustment for these factors to see what is really driving these results, but we don't get that in this particular study. Maybe people are trying to get themselves taken care of before the big storm hits? If so, we'd expect to see a spike in ED visits for other causes, but the negative controls in this study — sepsis and pulmonary embolism — had no association with weather events.

Why does this all matter? No, we should not use ED census as a way to predict the weather; meteorologists are still slightly better at that than we would be. Rather, this study reminds us that health, weather, and climate are connected. Wind, heat, and rain can have downstream effects on health conditions. As the globe warms, it's fairly clear that we can expect more thunderstorms. We can also, possibly, expect more COPD exacerbations.

F. Perry Wilson, MD, MSCE, is an associate professor of medicine and director of Yale's Program of Applied Translational Research. His science communication work can be found in the Huffington Post, on NPR, and here on Medscape. He tweets @methodsmanmd and hosts a repository of his communication work at www.methodsman.com.

https://bit.ly/3h1e0pH

To understand the machinery of life, this scientist breaks it on purpose

By tinkering with some of life's oldest components, a group of astrobiologists hopes to find clues about how life emerged.

Their recent research hints at an effect that prevents organisms from ever reaching evolutionary perfection

"I'm fascinated with life, and that's why I want to break it."

This is how Betül Kaçar, an assistant professor at the University of Arizona with appointments in the Department of Molecular and Cellular Biology, Department of Astronomy and the Lunar and Planetary Laboratory, describes her research. What may sound callous is a legitimate scientific approach in astrobiology. Known as ancestral sequencing, the idea is to "resurrect" genetic sequences from the dawn of life, put them to work in the cellular pathways of modern microbes - think Jurassic Park but with extinct genes in place of dinosaurs, and study how the organism copes.

In a recent paper published in the *Proceedings of the National Academy of Sciences*, Kaçar's research team reports an unexpected discovery: Evolution, it seems, is not very good at multitasking.

Kaçar uses ancestral sequencing to find out what makes life tick and how organisms are shaped by evolutionary selection pressure. The insights gained may, in turn, offer clues as to what it takes for organic precursor molecules to give rise to life - be it on Earth or faraway worlds. In her lab, Kaçar specializes in designing molecules that act like tiny invisible wrenches, wreaking havoc with the delicate cellular machinery that allows organisms to eat, move and multiply - in short, to live.

Kaçar has focused her attention on the translation machinery, a labyrinthine molecular clockwork that translates the information encoded in the bacteria's DNA into proteins. All organisms - from microbes to algae to trees to humans - possess this piece of machinery in their cells.

"We approximate everything about the past based on what we have today," Kaçar said. "All life needs a coding system - something that takes information and turns it into molecules that can perform tasks - and the translational machinery does just that. It creates life's alphabet. That's why we think of it as a fossil that has remained largely unchanged, at least at its core. If we ever find life elsewhere, you bet that the first thing we'll look at is its information processing systems, and the translational machinery is just that."

So critical is the translational machinery to life on Earth that even over the course of more than 3.5 billion years of evolution, its parts have undergone little substantial change. Scientists have referred to it as "an evolutionary accident frozen in time."

"I guess I tend to mess with things I'm not supposed to," Kaçar said. "Locked in time? Let's unlock it. Breaking it would lead the cell to destruction? Let's break it."

The researchers took six different strains of Escherichia coli bacteria and genetically engineered the cells with mutated components of their translational machinery. They targeted the step that feeds the unit with genetic information by swapping the shuttle protein with evolutionary cousins taken from other microbes, including a reconstructed ancestor from about 700 million years ago.

"We get into the heart of the heart of what we think is one of the earliest machineries of life," Kaçar said. "We purposely break it a little, and a lot, to see how the cells deal with this problem. In doing this, we think we create an urgent problem for the cell, and it will fix that."

Next, the team mimicked evolution by having the manipulated bacterial strains compete with each other - like a microbial version of "The Hunger Games." A thousand generations later, some strains fared better than others, as was expected. But when Kaçar's team analyzed exactly how the bacteria responded to perturbations in their translational components, they discovered something unexpected: Initially, natural selection improved the compromised translational machinery, but its focus shifted away to other cellular modules before the machinery's performance was fully restored.

To find out why, Kaçar enlisted Sandeep Venkataram, a population genetics expert at the University of California, San Diego.

Venkataram likens the process to a game of whack-a-mole, with each mole representing a cellular module. Whenever a module experiences a mutation, it pops up. The hammer smashing it back down is the action of natural selection. Mutations are randomly spread across all modules, so that all moles pop up randomly.

"We expected that the hammer of natural selection also comes down randomly, but that is not what we found," he said. "Rather, it does not act randomly but has a strong bias, favoring those mutations that provide the largest fitness advantage while it smashes down other less beneficial mutations, even though they also provide a benefit to the organism."

In other words, evolution is not a multitasker when it comes to fixing problems.

"It seems that evolution is myopic," Venkataram said. "It focuses on the most immediate problem, puts a Band-Aid on and then it moves on to the next problem, without thoroughly finishing the problem it was working on before."

"It turns out the cells do fix their problems but not in the way we might fix them," Kaçar added. "In a way, it's a bit like organizing a delivery truck as it drives down a bumpy road. You can stack and organize only so many boxes at a time before they inevitably get

jumbled around. You never really get the chance to make any large, orderly arrangement."

Why natural selection acts in this way remains to be studied, but what the research showed is that, overall, the process results in what the authors call "evolutionary stalling" - while evolution is busy fixing one problem, it does at the expense of all other issues that need fixing. They conclude that at least in rapidly evolving populations, such as bacteria, adaptation in some modules would stall despite the availability of beneficial mutations. This results in a situation in which organisms can never reach a fully optimized state.

"The system has to be capable of being less than optimal so that evolution has something to act on in the face of disturbance - in other words, there needs to be room for improvement," Kaçar said.

Kaçar believes this feature of evolution may be a signature of any self-organizing system, and she suspects that this principle has counterparts at all levels of biological hierarchy, going back to life's beginnings, possibly even to prebiotic times when life had not yet materialized.

With continued funding from the John Templeton Foundation and NASA, the research group is now working on using ancestral sequencing to go back even further in time, Kaçar said.

"We want to strip things down even more and create systems that start out as what we would consider pre-life and then transition into what we consider life."

The paper is online at https://www.pnas.org/content/117/31/18582 .

https://bit.ly/2Y6Fnau

Researchers demonstrate fundamentally new approach to ultrasound imaging

North Carolina State University researchers have demonstrated a new technique for creating ultrasound images.

The new approach is substantially simpler than existing techniques and could significantly drive down technology costs.

"Conventional ultrasound devices have a receiver that detects ultrasonic waves and converts them into an electrical signal, which is then sent to a computer that processes the signal and converts it into an image," says Xiaoning Jiang, co-corresponding author of a paper on the work and a Duncan Distinguished Professor of Mechanical and Aerospace Engineering at NC State. "We've created a device that effectively eliminates the electrical signal processing altogether."

Specifically, the researchers have developed a receiver that incorporates a piezoelectric crystal and an organic light-emitting diode (OLED). When an ultrasonic wave hits the crystal, it produces voltage, which causes the OLED to light up. In other words, the image appears on the OLED screen, which is built into the receiver itself.

"Our prototype is a proof-of-concept, so we designed it with an OLED array that is 10 pixels by 10 pixels; the resolution isn't great," says Franky So, co-corresponding author of the study. "However, I can easily make it 500 pixels by 500 pixels, boosting the resolution substantially." So is the Walter and Ida Freeman Distinguished Professor of Materials Science and Engineering at NC State.

"Conventional ultrasound imaging probes can cost upward of $100,000 because they contain thousands of transducer array elements, which drives up manufacturing costs," So says. "We can make ultrasound receiver-display units for $100 or so."

"This is really a completely new field for ultrasound, so we're only beginning to explore the potential applications," Jiang says. "However, there are obvious near-term applications, such as non-destructive testing, evaluation and inspections in the context of structural health monitoring."

The researchers are interested in collaborating with industry partners to explore commercial applications.

The paper, "Direct Acoustic Imaging using a Piezoelectric Organic Light-Emitting Diode," is published in ACS Applied Materials & Interfaces. First author of the paper is Hyeonggeun Yu, a former postdoctoral researcher at NC State who is now at the Korea Institute of Science and Technology. The paper was co-authored by Jinwook Kim and Howuk Kim, who are former Ph.D. students at NC State; and by Nilesh Barange, a former postdoctoral researcher at NC State.

Note to Editors: The study abstract follows.

"Direct Acoustic Imaging using a Piezoelectric Organic Light-Emitting Diode"

Authors: Hyeonggeun Yu, Jinwook Kim, Howuk Kim, Nilesh Barange, Xiaoning Jiang, and Franky So, North Carolina State University

Published: July 22, 2020, ACS Applied Materials & Interfaces

DOI: 10.1021/acsami.0c05615

Abstract: Conventional ultrasonic imaging requires acoustic scanning over a target object using a piezoelectric transducer array, followed by signal processing to reconstruct the image. Here, we report a novel ultrasonic imaging device that can optically display an acoustic signal on the surface of a piezoelectric transducer. By fabricating an organic light-emitting diode (OLED) on top of a piezoelectric crystal (lead zirconate titanate, PZT), an acousto-optical piezoelectric OLED (p-OLED) transducer is realized, converting an acoustic wave profile directly to an optical image. Due to the integrated device architecture, the resulting p-OLED features a high acousto-optic conversion efficiency at the resonant ultrasound frequency, providing a piezoelectric field to drive the OLED. By incorporating an electrode array in the p-OLED, we demonstrate a novel tomographic ultrasound imaging device that is operated without a need for conventional signal processing.

https://bit.ly/3fXnZL7

USC scientists identify the order of COVID-19's symptoms

The scientists at USC Michelson Center note that knowing the order of symptoms for the coronavirus will help doctors with diagnosis and treatment, and may even help patients decide to seek care or quarantine

USC researchers have found the likely order in which COVID-19 symptoms first appear: fever, cough, muscle pain, and then nausea, and/or vomiting, and diarrhea.

Knowing the order of COVID-19's symptoms may help patients seek care promptly or decide sooner than later to self-isolate, the scientists say. It also may help doctors rule out other illnesses, according to the study led by doctoral candidate Joseph Larsen and his colleagues with faculty advisors Peter Kuhn and James Hicks at the USC Michelson Center for Convergent Bioscience's Convergent Science Institute in Cancer.

Recognizing the order of symptoms also could help doctors plan how to treat patients, and perhaps intervene earlier in the disease.

"This order is especially important to know when we have overlapping cycles of illnesses like the flu that coincide with infections of COVID-19," said Kuhn, a USC professor of medicine, biomedical engineering, and aerospace and mechanical engineering. "Doctors can determine what steps to take to care for the patient, and they may prevent the patient's condition from worsening."

"Given that there are now better approaches to treatments for COVID-19, identifying patients earlier could reduce hospitalization time," said Larsen, the study's lead author.

Fever and cough are frequently associated with a variety of respiratory illnesses, including Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). But the timing and symptoms in the upper and lower gastrointestinal tract set COVID-19 apart.

"The upper GI tract (i.e., nausea/vomiting) seems to be affected before the lower GI tract (i.e., diarrhea) in COVID-19, which is the opposite from MERS and SARS," the scientists wrote.

The authors predicted the order of symptoms this spring from the rates of symptom incidence of more than 55,000 confirmed coronavirus cases in China, all of which were collected from Feb. 16-Feb. 24, 2020, by the World Health Organization. They also studied a dataset of nearly 1,100 cases collected from Dec. 11, 2019

through Jan. 29, 2020, by the China Medical Treatment Expert Group via the National Health Commission of China.

To compare the order of COVID-19 symptoms to influenza, the researchers examined data from 2,470 cases in North America, Europe and the Southern Hemisphere, which were reported to health authorities from 1994 to 1998. The scientific findings were published Thursday in the journal *Frontiers in Public Health*.

"The order of the symptoms matter. Knowing that each illness progresses differently means that doctors can identify sooner whether someone likely has COVID-19, or another illness, which can help them make better treatment decisions," Larsen, the lead author, said.

In addition to Larsen, Kuhn and Hicks, other study co-authors were Margaret R. Martin of Nexus Development PA LLC and John D. Martin at NanoCarrier Co., Ltd., in Chiba, Japan.

The study was funded by National Cancer Institute (Award Number U54CA143906 and P30CA014089) and the Carol Vassiliadis fellowship. Larsen was supported by the USC Dana and David Dornsife College of Letters, Arts and Sciences, and the Schlegel Family Endowment Fellowship.

https://bit.ly/3kU7zam

Syphilis may have spread through Europe before Columbus

Study indicates a fair possibility that Treponema pallidum already existed in Europe before Columbus ever set sails to America

Syphilis is a sexually transmitted disease - and while commonly dismissed due to the availability of modern treatments, it is in fact spreading at an alarming rate: Over the last decades, more than 10 million people around the world have been infected with the syphilis subspecies pallidum of the Treponema pallidum bacteria. Other treponematoses, such as yaws and bejel, are caused by other subspecies of Treponema pallidum. The origins of syphilis, which wreaked havoc in Europe from the late 15th to the 18th century, are still unclear. The most popular hypothesis so far holds Christopher Columbus and his sailors liable for bringing the disease to Europe from the New World.

Yaws already widespread in Europe

The new study indicates a fair possibility that Treponema pallidum already existed in Europe before Columbus ever set sails to America. The researchers found treponematoses in archaeological human remains from Finland, Estonia and the Netherlands. Both molecular dating of the ancient bacterial genomes and traditional radiocarbon dating of the samples were used to estimate the age of the pathogens causing these diseases. The results indicate that the genomes dated back to between the early 15th and 18th century.

In addition to the syphilis cases, the researchers found yaws in one of the individuals. Like syphilis, yaws is transmitted via skin contact, although rarely through sexual intercourse. Today, the disease is only found in tropical and subtropical regions. "Our data indicates that yaws was spread through all of Europe. It was not limited to the tropics, as it is today," says last author Verena Schünemann, professor of paleogenetics at the Institute of Evolutionary Medicine of the University of Zurich.

Genome of a previously unknown pathogen discovered

The research team also discovered something else: The skeleton found in the Netherlands contained a pathogen belonging to a new, unknown and basal treponemal lineage. This lineage evolved in parallel to syphilis and yaws but is no longer present as a modern-day disease. "This unforeseen discovery is particularly exciting for us, because this lineage is genetically similar to all present treponemal subspecies, but also has unique qualities that differ from them," says first author Kerttu Majander from UZH.

Because several closely related subspecies of Treponema pallidum existed throughout Europe, it is possible that the diseases persisted in overlapping regions, and sometimes infected the same patient. The spatial distribution in the northern periphery of Europe also

suggests that endemic treponematoses had already spread widely in Europe in the early modern period.

Not just Columbus

"Using our ancient genomes, it is now possible for the first time to apply a more reliable dating to the treponema family tree," says Schünemann. The genetic analyses conducted in this study suggest that the predecessor of all modern Treponema pallidum subspecies likely evolved at least 2,500 years ago. For venereal syphilis in particular, the latest common ancestor existed between the 12th and 16th century.

According to the newly discovered diversity of treponematoses in early modern Europe, syphilis may have either originated or perhaps further developed in the Old World. "It seems that the first known syphilis breakout cannot be solely attributed to Columbus' voyages to America," concludes Schünemann. "The strains of treponematoses may have co-evolved and interchanged genetic material before and during the intercontinental contacts. We may yet have to revise our theories about the origins of syphilis and other treponemal diseases".

https://bit.ly/31NUo1H

A new, 20-minute assay for COVID-19 diagnosis

Researchers have developed a new test that can diagnose COVID-19 in just 20 minutes

The findings, published in the *Journal of Medical Microbiology*, show the rapid molecular test called N1-STOP-LAMP, is 100% accurate in diagnosing samples containing SARS-CoV-2 at high loads.

The test is highly accurate and easy to use, making it a prime candidate for use in settings with limited testing capabilities. The method involves using a small portable machine, which can reliably detect SARS-CoV-2 from just one nasal swab. "In the race to control the COVID-19 pandemic, access to rapid, precision diagnostics is key. We have developed an alternative COVID-19 molecular test that can be readily deployed in settings where access to standard laboratory testing is limited or where ultra-rapid result turnaround times are needed" said University of Melbourne Professor Tim Stinear, Laboratory Head at the Doherty Institute.

This new test uses only one tube and involves only a single step, making it more efficient and lower cost than many of the current tests for SARS-CoV-2. The N1-STOP-LAMP method was found to be 100% accurate and correctly identified 87% of tests as positive when used to assess 157 confirmed-positive samples. The results were fast, with an average time-to-positive of 14 minutes for 93 of those clinical samples.

"We see this kind of technology having benefit in settings liked aged care facilities, or overseas laboratories with limited resources and equipment," Professor Stinear said. "The test requires a small shoebox-sized machine, as well as reagents, but everything is portable."

"STOP-LAMP is what's referred to as a 'near care' test, it is not intended to replace the current gold standard PCR testing. It's a robust diagnostic test for the specific and rapid detection of COVID-19. But it's important to note however, it trades some detection sensitivity for speed and ease-of-use".

https://wb.md/3l0doD8

Does Metformin Reduce Risk for Death in COVID-19?

Observational data suggest that metformin use in patients with type 2 diabetes might reduce the risk for death from COVID-19

Miriam E. Tucker

Accumulating observational data suggest that metformin use in patients with type 2 diabetes might reduce the risk for death from COVID-19, but the randomized trials needed to prove this are unlikely to be carried out, according to experts.

The latest results, which are not yet peer reviewed, were published online July 31. The study was conducted by Andrew B. Crouse, PhD, of the Hugh Kaul Precision Medicine Institute, University of Alabama at Birmingham, and colleagues.

The researchers found that among more than 600 patients with diabetes and COVID-19, use of metformin was associated with a nearly 70% reduction in mortality after adjustment for multiple confounders.

Data from four previous studies that also show a reduction in mortality among metformin users compared to nonusers were summarized in a "mini review" by André J. Scheen, MD, PhD, published August 1 in *Diabetes and Metabolism*.

Scheen, of the Division of Diabetes, Nutrition, and Metabolic Disorders and the Division of Clinical Pharmacology at Liège University, Liège, Belgium, discusses possible mechanisms behind this observation.

"Because metformin exerts various effects beyond its glucose-lowering action, among which are anti-inflammatory effects, it may be speculated that this biguanide might positively influence the prognosis of patients with [type 2 diabetes] hospitalized for COVID-19," he says.

"However, given the potential confounders inherently found in observational studies, caution is required before drawing any firm conclusions in the absence of randomized controlled trials," Scheen writes.

Indeed, when asked to comment, endocrinologist Kasia Lipska, MD, of Yale School of Medicine, New Haven, Connecticut, told *Medscape Medical News*: "Metformin users tend to do better in many different settings with respect to many different outcomes. To me, it is still unclear whether metformin is truly a miracle drug or whether it is simply used more often among people who are healthier and who do not have contraindications to its use."

She added, "I don't think we have enough data to suggest metformin use for COVID-19 mitigation at this point."

Alabama Authors Say Confounding Effects "Unlikely"

In the retrospective analysis of electronic health records from their institution, Crouse and colleagues reviewed data from 604 patients who were confirmed to have tested positive for COVID-19 between February 25 and June 22, 2020. Of those individuals, 40% had diabetes.

Death occurred in 11% (n = 67); the odds ratio for death among those with, vs without, diabetes was 3.62 ($P < .0001$).

Individuals with diabetes accounted for >60% of all deaths. In multiple logistic regression, age 50 – 70 vs <50, male sex, and diabetes emerged as independent predictors of death.

Of the 42 patients with diabetes who died, 34 (81%) had used metformin, and eight (19%) had not, a significant difference (odds ratio 0.38; $P = .0221$). Insulin use, on the other hand, had no effect on mortality ($P = .5728$).

"In fact, with 11% [being] the mortality of metformin users, [this] was comparable to that of the general COVID-19-positive population and dramatically lower than the 23% mortality observed in subjects with diabetes and not on metformin," the authors say.

The survival benefit observed with metformin remained after exclusion of patients with classic metformin contraindications, such as chronic kidney disease and heart failure (odds ratio, 0.17; $P = .0231$).

"This makes any potential confounding effects from skewing metformin users towards healthier subjects without these additional comorbidities very unlikely," Crouse and colleagues contend.

After further analysis that controlled for other covariates (age, sex, obesity status, and hypertension), age, sex, and metformin use remained independent predictors of mortality.

For metformin, the odds ratio was 0.33 ($P = .0210$).

But Lipska pointed out, "Observational studies can take into account confounders that are measured. However, unmeasured confounders may still affect the conclusions of these studies.... Propensity score matching to account for the likelihood of use of metformin could be used to better account for differences between metformin users and nonusers."

If Metformin Does Reduce COVID-19 Deaths, Multiple Mechanisms Likely

In his article, Scheen notes that several mechanisms have been proposed for the possible beneficial effect of metformin on COVID-19 outcomes, including direct improvements in glucose control, body weight, and insulin resistance; reduction in inflammation; inhibition of virus penetration via phosphorylation of ACE2; inhibition of an immune hyperactivation pathway; and neutrophil reduction. All remain theoretical, he emphasizes.

He notes that some authors have raised concerns about possible harms from the use of metformin by patients with type 2 diabetes who are hospitalized for COVID-19, particularly because of the potential risk for lactic acidosis in cases of multiple organ failure.

In Totality, Four Studies Suggest 25% Death Reduction With Metformin

Taken together, the four observational studies that Scheen reviews showed that metformin had a positive effect, with an overall 25% reduction in death ($P < .00001$), albeit with relatively high heterogeneity ($I^2 = 61\%$).

The largest of these, from the United States, included 6256 patients hospitalized with COVID-19 and involved propensity matching. A significant reduction in mortality with metformin use was seen in women but not men (odds ratio, 0.759).

The French Coronavirus-SARS-CoV-2 and Diabetes Outcomes (CORONADO) study of 1317 patients with diabetes and confirmed COVID-19 who were admitted to 53 French hospitals also showed a significant survival benefit for metformin, although the study wasn't designed to address that issue.

In that study, the odds ratio for death on day 7 in prior metformin users compared to nonusers was 0.59. This finding lost significance but remained a trend after full adjustments (0.80).

Two smaller observational studies produced similar trends toward survival benefit with metformin.

Nonetheless, Scheen cautions: "Firm conclusions about the impact of metformin therapy can only be drawn from double-blind randomized controlled trials (RCTs), and such trials are almost impossible in the context of COVID-19."

He adds: "Because metformin is out of patent and very inexpensive, no pharmaceutical company is likely to be interested in planning a study to demonstrate the benefits of metformin on COVID-19-related clinical outcomes."

Lipska agrees: "RCTs are unlikely to be conducted to settle these issues. In their absence, metformin use should be based on its safety and effectiveness profile."

Scheen concludes, however, "There are at least no negative safety indications, so there is no reason to stop metformin therapy during COVID-19 infection except in cases of severe gastrointestinal symptoms, hypoxia and/or multiple organ failure."

Lipska has received grants from the National Institutes of Health and works under contract for the Centers for Medicare & Medicaid Services to develop publicly reported quality measures. Scheen has disclosed no relevant financial relationships.

medRxiv. Published online July 31, 2020. Full text

Diabetes Metab. Published online August 1, 2020. Full text

https://bit.ly/3h4uixT

Is the COVID-19 virus pathogenic because it depletes specific host microRNAs?

UAB and Polish researchers propose that the COVID-19 virus acts as a microRNA "sponge" to deplete miRNA levels in ways that aid viral replication and stymie the host immune response.

BIRMINGHAM, Ala. - Why is the COVID-19 virus deadly, while many other coronaviruses are fairly innocuous and just cause colds? A team of University of Alabama at Birmingham and Polish researchers propose an answer -- the COVID-19 virus acts as a microRNA "sponge." This action modulates host microRNA levels in ways that aid viral replication and stymies the host immune response.

This testable hypothesis results from analysis of current literature and a bioinformatic study of the COVID-19 virus and six other coronaviruses. It is published as a perspective in the *American Journal of Physiology-Lung Cellular and Molecular Physiology*.

Human microRNAs, or miRNAs, are short, non-coding RNAs with about 22 bases. They act to regulate gene expression by their complementary pairing with specific messenger RNAs of the cell. That pairing silences the messenger RNA, preventing it from being translated into a protein. Thus, miRNAs are a fine-tuned controller of cell metabolism or the cell's response to stress and adverse challenges, like infection by a virus.

The miRNAs are only about 0.01 percent of total human cell and tissue RNA, while replicating viral RNA of a virus like the COVID-19 virus may reach 50 percent of the total cellular RNA. So, the UAB and Polish researchers say, if the COVID-19 virus has binding sites for specific miRNAs -- and these sites are different from the binding sites for miRNAs found on coronaviruses that cause colds -- the more pathogenic COVID-19 virus may selectively sponge up certain miRNAs to dysregulate the cell in ways that make it a dangerous human coronavirus.

The sponge idea is not novel. Viral RNA sponges have been shown capable of removing host miRNA by the Epstein-Barr virus, and sponge activity has also been shown for the herpes and hepatitis C viruses.

There were two human coronaviruses prior to the COVID-19 virus -- whose formal name is SARS-CoV-2 -- that foreshadowed the devastating consequences of the COVID-19 virus. The first was the severe acute respiratory coronavirus, or SARS virus, in 2002; the second was the Middle East respiratory syndrome coronavirus, or MERS virus, in 2012. Neither had the high infectivity of the COVID-19 virus; but both were dangerous, causing 774 and 866 deaths, respectively, according to the National Institutes of Health.

In the present study, the researchers used computer-aided bioinformatic analysis to find potential miRNA target sites for 896 mature human miRNA sequences on seven different coronavirus genomes. These genomes included the three pathogenic coronaviruses -- the SARS, MERS and COVID-19 viruses -- and four non-pathogenic coronaviruses.

The researchers found that the number of target sites was elevated in the pathogenic viruses compared to the non-pathogenic strains. Furthermore, they found that pathogenic human coronaviruses attracted sets of miRNAs that differ from the non-pathogenic human coronaviruses. In particular, a set of 28 miRNAs were unique for the COVID-19 virus; the SARS and MERS viruses had their own unique sets of 21 and 24 miRNAs, respectively.

Focusing on the 28 unique miRNAs for the COVID-19 virus, the researchers found that the majority of these miRNAs are well expressed in bronchial epithelial cells, and their dysregulation has been reported in human lung pathologies that include lung cancers, chronic obstructive pulmonary disease, cystic fibrosis and tuberculosis. Furthermore, many of the miRNAs have been proposed to act as tumor suppressors that target the pathways for programmed cell death, or apoptosis, that are supposed to make a cell kill itself when infected, mutated or stressed in other ways. Reduction of those miRNAs has been associated with poor cancer prognosis.

"Hence, the COVID-19 virus -- by its potential reduction of the host's miRNA pool -- may promote infected cell survival and thus continuity of its replication cycle," the researchers said.

The authors gave a detailed explanation of how the virus replicates inside an infected cell, including how the cell assists protein folding and how the virus begins assembly in the cell's endoplasmic reticulum and Golgi system. They also described many of the cellular proteins involved in these steps. This viral replication is known to produce stress and can provoke an unfolded protein response that causes a cell to undergo programmed death.

"Taken together," the researchers said, "the viral strategies to increase the endoplasmic reticulum membranes and endoplasmic reticulum folding capacity and block unfolded protein response-associated translational attenuation, inflammatory responses and apoptosis are critical components for virus production."

The authors then showed, by citing literature, that nine of the specific cellular miRNAs that potentially are sponged by the COVID-19 virus could help achieve those viral needs.

"The host miRNAs potentially controlled by the pathogenic human coronaviruses may be the key to gaining control over a very limited and specific set of miRNAs targets," they said. The researchers used computer-assisted gene ontology programs to find the genes and cellular pathways affected by the pathogenic human coronaviruses, and by the COVID-19 virus in particular.

The pathways they found "further supports the hypothesis that pathogenic human coronaviruses -- including the COVID-19 virus -- utilize the host miRNAs to adjust cellular processes in order to facilitate their viral protein production."

"Our hypothesis will require validations," they said, "starting with the assessment of these miRNA levels in infected tissues and ending with restoring the host miRNA balance with miRNA analogs. Furthermore, completely understanding how viruses take advantage of the endoplasmic reticulum and unfolded protein response pathway may also lead to the novel therapeutic strategies."

This hypothesis by the UAB and Polish researchers, who all contributed equally to the paper, may explain some other biological oddities of the COVID-19 virus.

One is the varying susceptibilities to infection seen among patients, including a more severe morbidity and mortality for older patients. There may be individual differences among patient miRNA profiles, they said, and one "recent study has suggested that COVID-19 virulence in aged patients may be due to a lower abundance of miRNAs, and this may be a contributing factor in disease severity."

Another biological question is how the virus co-exists in its normal animal source -- bats. "Notably," the researchers said, "a recent study proposed that bats, considered as host of origin for the COVID-19 virus, have tolerance to potentially deadly viruses because of specific miRNAs."

Authors of the perspective paper, "SARS-CoV-2 may regulate cellular responses through depletion of specific host miRNAs," are Rafal Bartoszewski, Medical University of Gdansk, Gdansk, Poland; Michal Dabrowski, Nencki Institute of Experimental Biology of the Polish Academy, Warsaw, Poland; Bogdan Jakiela and Marek Sanak, Jagiellonian University Medical College, Krakow, Poland; Sadis Matalon and Kevin S. Harrod, UAB Department of Anesthesiology and Perioperative Medicine; and James F. Collawn, UAB Department of Cell, Developmental and Integrative Biology.

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https://bit.ly/347Ixyw

Here's Why Narcissists Never Really Learn From Their Mistakes

When something unforeseen and unfortunate happens, a narcissist appears more inclined to throw up their hands and cry, "No one could have seen this coming!"

Carly Cassella

Sometimes even those with narcissistic tendencies don't like looking in the mirror. New research has found that people who excessively approve of themselves are unwilling to reflect on their mistakes.

When something unforeseen and unfortunate happens, a narcissist appears less inclined to ask, "What could I have done differently?" and more inclined to throw up their hands and cry, "No one could have seen this coming!"

At first, this might sound like a humble statement for a narcissist. It's certainly more modest than claiming you knew it all along (a concept known as hindsight bias).

But when someone's predictions have been clearly proved wrong, the researchers behind the latest study suggest narcissists go into self-protection mode and start blaming it on the unpredictability of the universe.

"We argue that, due to their exaggerated self-enhancement and self-protection tendencies, narcissists show stronger hindsight bias when their predictions are accurate and a reverse hindsight bias when their predictions are inaccurate, both of which harm their learning and future decision making," the authors of the new study argue.

Conducting four variations on the same hiring experiment, researchers tested the various levels of narcissism present among students, employees, and managers, and looked at how that might play out in the workplace.

To do this, volunteers were asked in an online survey whether they identified more with statements like "I think I am a special person" than statements like "I am no better or worse than most people."

Shortly after this quiz, applicants were offered an opportunity to sign up for another in-person study. To avoid influencing expectations, the researchers took efforts to keep the participants unaware that the questionnaire was connected to the follow-up study.

This more personal half of the study involved groups being asked to read a bunch of qualifications for a hypothetical job and choose who to hire. They were then given their pick's performance assessment and asked whether they made the right decision.

Subtle variations in the methodology and performance outcomes of all four experiments allowed researchers to analyse how narcissism can impact hindsight bias and our ability to reflect on what we should have done, known as 'should counterfactual thinking'.

In the end, the authors found those who scored high for narcissism were less likely to admit they should have done something different in hindsight, even when their predictions were inaccurate.

The authors aren't sure why this is the case, but they say the study suggests narcissists are "especially prone to blindly feel like winners after success". Whereas after failure, they do not engage with their mistakes.

Many people have called Donald Trump a narcissist for showcasing both of these characteristics, the authors point out - for example, when he claimed to predict the outcomes of the Iraq war "better than anybody", versus when he said "Nobody knew health care could be so complicated" after failing to make a health care deal.

This is sometimes called the 'failure-to-ask-why syndrome', and when the answer is a fault of our own, it can seriously impede our ability to take responsibility and learn from our mistakes.

The authors use the financial crisis that began in 2007 as an example of just that.

"Despite many Wall Street bankers claiming the financial crisis was impossible to predict, the Financial Crisis Inquiry Commission concluded that the crisis was in fact foreseeable and avoidable," they write.

"Thus, perceiving an inaccurately predicted outcome as unforeseeable implies an external attribution; as such, lessons are not learned and the decision-making process remains unchanged."

After all, it's hard to improve if there's nothing deemed wrong in the first place. In fact, this defensive behaviour could be why some studies have found narcissists are generally happier and less stressed out than their peers.

Who needs to worry when you're not to blame for anything that goes wrong?

The study was published in *Management*.

https://bit.ly/312d1jm

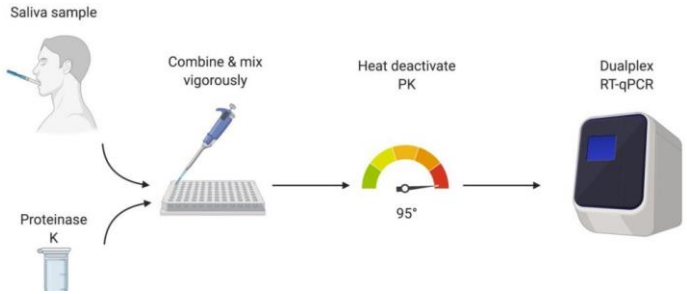
FDA Grants Emergency Authorisation to Cheap New COVID-19 Saliva Test

The test is also accessible and easy, and those tested could get results in a matter of hours

Inyoung Choi, Business Insider

On Saturday, the US Food and Drug Administration granted emergency use authorization to a saliva-based test funded by the NBA and National Basketball Players Association to be available for public use, the agency announced. The test was developed by researchers at Yale and jointly funded by the NBA and NBPA, ESPN reported.

Called "SalivaDirect", the saliva-based test could be priced at an incredibly low rate. Experts told ESPN that the cost per sample could be as low as US$4, but patients are more likely to end up paying between $15 to $20 dollars.



***The SalivaDirect process.* Anne Wyllie/BioRender**

The test is also accessible and easy, and those tested could get results in a matter of hours, Nathan Grubaugh, one of the senior authors of the saliva studies told ESPN.

The NBA bubble in Orlando currently uses nasal swabs, but the easy and cheap saliva-testing could potentially impact the NBA's plans for future seasons, sources told ESPN.

The saliva tests were given to NBA players and staff, along with regular nasal swab tests to compare the results. Yale researchers discovered that the results of both kinds of tests were nearly identical, according to ESPN.

ESPN also reported that Yale, the NBA, and the NBPA do not plan to charge royalties from administering the tests.

"My goal is not to test athletes," Grubaugh told ESPN. "That's not my target population. My target population is everybody."

In April, the FDA authorized a saliva-based coronavirus test developed by researchers at Rutgers. ESPN reported that those tests cost patients between US$60 to $150 dollars, but that the new SalivaDirect test removed the "extraction of RNA from samples".

"(The Yale test) loses a little bit of sensitivity, but what we gain is speed and that it should be up to 10 times cheaper," Grubaugh told ESPN.

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https://nyti.ms/3458OqF

Coronavirus Live Updates: Scientists See Signs of Lasting Immunity, Even After Mild Infections

Even mild Covid-19 cases confer 'durable immunity,' new studies find.

Scientists who have been monitoring immune responses to the coronavirus for months are now starting to see encouraging signs of strong, lasting immunity, even in people that developed only mild symptoms of Covid-19, a flurry of new studies has found.

Disease-fighting antibodies, as well as immune cells called B cells and T cells capable of recognizing the virus, appear to persist months after infections have resolved — an encouraging echo of the body's robust immune response to other viruses.

“This is exactly what you would hope for,” said Marion Pepper, an immunologist at the University of Washington and an author on one of the new studies, which is currently under review at the journal Nature. “All the pieces are there to have a totally protective immune response.”

“This is very promising,” said Smita Iyer, an immunologist at the University of California, Davis, who is studying immune responses to the coronavirus in rhesus macaques and was not involved in these papers. “This calls for some optimism about herd immunity, and potentially a vaccine.”

Research on the coronavirus is proceeding so quickly, and in such volume, that the traditional review process often cannot keep pace. For the studies discussed here — as with un-peer-reviewed studies in general — The Times arranged for several experts to read and evaluate them.

Although researchers cannot forecast how long these immune responses will last, many experts consider the data a welcome indication that the body has a good chance of fending off the coronavirus if exposed to it again.

“Things are really working as they’re supposed to,” said Deepta Bhattacharya, an immunologist at the University of Arizona and an author on one of the new studies, which has not yet been peer reviewed.

Protection against reinfection cannot be fully confirmed until there is proof that most people who encounter the virus a second time are actually able to keep it at bay, Dr. Pepper said. But the findings could help quell recent concerns over the virus’s ability to dupe the immune system into amnesia, leaving people vulnerable to repeat bouts of disease.

As public health officials look to fall and winter, the specter of a new surge of Covid-19 gives them chills. But there is a scenario they dread even more: a severe flu season resulting in a “twindemic.”

Even a mild flu season could stagger hospitals already coping with Covid-19 cases. And although officials don’t know yet what degree of severity to anticipate this year, they worry that large numbers of people could forgo flu shots, increasing the risk of widespread outbreaks.

Flu, a life-threatening respiratory illness that crowds emergency rooms and intensive care units, shares symptoms with Covid-19: fever, headache, cough, sore throat, muscle aches and fatigue. Flu could leave patients vulnerable to a harsher attack of Covid-19, doctors believe, and that coming down with both viruses at once could be disastrous.

The concern about a twindemic is so great that officials around the world are pushing the flu shot even before it becomes available in clinics and doctors’ offices. Dr. Robert Redfield, director of the U.S. Centers for Disease Control and Prevention, has been talking it up, urging corporate leaders to figure out ways to inoculate employees. The C.D.C. usually purchases 500,000 doses for uninsured adults but this year ordered an additional 9.3 million doses.

Because common places of access, including offices and school health clinics, will be largely off limits, pharmacies and supermarkets are expected to play greater roles in administering the shots. As of this week, CVS and Walgreens will have doses ready.

The flu vaccine is rarely mandated in the U.S. except by some health care facilities and nursery schools, but this month the statewide University of California system announced that because of the pandemic, it is requiring all 230,000 employees and 280,000 students to get the flu vaccine by November 1.

Fighting flu proactively during the continuing pandemic presents significant challenges: not only how to administer the shot safely and readily, but also how to prompt people to get a shot that a

majority of Americans have typically distrusted, dismissed and skipped.

Public campaigns will describe the shot as a critical weapon during the pandemic. “Hopefully people will say, ‘There’s no Covid vaccine so I can’t control that, but I do have access to the flu vaccine and I can get that,’” said Patsy Stinchfield, senior director of infection prevention at Children’s Minnesota and a member of the C.D.C.’s influenza work group. “It gives you a little power to protect yourself.”

Can we have class outside today? More and more often, the answer is yes.

As school districts around the U.S. wrestle with how to bring students back to the classroom, more and more are asking a basic question: Is a room even necessary?

School officials, including in Seattle, Massachusetts and Detroit, are weighing the possibility of holding class outdoors.

Vermont, which has kept its virus cases low, appears to be in the forefront.

At the Lake Champlain Waldorf school, classes will be taught in an outdoor amphitheater, according to the NBC affiliate NECN, with heaters brought in when temperatures drop. In South Burlington, school officials are planning to put up tents, though parents can also opt for online learning.

“This is not what any of us expected, but we’re trying to use all of our creativity and ingenuity,” Amy Brennan, a community relations official at the Lake Champlain Waldorf School, told NECN.

Activists around the country are pushing for more outdoor education, according to an article in The Atlantic.

The incentive to do so during a pandemic is obvious, when proximity — especially indoors — increases the risk of virus transmission.

“It would make a huge difference if classes could be held outdoors versus indoors,” said Dr. Leana Wen, an emergency physician and public health professor who previously served as Baltimore’s health commissioner.

The approach is not without challenges. Poor weather could derail plans, and accessibility questions need to be resolved.

Dr. Ashish Jha, the director of the Harvard Global Health Institute, says that he is a “big fan” of the idea but that when he advises school districts, he tells them “not to look at this as a silver bullet.”

It does, however, offer flexibility.

“Even if you can get half the kids out, then it clears out that space for other kids to space out more indoors,” Dr. Jha said.

Some students in Denmark returned to classes with lessons held outdoors, and Italy plans do the same.

And there are past examples: The Metro desk of The Times looked back at open-air schools in the early 1900s, when tuberculosis was surging.

The C.D.C. begins developing a plan to distribute a coronavirus vaccine.

The Centers for Disease Control and Prevention is consulting with four states and a large city to develop plans for distributing a coronavirus vaccine, the first doses of which are expected to be available later this year or early next.

The agency chose the communities because they represent different kinds of challenges as the government prepares to begin the largest such campaign ever undertaken. The communities include small and large states, some that are doing well with their current epidemic response and at least one that is not, according to a federal official familiar with the discussions.

The states are California, Florida, Minnesota, and North Dakota; the city is Philadelphia.

Each has a different demographic, ethnic makeup and population density, as well as its own infrastructure to store and deliver doses of vaccine. State and city officials are advising the C.D.C. and the Department of Defense, which are coordinating the federal response and determining how to most efficiently deliver doses of vaccine to the individuals who are most vulnerable to Covid-19, the disease caused by the virus.

Federal officials said last week that the administration expected to deliver tens of millions of vaccine doses by early 2021.

The challenges facing a nationwide vaccine campaign are enormous, including how best to store the vaccine and what kinds of clinics could handle the volume of demand. The C.D.C. reportedly favors a centralized distribution system, and the Defense Department apparently disagrees, according to the official familiar with the discussions.

Dr. Scott Gottlieb, former director of the Food and Drug Administration, said on Sunday that the government should enlist private companies to distribute a vaccine, once it is developed.

“If the government tries to take physical possession of the vaccines and distribute them,” Dr. Gottlieb said on the CBS program “Face the Nation,” “that could lead to hiccups and delays in getting vaccines to the consumers. What they should be doing is directing the existing supply chain.”