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New guidelines for phage preparation can accelerate lifesaving treatment

The goal: Bring lab therapeutics to patients' bedsides in half the current time frame.

When clinicians resort to phage therapy for patients who don't respond to antibiotics, the patients are usually very ill and time is of the essence. But the average time for labs to produce therapeutic phages is more than a month.

The main reason for this is the lack of a standardized phage purification process for research labs, despite the fact that phage therapy -- which uses viruses to destroy disease causing bacteria -- has been around for over a century.

Now, a San Diego State University lab that produces phage therapeutics for clinicians across the country for compassionate use has developed standardized guidelines intended to not only streamline the process using existing lab equipment, but also shorten it to two to three weeks, cutting the typical processing time by half.

"Many of our patients have so little time, so speed is of the essence and this protocol would really make a difference, since one run can produce enough doses to treat a patient for months," said Dwayne Roach, the Conrad Prebys chair of virology and assistant professor at SDSU.

The protocol, he said, combines traditional techniques with modern filtration technology to produce higher phage yields and reduce endotoxin levels compared to previously developed methods.

The open source guidelines were published in a paper in *Nature Protocols* in July.

Bacteriophages and phage therapy

Typical candidates for phage therapy are patients who have multi-drug resistant bacteria, a more and more common fallout of overusing antibiotics. Phage is short for bacteriophage, which literally means "bacteria eater." They are viruses that only attack bacteria, not people, and are found in soil, water and sewage, requiring them to be purified before use.

Phage therapy is not approved yet in the United States and Europe, except on a case-by-case basis under compassionate use. The military is also interested in phage therapy for the battlefield, where it could be used as a sterilizing wash to remove bacteria from wounds.

Since this is still an emerging field, labs take varying approaches to phage purification. The protocols developed by the SDSU researchers are straightforward, and use simple, standard microbiology lab equipment to remain affordable. They are suitable even for labs in countries with limited resources that wish to ramp up phage production.

Lack of protocols a key bottleneck

Since Roach's lab has a library of phages on hand, much of the back-end work of collecting and cultivating them has already been completed. The protocols allow his team to supply clinicians with the best-fit phages in as little as a week.

"Our protocol provides a standard of production for medicinal phages that consistently provides potentially thousands of phage treatment doses," said Tiffany Luong, first author and a doctoral student in Roach's lab. "We provide instruction and rationale for each step in our process which allows the user to tailor the procedure to their specific equipment and bacterial species."

Identifying groups of phages that are effective against multi-drug resistant bacteria has become easier over the years.

But Dr. Robert 'Chip' Schooley, director of the Center for Innovative Phage Applications and Therapeutics at the University of California San Diego, said however that the absence of rigorous, scalable approaches for producing therapeutic phages in academic

laboratories and delivering them to the patient's bedside is a major bottleneck.

"Dr. Roach's protocol guidelines are an outstanding example of the rigor required to safely take phages into the clinic," Schooley said. "These guidelines will be of great interest to other academic laboratories and to regulatory agencies as we move into the next phases of phage therapeutics."

Reducing endotoxins

When Roach's team began working with physicians in spring 2019, they had to figure out how to streamline the process. By scrutinizing each step and comparing different methods, the team identified cross-flow filtration -- when the flow travels across the surface of the filter instead of into it -- as the most efficient and effective purification method, and Roach presented the results and accelerated timeline at a conference later in the year.

While Roach and Luong looked at process optimization, Ann-Charlott Salabarria, a postdoctoral researcher, worked on setting parameters for ensuring safety of the end product with multiple tests, including confirming that endotoxin levels met U.S. Food and Drug Administration (FDA) guidelines.

One of the FDA's major concerns with phage products is its endotoxin levels, which can harm patients and need to be removed as part of the purification process. The published protocol will help ensure the phage products are safe above and beyond the FDA minimum requirements, Roach explained.

"Our tests do validate that this process removes almost all endotoxins and exotoxins," Roach said. "We wanted to publish our protocol as a resource for other labs because purification has been very time consuming, taking away time from research."

Phage strain selection is another important aspect to developing phage therapeutics. To screen out unwanted genes in phage genomes, Roach enlisted the help of SDSU microbial geneticist and bioinformatics expert Robert Edwards.

"Phage genomes contain so many different components and may mobilize other toxins or antibiotic resistance genes," Edwards said. "It is absolutely imperative that we understand these viruses at the molecular level to ensure that we are not introducing anything potentially harmful into already ill patients."

The researchers will continue to focus on improving safety in phage therapy, by testing it on tissue and mice cell cultures.

"We hope this protocol will allow more research labs to participate in re-introducing phages to Western medicine," Luong said.

Edwards is funded by a National Institutes of Health grant and Roach received funding under an endowment from Conrad Prebys.

https://bit.ly/31qyfdj

This 'Anti-Solar Panel' Could One Day Produce Energy Even at Night

Scientists are ironing out the kinks for an 'anti-solar power' cell, one that can harvest energy at nighttime, even when the sun isn't shining.

Carly Cassella

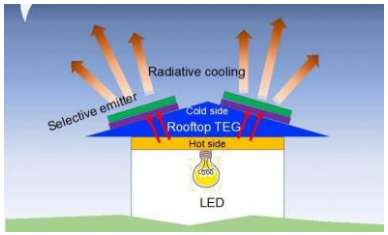
Instead of absorbing light from the Sun and converting it into electricity, like a normal solar panel would, this type of technology works in reverse.

At night, when there's no incoming heat for solar panels to capture, there's still outgoing heat we can make use of. By pointing a warm panel up towards the cold sink of space, this heat begins to radiate outwards as invisible infrared light.

This is known as radiative cooling, and if that outgoing heat can somehow be harnessed, it could cheaply light our cities at night. Storing solar power during the day is a relatively expensive proposition, so directly producing some nighttime power could help to reduce that load.

Using a thermodynamic model of a thermoelectric power generator, scientists from Stanford University have now worked out a rooftop proof-of-concept that could theoretically generate 2.2 watts per square meter without the need for a battery or an external energy source

While others have attempted similar nighttime cells, this particular design could produce 120 times more energy. In fact, it's nearly on par with the performance of a Carnot heat engine, which is a theoretical thermodynamic limit for the "perfect" engine. "This result is significantly higher than the previous reported results and points to the potential applicability of harvesting electrical power at night," the authors write.



(Lingling et al., Optics Express, 2020)

The concept is based on existing technology that combines and optimises radiative cooling with a thermoelectric power generator - one that takes up less than 1 percent of the whole device's footprint, which is a good sign for scalability, as the thermoelectric power generator is the most expensive part of the system.

Using computer models based on real-life parameters, the authors put their optimised simulation to the test. Placed on a rooftop, they claim the size of their cell creates the best balance between heat loss and thermoelectric conversion.

"We are working to develop high-performance, sustainable lighting generation that can provide everyone - including those in developing and rural areas - access to reliable and sustainable low cost lighting energy sources," says electrical engineer Lingling Fan from Stanford University.

"A modular energy source could also power off-grid sensors used in a variety of applications and be used to convert waste heat from automobiles into usable power."

Of course, those practical applications are yet to be realised. The authors admit that while their demonstration of nighttime electrical power generation is "remarkable", it's still not enough to fulfil many of the desires mentioned above; still, a technology that doesn't rely on the burning of fossil fuels for our energy needs is worth exploring.

The study was published in *Optics Express*.

https://bit.ly/3aImcIZ

Cashew shell compound appears to mend damaged nerves

Anacardic acid found in the shell of the cashew nut promotes the repair of myelin

In laboratory experiments, a chemical compound found in the shell of the cashew nut promotes the repair of myelin, a team from Vanderbilt University Medical Center reports today in the *Proceedings of the National Academy of Sciences*.

Myelin is a protective sheath surrounding nerves. Damage to this covering -- demyelination -- is a hallmark of multiple sclerosis and related diseases of the central nervous system.

"We see this as an exciting finding, suggesting a new avenue in the search for therapies to correct the ravages of MS and other demyelinating diseases," said the paper's senior author, Subramaniam Sriram, MBBS, William C. Weaver III Professor of Neurology and chief of the Division of Neuroimmunology.

Previous work led by Sriram showed that a protein called interleukin 33, or IL-33, induced myelin formation. IL-33 is, among other things, an immune response regulator, and multiple sclerosis is an autoimmune disorder.

The cashew shell compound is called anacardic acid. Sriram and team grew interested in it because it's known to inhibit an enzyme involved in gene expression called histone acetyltransferase, or

HAT, and the team had discovered that whatever inhibits HAT induces production of IL-33.

The report includes a range of new findings that point to potential therapeutic use of anacardic acid for demyelinating diseases:

- ***In vitro, the addition of the compound to rat cells most responsible for myelination -- oligodendrocyte precursor cells, or OPCs -- spurred induction of IL-33 and rapidly increased the expression of myelin genes and proteins, including dose-dependent increases in myelin basic protein;***
- ***In two animal models of demyelination, treatment with the compound increased the relative presence of IL-33-expressing OPCs and led to reduced paralysis;***
- ***In an animal model of demyelination treated with the compound, dissection and electron microscopy showed dose-dependent increases in myelination.***

"These are striking results that clearly urge further study of anarcardic acid for demyelinating diseases," Sriram said.

Joining Sriram for the study were Asa Ljunggren-Rose, Chandramohan Natarajan, Pranathi Matta, Akansha Pandey and Isha Upender.

https://bit.ly/3aV3TAB

How Covid-19 smell loss differs from the common cold

Although Covid-19 patients also lose their sense of smell, they can breathe freely, do not tend to have a runny or blocked nose, and they cannot detect bitter or sweet tastes

Peer reviewed - experimental study - humans

New research from a European group of smell disorder experts, including Prof Philpott at the University of East Anglia, shows how smell loss associated with Covid-19 infection differs from what you typically might experience with a bad cold or flu.

The new study published today is the first to compare how people with Covid-19 smell and taste disorders differ from those with other causes of upper respiratory tract infections.

The main differences found are that, although Covid-19 patients also lose their sense of smell, they can breathe freely, do not tend to have a runny or blocked nose, and they cannot detect bitter or sweet tastes.

These findings lend weight to the theory that Covid-19 infects the brain and central nervous system.

The research team hope that their work could help develop smell and taste tests for fast Covid-19 screening - in primary care and emergency departments.

Lead researcher Prof Carl Philpott, from UEA's Norwich Medical School, said: "The loss of smell and taste is a prominent symptom of Covid-19, however it is also a common symptom of having a bad cold. We wanted to find out exactly what differentiates Covid-19 smell loss with the kind of smell loss you might have with a cold and blocked-up nose."

The research team carried out smell and taste tests on 10 Covid-19 patients, 10 people with bad colds and a control group of 10 healthy people - all matched for age and sex.

Prof Philpott said: "We wanted to see if their smell and taste test scores could help discriminate between Covid-19 patients and those with a heavy cold.

"We know that Covid-19 behaves differently to other respiratory viruses, for example by causing the body's immune system to over-react, known as a cytokine storm, and by affecting the nervous system.

"So we suspected that patterns of smell loss would differ between the two groups.

"We found that smell loss was much more profound in the Covid-19 patents. They were less able to identify smells, and they were not able to identify bitter or sweet tastes. In fact it was this loss of true taste which seemed to be present in the Covid-19 patients compared to those with a cold.

"This is very exciting because it means that smell and taste tests could be used to discriminate between Covid-19 patients and people with a regular cold or flu.

"Although such tests could not replace formal diagnostic tools such as throat swabs, they could provide an alternative when conventional tests are not available or when rapid screening is needed - particularly at the level of primary care, in emergency departments or at airports.

"This research also shows that there are altogether different things going on when it comes to smell and taste loss for Covid-10 patients, compared to those with a bad cold.

"It has previously been suggested that the Covid-19 virus affects the central nervous system, based on the neurological signs developed by some patients. There are also similarities with SARS, which has also been reported to enter the brain, possibly via smell receptors in the nose.

"Our results reflect, at least to some extent, a specific involvement at the level of central nervous system in some COVID-19 patients.

"It is particularly interesting that Covid-19 seems to particularly affect sweet and bitter taste receptors, because these are known to play an important role in innate immunity.

"More research is needed to see whether genetic variation in people's bitter and sweet taste receptors might predispose them to Covid-19, or conversely, whether Covid-19 infection changes how these receptors function, either directly or through a cytokine storm - the over-reaction of the body's immune system."

This research was led by the Cliniques Universitaires Saint-Luc (Belgium), Université catholique de Louvain (Belgium) in collaboration with researchers at University of East Anglia/The Norfolk Smell and Taste Clinic at the James Paget University Hospital (UK), Aristotle University (Greece), Acibadem Taksim Hospital in Istanbul (Turkey), Biruni University (Turkey) and University Hospital of Foggia (Italy).

'Comparison of COVID-19 and Common Cold Chemosensory Dysfunction' is published in the journal Rhinology on August 19, 2020.

https://bit.ly/32fF6TC

Cold-Causing Coronaviruses Don't Seem to Confer Lasting Immunity

Studies on SARS-CoV-2's milder cousins hint that our immune systems are quick to forget the viruses, but it's unclear whether the same is true for the agent that causes COVID-19.

Shawna Williams

Sometime in the late 1980s, in a town in southwest England called Salisbury, 15 volunteers agreed to have a cold-causing coronavirus known as 229E squirted into their noses in a saline solution. Ten of the volunteers were successfully infected, as determined by viruses recovered from their noses in the days following, although only eight displayed symptoms. Researchers monitored the levels of antibodies and immune cells in their blood over the ensuing weeks.

A year later, 14 of the same volunteers came back for another round. Of the nine people who'd become infected with the first exposure, six became infected again, but none developed colds. Moreover, they only shed virus from their noses for a couple of days, compared with an average of five and a half days the first time around. As for the five people who'd resisted infection the first time around, all became infected this time, but only one developed symptoms.

The researchers struggled to explain the results. "These data do not fit any simple model," they wrote in their report. "It may be that the small amounts of antibody remaining in the original infected group contributed to resistance to reinfection in some volunteers. It may also have prevented colds and shortened the duration of virus shedding."

Three decades on, as a pandemic caused by a different coronavirus rages, researchers are still scratching their heads over whether coronaviruses—in particular, SARS-CoV-2—provoke lasting immunity in people they infect. With no long-term data yet on the

immune and other effects of SARS-CoV-2 infection, some scientists are returning to 229E and three other coronaviruses that have been with humans much longer—OC43, NL63, and HKU1—in hopes of finding clues to this question.

Tracking infections

One study hoping to shed light on immunity after a coronavirus infection, posted on *medRxiv* in June and not yet peer-reviewed, drew on blood samples from healthy control subjects in an ongoing HIV project that began in 1985. Researchers based at the Amsterdam University Medical Center (UMC) and their colleagues at other institutions analyzed stored samples from 10 subjects who had their blood collected every three to six months for at least 10 years, looking for antibodies to proteins from the four known cold-causing coronaviruses that would indicate a recent viral infection.

The research team knew of the earlier 229E reinfection study, so they weren't surprised to see multiple 229E infections in the same subjects crop up in their own data, as revealed by increases in antibody levels, says Arthur Edridge, a physician and Amsterdam UMC graduate student who is the paper's first author. "What was surprising for us is that [reinfection] actually seemed to be a common feature for all the seasonal coronaviruses that we studied," he says. All but one study subject had been infected with a particular coronavirus multiple times over the period of the study, and in some cases the time between infections with the same virus was as little as six months to a year, indicating an "alarmingly short duration of protective immunity," the authors write in their paper.

Edridge cautions that it's not clear whether SARS-CoV-2 will follow the same pattern as these more familiar coronaviruses—but if it does, then the idea that allowing the virus to spread in order to achieve herd immunity wouldn't be a successful strategy, he adds.

Another recent study to find evidence of coronavirus reinfection was an analysis of data from a respiratory virus monitoring program conducted between 2016 and 2018. That study, which included 214 children and adults in New York City and relied on self-reports of symptoms and viral RNA swabbed from the back of the throat, found 12 instances of reinfection by the same coronavirus, although nine of these were in children, whose immune systems are less developed than those of adults. Reinfections were found for three of the four cold-causing coronaviruses (OC43, HKU1, and 229E).

It's not clear whether SARS-CoV-2 will follow the same pattern as these more familiar coronaviruses—but if it does, then the idea that allowing the virus to spread in order to achieve herd immunity wouldn't be a successful strategy.

Marta Galanti, a postdoc at Columbia University and the study's first author, notes that the reinfections fell into two clusters in terms of timeline: at four to eight weeks after the initial infection, and at 8 to 10 months after the initial infection. She and her coauthor weren't able to rule out the possibility that the earlier reinfections were in fact persistent first infections, she says, although they're working on this in a follow-up study.

Like Edridge, Galanti is clear that the reinfection results don't necessarily apply to SARS-CoV-2. But, she says, they indicate that "we have to be prepared [for] the possibility that the multiple subsequent infections can happen" with the novel coronavirus.

"Maybe it's possible that if you only have these mild respiratory symptoms [with SARS-CoV-2 infection], you don't develop a really strong immune response, and you could get reinfected," says Rachel Roper, an immunologist at East Carolina University who was not involved in either of the studies. But she still thinks there's uncertainty about whether reinfections occur with endemic coronaviruses, and she adds that infection with murine hepatitis virus, a coronavirus that causes serious disease in mice, confers lifelong immunity, as she suspects more severe cases of COVID-19 would. "If you had a serious infection the first time, all indications

are you've got a stronger immune response," and would either be immune to a second infection or experience only mild symptoms the second time around.

Prospects for long-term immunity

In general, whether a viral infection elicits long-term immunity depends on characteristics of both the virus and the host, says Akiko Iwasaki, an immunologist at Yale University. She adds that studies have found that the number of antibodies produced by COVID-19 patients varies widely, which may indicate that their protection against future infection also varies. Other studies have shown that levels of antibodies to SARS-CoV-2 tend to wane after a few months. But Iwasaki adds that antibodies don't reveal the full picture of immunity, as even if antibodies to a virus are at undetectable levels, people who've been exposed to the pathogen before may be able to mount a quick response thanks to T cells and B cells that "remember" the previous infection.

Even if immunity to SARS-CoV-2 does turn out to be short-lived after infection, it might not be bad news for vaccine development, says Roper. "A lot of viruses, when they infect, also do things to turn off the mammalian immune response," she says. "Hopefully, when we design vaccines, the vaccines won't have those proteins that shut off the host immune response. So it should be possible to get a better immune response to the vaccine than you do to the virus."

https://bit.ly/2CUFP4c

Coronavirus SARS-CoV-2 spreads more indoors at low humidity

Indian-German research team recommends at least 40 percent humidity in public buildings

Leipzig/New Delhi. - The airborne transmission of the coronavirus SARS-CoV-2 via aerosol particles in indoor environment seems to be strongly influenced by relative humidity. This is the conclusion drawn by researchers from the Leibniz Institute for Tropospheric Research (TROPOS) in Leipzig and the CSIR National Physical Laboratory in New Delhi from the analysis of 10 most relevant international studies on the subject.

Therefore, they recommend controlling the indoor air in addition to the usual measures such as social distancing and masks. A relative humidity of 40 to 60 percent could reduce the spread of the viruses and their absorption through the nasal mucous membrane.

To contain the COVID-19 pandemic, it is therefore extremely important to implement standards for indoor air humidity in rooms with many people, such as hospitals, open-plan offices or public transport, writes the research team in the scientific journal Aerosol and Air Quality Research.

According to the WHO, the coronavirus SARS-CoV-2 has led to at least 21 million infected persons and over 750,000 deaths worldwide in over half a year. The health and economic effects of the pandemic pose major social challenges for practically all countries. Worldwide, therefore, ways are being sought to stem the spread of the virus in order to avoid drastic measures such as lockdowns and contact restrictions.

For a long time, the main transmission route of viral droplets was considered to be direct human-to-human contact, because of infected people sneezing or coughing and secreting the virus.

Because these drops are relatively large and heavy, they fall very quickly to the ground and can only cover very short distances in the air. The recommendation to keep a minimum distance of 1.5m to 2m (social distancing) is based on this assumption.

Recently, however, COVID-19 outbreaks have also been recorded, which seem to be due to the simultaneous presence of many people in one room (choir rehearsals, slaughterhouses, etc.).

A safety distance of 1.5m is apparently not sufficient when infected and healthy people are together in one room for a long time.

For example, Dutch researchers have now been able to prove that tiny drops of 5 micrometres in diameter, such as those produced when speaking, can float in the air for up to 9 minutes.

In July, 239 scientists from 32 countries - including the chemist Prof. Hartmut Herrmann from TROPOS - therefore appealed to the World Health Organization (WHO) to focus more closely on the long-lived infectious particles suspended in the air.

In order to contain the spread via the aerosol particles floating in the air, the researchers recommend not only continuing to wear masks but also, and above all, good indoor ventilation.

An Indo-German research team is now pointing out another aspect that has received little attention so far and could become particularly important in the next flu season: Indoor humidity.

Physicists at the Leibniz Institute for Tropospheric Research (TROPOS) in Leipzig and the CSIR National Physical Laboratory in New Delhi have been studying the physical properties of aerosol particles for years in order to better estimate their effects on air quality or cloud formation.

"In aerosol research, it has long been known that air humidity plays a major role: The more humid the air is, the more water adheres to the particles and so they can grow faster. So, we were curious: what studies have already been conducted on this," explains Dr. Ajit Ahlawat from TROPOS.

Therefore, they evaluated a total of 10 most relevant international studies between 2007 and 2020 by other researchers who investigated the influence of humidity on survival, spread and infection with the pathogens of influenza and the corona viruses SARS-CoV-1, MERS and SARS-CoV-2.

Result: Air humidity influences the spread of corona viruses indoors in three different ways: (a) the behaviour of microorganisms within the virus droplets, (b) the survival or inactivation of the virus on the surfaces, and (c) the role of dry indoor air in the airborne transmission of viruses.

Although, low humidity causes the droplets containing viruses to dry out more quickly, the survivability of the viruses still seems to remain high.

The team concludes that other processes are more important for infection: "If the relative humidity of indoor air is below 40 percent, the particles emitted by infected people absorb less water, remain lighter, fly further through the room and are more likely to be inhaled by healthy people.

In addition, dry air also makes the mucous membranes in our noses dry and more permeable to viruses," summarizes Dr. Ajit Ahlawat.

The new findings are particularly important for the upcoming winter season in the northern hemisphere, when millions of people will be staying in heated rooms. "Heating the fresh air also ensures that it dries. In cold and temperate climate zones, therefore, the indoor climate is usually very dry during the heating season. This could encourage the spread of corona viruses," warns Prof. Alfred Wiedensohler of TROPOS.

The air humidity determines how much water a particle can bind.

At higher air humidity, the surface of the particles changes considerably: a kind of water bubble forms - a miniature ecosystem with chemical reactions.

The liquid water content of aerosols plays an important role in many processes in the atmosphere, as it influences the optical properties, leading for example to haze or altered effects of aerosols on the climate.

At a higher humidity, the droplets grow faster, fall to the ground earlier and can be inhaled less by healthy people.

"A humidity level of at least 40 percent in public buildings and local transport would therefore not only reduce the effects of COVID-19, but also of other viral diseases such as seasonal flu.

Authorities should include the humidity factor in future indoor guidelines," demands Dr. Sumit Kumar Mishra of CSIR - National Physical Laboratory in New Delhi.

For countries in cool climates, the researchers recommend a minimum indoor humidity. Countries in tropical and hot climates, on the other hand, should take care that indoor rooms are not extremely undercooled by air conditioning systems.

When air is extremely cooled, it dries out the air and the particles in it, making people inside the room feel comfortable. But the dry particles will remain in the air for longer duration.

From a researchers' point of view, more attention should be paid to indoor air to prevent future outbreaks of viral disease. The moisture content of indoor air is an important aspect but not the only one. Fresh air from outside can also reduce the risk of transmission. And of course, the measures already known and practised: Keep social distancing, having as few people per room volume as possible, and wearing masks. The lowest risk of infection still where there are no viruses in the air. **Tilo Arnhold**

Publication:

Ahlawat, A., Wiedensohler, A. and Mishra, S.K. (2020). An Overview on the Role of Relative Humidity in Airborne Transmission of SARS-CoV-2 in Indoor Environments. Aerosol Air Qual. Res. (in press). DOI: 10.4209/aaqr.2020.06.0302

https://doi.org/10.4209/aaqr.2020.06.0302

https://bit.ly/2Ypi8Ze

Female led countries' COVID-19 outcomes 'systematically and significantly better'

Female national leaders locked down earlier and suffered half as many COVID deaths on average as male leaders, according to analysis across 194 countries by the University of Liverpool.

With New Zealand now the first country to record zero cases over consecutive days and Germany the first to resume competitive top level sports, their respective female leaders have received plenty of praise, but researchers found that even when outliers like New Zealand and Germany—and the U.S. for male leaders—were removed from the statistics, the case for the relative success of female leaders was only strengthened.

University of Liverpool Management School Developmental Economist, Professor Supriya Garikipati and her colleague at the University of Reading, Professor Uma Kambhampati, analyzed differing policy responses and subsequent total COVID cases and deaths across 194 countries for the first quarter of the pandemic, up to May 19.

Professor Supriya Garikipati said: "Our results clearly indicate that women leaders reacted more quickly and decisively in the face of potential fatalities. In almost all cases, they locked down earlier than male leaders in similar circumstances. While this may have longer-term economic implications, it has certainly helped these countries to save lives, as evidenced by the significantly lower number of deaths in these countries."

To reach this conclusion, the academics introduced a number of variables to help analyze the raw data and draw reliable country comparisons.

They considered GDP, total population, urban population density and the proportion of elderly residents; they also looked at annual health expenditure per capita, openness to international travel and general level of societal gender equality.

And with only 19 of the 194 countries being led by women, they created "nearest neighbor" countries across the above demographics to balance out the small sample size, leading to comparisons such as Serbia (female led) and Israel (male led); New Zealand (female) and Ireland (male); Germany (female) and the UK (male) and Bangladesh (female) and Pakistan (male).

Professor Garikipati said: "Nearest neighbor analysis clearly confirms that when women-led countries are compared to countries similar to them along a range of characteristics, they have

performed better, experiencing fewer cases as well as fewer deaths." On average, the researchers found that female led countries locked down "earlier"—at significantly fewer deaths—than male led countries.

While this may play into gender stereotypes around risk aversion, Professor Garikipati counters that "while women leaders were risk averse with regard to lives, they were prepared to take significant risks with their economies by locking down early" suggesting "risk aversion may manifest differently in different domains, with women leaders being significantly more risk averse in the domain of human life, but more risk taking in the domain of the economy."

Interestingly, when researchers applied the "openness to travel" control, they found that female-led countries did not experience significantly lower COVID cases but did report lower deaths, suggesting "better policies and compliance in these countries."

And to further check the robustness of their findings, Professor Garikipati and her team dropped the countries most often referred to—Germany, New Zealand and the U.S.—from the data to check for undue influence, but found this only "strengthened the results."

They were also unable to include the female-led Taiwan (500 cases, seven deaths in the research period) as the World Bank no longer provides data for it separately from China.

Professor Garkipati said: "Our findings show that COVID outcomes are systematically and significantly better in countries led by women and, to some extent, this may be explained by the proactive policy responses they adopted. Even accounting for institutional context and other controls, being female-led has provided countries with an advantage in the current crisis."

"Leading the fight against the pandemic: Does gender 'really' matter?" was published in *SSRN Electronic Journal*.

More information: *Supriya Garikipati et al. Leading the Fight Against the Pandemic: Does Gender 'Really' Matter?, SSRN Electronic Journal (2020). DOI: 10.2139/ssrn.3617953*

https://nyti.ms/2QhuCh6

Why Pooled Testing for the Coronavirus Isn't Working in America

Combining samples for coronavirus testing, an approach once hailed by U.S. health officials, only works when the vast majority of tests are negative.

By Katherine J. Wu

Earlier this summer, Trump administration officials hailed a new strategy for catching coronavirus infections: pooled testing.

The decades-old approach combines samples from multiple people to save time and precious testing supplies. Federal health officials like Dr. Anthony S. Fauci and Adm. Brett Giroir said pooling would allow for constant surveillance of large sectors of the community, and said they hoped it would be up and running nationwide by the time students returned to school.

But now, when the nation desperately needs more coronavirus tests to get a handle on the virus's spread, this efficient approach has become worthless in many places, in part because there are simply too many cases to catch.

Pooled testing only works when the vast majority of batches test negative. If the proportion of positives is too high, more pools come up positive — requiring each individual sample to then be retested, wasting precious chemicals.

Nebraska's state public health laboratory, for example, was a pooling trailblazer when it began combining five samples a test in mid-March, cutting the number of necessary tests by about half.

But the lab was forced to halt its streak on April 27, when local positivity rates — the proportion of tests that turn up positive — surged past 10 percent. With that many positives, there was little benefit in pooling.

"It's definitely frustrating," said Dr. Baha Abdalhamid, the assistant director of the laboratory. In combination with physical distancing

and mask-wearing, pooling could have helped keep the virus in check, he added. But the pooling window, for now, has slammed shut.

Some laboratories have set their pooling thresholds even lower than a 10 percent positivity rate, effectively walling themselves off from the strategy as cases continue to climb by the thousands per week in most states.

Even in places where positivity rates are low, pooling isn't always the best testing option. Deployed under the wrong circumstances, the strategy could actually exacerbate lab supply shortages and testing delays, experts said.

"A lot of us are still in the evaluation stage, trying to figure out what problems this will solve," said Rachael Liesman, director of clinical microbiology at University of Kansas Medical Center, which processes several thousand coronavirus tests a week, but has yet to bring pooling online. "But it could create new problems, too."

Despite relatively widespread acceptance in countries like Israel, Germany, South Korea and China, pooling's rise to prominence in the United States has been sluggish. It wasn't until July 18 that Quest Diagnostics became the first commercial lab to receive emergency authorization for pooled testing from the Food and Drug Administration. Since then, Quest has deployed its approach — which batches four samples at a time — in three of its labs, in California, Massachusetts and Virginia, with plans to roll out more on an undisclosed timeline, according to a company representative.

Another large testing company, LabCorp, was given the go-ahead on pooling on July 25, but has yet to debut the procedure in any of its facilities.

Certain hospital systems have also received emergency approval from the F.D.A. to run pooled tests. UC San Diego Health, for example, can run pools of five samples on a machine made by the pharmaceutical company Roche, and will likely receive clearance for two more in the coming weeks, according to Dr. David Pride,

The strategy has already made significant headway in some parts of the country. In New York, where test positivity rates have held at or below 1 percent since June, universities, hospitals, private companies and public health labs are using the technique in a variety of settings, often to catch people who aren't feeling sick, said Gareth Rhodes, an aide to Gov. Andrew Cuomo and a member of his virus response team. Last week, the State University of New York was cleared to start combining up to 25 samples at once.

At Poplar Healthcare, a lab services company based in Memphis, a team led by James Sweeney, its chief executive, is pooling several thousand samples each week. By batching up to seven samples, Poplar is now funneling crucial intel back to schools, fire departments and more, Mr. Sweeney said. In a lot of these groups, coronavirus positivity rates are below 1 percent, he added.

Pooling accounts for about one-third of the samples that are processed at Poplar, Mr. Sweeney said, adding "that percentage is going to get much higher."

But in many other regions, experts are having trouble clearing the hurdles to benefit from pooling — in part because needs differ so vastly from institution to institution, and even from test to test.

"There's been a lot of concerns about all the challenges," said Dr. Bobbi Pritt, director of the clinical parasitology laboratory at Mayo Clinic, which processes tens of thousands of coronavirus tests each week, but has yet to roll out pooling.

Experts disagree, for instance, on the cutoff at which pooling stops being useful. The Centers for Disease Control and Prevention's coronavirus test, which is used by most public health laboratories in the United States, stipulates that pooling shouldn't be used when positivity rates exceed 10 percent. But at Mayo Clinic, "we'd have

to start to question it once prevalence goes above 2 percent, definitely above 5 percent," Dr. Pritt said.

And prevalence isn't the only factor at play. The more individual samples grouped, the more efficient the process gets. But at some point, pooling's perks hit an inflection point: A positive specimen can only get diluted so much before the coronavirus becomes undetectable. That means pooling will miss some people who harbor very low amounts of the virus.

"Are we going to cause harm if we miss them? I think that's still a difficult question to answer," Dr. Liesman said. These people may be less likely to pass the virus to others, and may be at lower risk of getting severely ill. But that's no guarantee. Some might simply be early on in their infection.

Pooling can also be onerous for lab technicians — many of whom have been working grueling hours for months on end. Though simple in theory, batching samples is tedious and time-consuming, as researchers carefully transfer precise amounts of liquid from one tube to another hundreds, perhaps thousands, of times over.

"We've really been struggling in the lab already from repetitive use injuries," Dr. Liesman said. Adding pooling to a lab's repertoire, she said, has the potential to exacerbate that toll. "Pooling could help us do more tests with fewer reagents," or chemicals, she said. "But if one of your issues is staffing, this doesn't really help us at all."

Retesting positive pools also requires a large database of samples so that each member of the pool can be identified and cross-checked. And any sort of mislabeling errors, or cross-contamination between samples, could disrupt the entire workflow and risk an incorrect result.

Robots called liquid handlers, which can automatically batch samples, could be a game-changer for many labs. But given the current testing crisis, many of these pooling-capable machines are in extraordinarily high demand. At UC San Diego Health, Dr. Pride's team has been waiting about two months for the arrival of three new liquid handling instruments. One finally arrived on Monday.

To circumvent some of the issues, experts from disparate fields are cobbling together a few technical tricks. For example, in states, cities or even neighborhoods where coronavirus prevalence rates are high, less-hard-hit populations — "cold spots" — can still be plucked out and pooled, Dr. Abdalhamid said.

When applied to existing social groups, pooling could also help with contact tracing. As children return to schools, for instance, entire classrooms could be tested together. Any pools that come up positive could prompt immediate isolation for everyone involved, with swift, individual testing afterward, Dr. Christina Kong, medical director of the Pathology and Clinical Laboratory for Stanford Health Care, said in an email.

Massaged to fit each laboratory's specific needs, pooling could still prove immensely useful for a large swath of the community, said Daniel Lakeland, who is partnering with researcher Hadi Meidani to develop a pooling "consulting" service. The two eventually hope to roll out a model that can crunch local prevalence numbers and a few other factors, then advise organizations on how to set up their pools. Depending on the circumstances, some pools might even be able to accommodate dozens of specimens at once.

But until those solutions are in hand, researchers are making do as best they can.

Every week, Dr. Abdalhamid of Nebraska's public health lab checks the numbers, hoping for a sustained decline in local coronavirus cases. For months, the region's positivity rate has stubbornly held around 20 percent.

But Dr. Abdalhamid hasn't yet given up, he said: "Hopefully, when it hits 10 or below, we'll get back to pooling right away."

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Is risk of Alzheimer's linked to specific sleep patterns?

More likely to be a "morning person," have shorter sleep duration and other measures of sleep disturbance

Minneapolis - Disturbed sleep patterns do not cause Alzheimer's disease but people who are at high genetic risk of developing Alzheimer's disease may be more likely to be a "morning person," have shorter sleep duration and other measures of sleep disturbance and are less likely to have insomnia, according to a study published in the August 19, 2020, online issue of *Neurology*®, the medical journal of the American Academy of Neurology.

"We know that people with Alzheimer's disease often report depression and various sleep problems, like insomnia," said study author Abbas Dehghan, Ph.D., of Imperial College London in the United Kingdom. "We wanted to find out if there are causal relationships between different sleep patterns and depression and Alzheimer's."

To evaluate the relationship between different sleep patterns, major depressive disorder, and Alzheimer's disease, researchers analyzed the result of different genetic studies collected from databases that included: 21,982 people diagnosed with Alzheimer's disease who were compared to 41,944 without Alzheimer's disease; 9,240 with major depressive disorder who were compared to 9,519 without major depressive disorder; and 446,118 people with measurements of sleep-related characteristics.

Risk of Alzheimer's was determined based on genetic studies where Alzheimer's was diagnosed by autopsy or clinical examination.

Researchers analysed the genetic information using a study design called Mendelian randomization that can determine if there is cause and effect.

Researchers found no evidence that sleep-related characteristics caused Alzheimer's disease. They also found no evidence of cause and effect between major depressive disorder and Alzheimer's.

Researchers did find a small association between the following: people with twice the genetic risk for Alzheimer's disease were 1% more likely to call themselves "morning people" compared to people at lower genetic risk; and people with twice the genetic risk of Alzheimer's had a 1% lower risk of insomnia. However, this effect of this association is small and shows only a possible link, not cause and effect.

A limitation of the study was that most of the people in the study were of European ancestry, so the results may not apply to the people of different ethnicity.

This study was supported by U.K. Dementia Research Institute and the NIHR Imperial College Healthcare Trust.

https://go.nature.com/32fSDun

The antibiotic paradox: why companies can't afford to create life-saving drugs

Paratek Pharmaceuticals successfully brought a new antibiotic to the market. So why is the company's long-term survival in question?

Maryn McKenna

As the COVID-19 pandemic caught hold early this year, a small drug company outside Philadelphia was struggling to market a compound that could help patients battling for their lives.

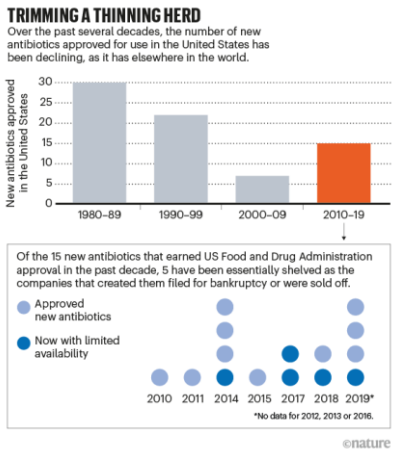
Paratek Pharmaceuticals had spent more than 20 years developing and testing an antibiotic named omadacycline (Nuzyra), which went on sale in the United States in 2019 for use against bacterial infections. Although antibiotics can't fight the virus that causes COVID-19, almost 15% of people hospitalized with the disease go on to develop bacterial pneumonias, some of which are resistant to existing antibiotics.

Before COVID-19, antibiotic resistance was estimated to kill at least 700,000 people each year worldwide. That number could now climb as more people with the viral disease receive antibiotics to treat secondary infections, or to prevent infections that come from being on a ventilator. That's where a drug such as omadacycline might help — if it can be delivered to people in time to save lives.

"COVID is a wake-up call," says Evan Loh, chief executive of Paratek, which has offices in Pennsylvania and Boston, Massachusetts. Diagnostics, antibodies and vaccines are all key to preparing for a pandemic, he says, and "We need antibiotics, to give people the best chance of surviving this particular infection."

But drug makers who produce antibiotics face unique challenges.

In a bitter paradox, antibiotics fuelled the growth of the twentieth century's most profitable pharmaceutical companies, and are one of society's most desperately needed classes of drug. Yet the market for them is broken. For almost two decades, the large corporations that once dominated antibiotic discovery have been fleeing the business, saying that the prices they can charge for these life-saving medicines are too low to support the cost of developing them. Most of the companies now working on antibiotics are small biotechnology firms, many of them running on credit, and many are failing.



Sources: C. L. Ventola *Pharm. Ther*. 40, 277–283 (2015); Axios

In just the past two years, four such companies declared bankruptcy or put themselves up for sale, despite having survived the perilous, decade-long process of development and testing to get a new drug approved. When they collapsed, Achaogen, Aradigm, Melinta Therapeutics and Tetraphase Pharmaceuticals took out of circulation — or sharply reduced the availability of — 5 of the 15 antibiotics approved by the US Food and Drug Administration (FDA) since 2010 (see 'Trimming a thinning herd').

Paratek has so far avoided the rip tide that pulled so many others down, through a combination of conservative spending, experience and good fortune, including a lucrative government contract awarded late last year. But omadacycline's earnings, although steady, have not yet ensured Paratek's long-term survival.

"At the end of the day, Paratek is still going to have to sell a drug," says David Shlaes, a former pharmaceutical executive who is now an antibiotic-development consultant and author. "And it's not at all clear it's going to be able to sell as much as it needs to sell to make a profit."

Costly business

Bringing a new antibiotic to market represents a Herculean feat. Only about 14% of antibiotics and biologicals in phase I trials are likely to win approval, according to the World Health Organization. A team of economists estimated[1] in 2016 that the cost of getting from first recognition of an active drug molecule to FDA approval in the United States was US$1.4 billion, with millions more required for marketing and surveillance after approval. When companies such as Eli Lilly or Merck made antibiotics in the mid-twentieth century, those costs could be spread across their many divisions. And when, as used to happen, big companies bought smaller ones whose new drugs showed preclinical promise, the purchase price covered any debt the small companies had incurred.

Those business models no longer exist. The trio that runs Paratek knows this because all three are big-company veterans. Loh worked at Wyeth Pharmaceuticals in Philadelphia with Adam Woodrow, Paratek's president and chief commercial officer, and with Randy Brenner, chief development and regulatory officer, on the

successful antibiotic tigecycline (Tygacil), which was approved in 2005. (Wyeth sold its antibiotic portfolio to Pfizer in 2009.)

"When you come from a big company to a small company, your focus becomes: 'How do I make sure this company survives?'" says Brenner, who previously also worked at Pfizer in New York City and at Shire in Lexington, Massachusetts (now a subsidiary of Takeda Pharmaceutical Company in Tokyo). "Bigger companies don't need to think like that. No matter what happens to a product, the company survives."

Tigecycline is based on tetracyclines, one of the earliest classes of antibiotic; they were first used in 1948, just six years after penicillin's debut. Over the years, successive generations of tetracyclines arrived on the market and were undermined by resistance. Tigecycline's structure incorporates tweaks that let it avoid those resistance mechanisms, but this comes at a cost: the drug can only be given intravenously.

This was a limitation. An intravenous drug would usually be given in hospitals and medical centres, making it both more expensive and less accessible to patients. So, as tigecycline was being developed, physician-researcher Stuart Levy — one of the giants of US antibiotic-resistance research, based at Tufts University in Boston — proposed formulating yet another tetracycline relative that could also be delivered in pill form. With that goal in mind, he co-founded Paratek in 1996 with Walter Gilbert, a molecular biologist at Harvard University in Cambridge, Massachusetts, who had won a share of the 1980 Nobel Prize in Chemistry.

In its early years, Paratek formed partnerships with larger companies — the German company Bayer, then Merck, then Novartis in Basel, Switzerland. But each deal dissolved as the corporations shifted focus or regulatory changes made omadacycline a bad financial bet. By 2012, when Loh was recruited, Paratek had accomplished phase I and II clinical trials of its compound, and had amassed abundant data on its safety — but it was running out of money. Loh cut the staff from about 34 people to 6, closing the research laboratory while the executive team scrounged for funds. For nine months, they went without salaries.

"I had an insolvency attorney on retainer for 18 months," he recalls. "I talked to him every week. Should I open the doors on Monday? Did I have enough cash to do that?"

In 2014, Paratek went public in a manoeuvre called a reverse merger, folding itself into a US company named Transcept Pharmaceuticals that was already listed on the NASDAQ stock exchange, but which had seen disappointing sales and was running with a skeleton crew. The deal earned Paratek $110 million, enabling it to launch omadacycline's phase III trials and begin a careful restaffing programme. In October 2018, the FDA approved the drug in oral and intravenous formulations against two conditions: complicated skin infections and community-acquired bacterial pneumonia. The 22-year journey was over — but the landscape into which omadacycline would launch was nevertheless still hazardous.

Loh, a cardiologist who had led transplant programmes at two academic medical centres before turning to the pharmaceutical industry, knew that the drug was needed. But he was aware it would not be easy.

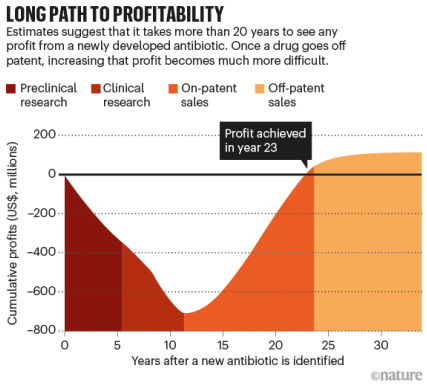
"There's nothing that happens in a hospital that can be successful if you don't have an antibiotic," he says. "You can't have surgeries. You can't have transplants. You can't do anything. We have a product that we believe saves lives. Until we can make that successful for the long term, our mission is not done."

Limited lifespan

Antibiotics present an enduring economic puzzle. These drugs changed the world. Yet despite their unique power, the free market doesn't value them.

The reasons are complex. Start with the obvious: antibiotics kill bacteria, living things that are constantly adapting to threats against their survival. As soon as a new compound is used, pathogens start evolving strategies to foil the attack. That means an antibiotic's useful life, and thus its earning potential, can be limited — a situation that doesn't occur for most other drugs.

The duration of a new antibiotic's lifespan wouldn't be that important if a company could sell a lot of it quickly, but both structural and ethical barriers work against that (see 'Long path to profitability'). Take the structural ones first. Relatively few patients have resistant infections that need treatment with new antibiotics, whereas most other drug categories are used to treat large numbers of people. The US Centers for Disease Control and Prevention estimates that there are 2.8 million resistant infections annually in the United States. For comparison, 7.4 million people in the United States take insulin to treat diabetes on a daily basis.



Source: Securing New Drugs for Future Generations (Review on Antimicrobial Resistance, 2015)

By one estimate, a new antibiotic needs to make at least $300 million in annual revenue to be sustainable[2]. Other researchers estimate[3] that the entire US market for new antibiotics that work against carbapenem-resistant Enterobacteriaceae — one of the most resistant and most stubborn classes of infection — is $289 million per year.

In other words, "there's room in this marketplace for maybe one drug", Shlaes says. "There's not room for more than one drug if people want a return on their investment."

Only a few of the companies now making antibiotics earn $100 million or more a year from them, according to analyses by the investment firm Needham in New York City. Most of the rest hover between $15 million and $50 million per year.

Then there are the ethical quandaries. Because any exposure of bacteria to an antibiotic risks the development of resistance, using that drug to treat one patient risks diluting its power to save others in the future. Thus, rules observed across health care, broadly called antibiotic stewardship, call for new antibiotics to be deployed slowly. That protects their reliability in the long term, but ruins their sales. For instance, in 2018, three new antibiotics — including the one made by recently bankrupt Achaogen — were used in only 35% of cases that would have qualified for them[4]. That was a win for stewardship, perhaps. It was a literal loss for the companies whose drugs would otherwise have been used.

John Rex, a physician and long-time drug developer who is chief medical officer at the antifungals company F2G in Manchester, UK, and Vienna, sums up the paradox in this way: "Invent a bad antibiotic, and no one will use it. Invent a really good antibiotic, and really no one will use it."

Into the abyss

The 100-person team that makes up Paratek approached the end of 2019 in an unsettled mood. They were staring into what Woodrow calls "the abyss of commercialization: this three-year period where you spend a tremendous amount of money before you get any traction in terms of real sales". The antibiotic was selling steadily, but slowly — it was on track to earn $13 million that year. Meanwhile, Woodrow, Loh and Brenner had committed to doing post-approval studies and surveillance that they estimated would cost $70 million. And they had lost a guiding light: Levy, their co-founder, died in September 2019.

Then Christmas came early. The Biomedical Advanced Research and Development Authority (BARDA), a US federal agency, awarded Paratek a 5-year, $285-million contract to procure omadacycline for front-line troops who might be exposed to the bioweapon anthrax. (The purchase validated Levy's early insight on the value of an oral drug: endangered troops could pop the pills and move on, rather than be tied to intravenous drips.)

On receiving the news, Loh felt like he could finally exhale. "This is a massive number — a gift," he said not long afterwards. "It gives us time to gain traction."

The BARDA money acted like a bridge across the chasms that other companies had fallen into. In a small way, it also demonstrated the potential of incentives for repairing the antibiotic market, which policymakers in the United States and Europe have been debating for several years. There are two types, referred to as push and pull. 'Pushes' propel new drug candidates from small companies through clinical trials and past approval. 'Pulls' aim to ease the financial crunch after approval, when companies must promote their drug without violating antibiotic stewardship.

Push incentives have had some success. The non-profit organization CARB-X (Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator), based at Boston University, has gathered about $500 million in funding from US, UK and other European governments and philanthropies, and is distributing the money to small companies. Since CARB-X was founded in 2016, it has given 67 companies about $250 million to support promising preclinical and phase I research.

BARDA — which is funding the separate search for coronavirus vaccines and therapeutics — also gives push grants that support companies doing the later clinical trials that bring drugs to approval. However, BARDA's contract with Paratek was different. It was effectively a pull incentive, an infusion of cash arriving after omadacycline had been approved, at a point when post-approval surveillance and studies to support use of the drug for other infections would eat up slender earnings.

Other forms of pull incentive have been proposed by analysts and lawmakers, among others, and considered by the US Congress, but they are much more controversial. These range from granting pharma companies extra time before other drugs they own become generic, called extended market exclusivity, to giving companies market-entry rewards of billions of dollars that release them from the need to push sales of their drug, which would otherwise accelerate the development of resistance. Yet another proposed pull incentive — which would raise the reimbursements paid to hospitals by the US government for new antibiotics — was briefly added to the $2-trillion US stimulus bill written in response to the coronavirus pandemic. The incentive was taken out again before the bill became law.

No one has yet found a path past political reality: in the eyes of many voters and politicians, pharma companies are opportunists, inflating US drug prices to unconscionable heights. There were multiple congressional hearings on drug prices in 2019 alone, and in July, President Donald Trump signed several executive orders aimed at forcing prices down. Making things easier for any drug company, even a small one producing a much-needed antibiotic, faces strong political resistance.

Alan Carr, a molecular biochemist and senior analyst at Needham, says there is not yet a clear path to what works to support antibiotic research — not for incentives, and not for investors, either. "What has complicated things for investors is that there is a need for new antibiotics — but not in every space within antibiotics," he says. "There are certain infections where there's a real unmet need where we don't have any antibiotics. And then there are other areas where we have plenty. Unfortunately, what has happened is that investors

have lumped the whole space together. So they want nothing to do with any of them."

Pandemic curveball

The BARDA contract turned Paratek from a company with less than a year's worth of cash in the bank to one that could count on funding to the end of 2023. That guaranteed its immediate future, although it did nothing to solve the long-term problem of needing to earn more from the drug than the market seemed willing to pay. And then the coronavirus hit.

When cases of SARS-CoV-2 started increasing in the United States, Loh and his team were unnerved. The Paratek sales force had been doing the normal rounds, explaining omadacycline to infectious-disease specialists and hospital pharmacists, hoping to have it picked up by the formulary committees that govern which medications hospitals routinely keep to hand. Its work was paying off. Month after month, sales of omadacycline were rising by more than 10%. When the lockdowns started, all of those meetings ended. The company worried its sales would stall as well. But in monthly data gathered since the epidemic began, the steady increase has continued.

"New prescribers, in a lockdown period — I expected that to go to zero," says Christine Coyne, Paratek's vice-president of marketing. "But we are still seeing double-digit growth."

It is too soon to say what drives those sales. Enough case reports have now been published[5,6] for researchers to feel confident that bacterial pneumonia is a complication of COVID-19 in 15–20% of patients. And in parts of the United States, the most common cause of bacterial pneumonia (*Streptococcus pneumoniae*) is resistant to azithromycin, the most common generic antibiotic, in up to 50% of cases. That could drive adoption of a new drug for which resistance has not been recorded. Other publications confirm that significant amounts of antibiotics are being prescribed to people with COVID-19 who are on ventilators, even when pneumonia has not been diagnosed (for a review, see ref. 7). This is an insurance policy against patients getting hospital-acquired infections, and because, in the absence of enough personal protective equipment, the procedures needed to confirm bacterial pneumonia are too risky for staff to undertake.

As a side effect of the pandemic, many other antibiotics are in short supply. That's a result of both interruptions in international trade — the active ingredients of most antibiotics come from China — and domestic influence. For instance, after Trump announced his support in March for the unproven and now largely discredited combination of hydroxychloroquine and azithromycin, several manufacturers of azithromycin announced that panic buying had triggered shortages.

If those events are boosting sales, that is to Paratek's benefit. They also underline the good fortune of the BARDA contract coming when it did. The company's supply chain avoids China and is based entirely in Europe. And, as a condition of protecting national defence, a clause in the BARDA contract requires the company to build a parallel supply chain fully within the United States, to avoid disruptions from any future outbreaks.

To the Paratek team, omadacycline's applicability to this ongoing crisis is validation of the company's commitment to stick with a product that it believed was needed. Equally, it has demonstrated how important it is to anticipate emergencies, and to provide for crucial medical interventions before one begins. The United States failed to do that for masks, respirators and other equipment that protects health-care workers from infection. It almost failed to do that for the provision of antibiotics, too.

"Coronavirus ought to say to the public, 'If you don't have technology on the shelf when something like this happens, you can't wait a year or two — or even three or five — in order to get it

there,'" Loh says. "You can't be at the bedside and say to a company: 'Can you make this for me today?'"

Nature ***584***, *338-341 (2020) doi: 10.1038/d41586-020-02418-x*

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Employee fraud decreases when they see family photos

Displaying family photos in the workplace cuts down on employee fraud and other unethical behavior, new Washington University in St. Louis research finds.

by Jill Young Miller

For instance, in one study the researchers conducted, participants who looked at pictures of family or friends filed expense reports claiming about $8 less on average than workers without pictures. While $8 may not seem like much, it can add up quickly.

"If numerous employees submit monthly expense reports to a company, it's easy to imagine the financial impact of the reduction in unethical behavior over time," said Ashley Hardin, assistant professor of organizational behavior at Olin Business School.

Hardin is the lead author of "Show me the … family: How photos of meaningful relationships reduce unethical behavior at work," in the journal *Organizational Behavior and Human Decision Processes*.

Photos at work

More than 70% of workers display photos in their workspace, and people have a great deal of choice in what they put up, Hardin said.

At the same time, companies have considerable influence over whether employees have photos in their workstations by signaling their acceptability.

Hardin and co-authors theorized that having photos of "close others" in view "decreases the hegemony of an economic schema in people's minds"—in other words, reduces the prioritization of self-interest, among other things, which decreases their propensity to misbehave. These hypotheses were supported across four studies they conducted.

Photos are a cue to the self and others because they convey information about values and interests, previous research found. Until now, however, the effect of personalizing one's workplace with photos on financial transgressions was unexplored.

The authors conducted a field survey and three experiments; they found a negative relationship between employees who display photos of family or friends at work—rather than photos of landscapes—and financial transgressions.

Practical implications

Given the frequency and cost of unethical behavior at work, "there is great interest in understanding what contributes to these behaviors and how to curb such conduct," the authors wrote. Hardin conducted the research with Christopher Bauman of the University of California, Irvine, and David Mayer of the University of Michigan.

Their results consistently indicate that the presence of photos of close others—family and friends—reduces the likelihood that individuals will over-report their earnings, pad expense reports or engage in other bad behavior.

"Our findings are relevant for individuals at work. For example, individuals who want to guard against their own unethical behavior

could display photos of friends and family in their workspaces," Hardin said.

And companies should consider encouraging employees to display photos of family and friends. "More broadly, companies and individuals alike should be mindful of how their physical surroundings may be influencing their behavior," the authors wrote.

"Whereas some organizations encourage segmentation of work and life by penalizing those who bring outside topics into work, our findings suggest that this segmentation may have an unexpected downside in terms of unethical behavior.

"Our results suggest that subtle adjustments to the physical context can alter employee behavior, and it should, therefore, be possible to design organizational interventions that help to inhibit fraud and other forms of undesirable behavior."

More information: *Ashley E. Hardin et al. Show me the ... family: How photos of meaningful relationships reduce unethical behavior at work, Organizational Behavior and Human Decision Processes (2020). DOI: 10.1016/j.obhdp.2020.04.007*

https://bit.ly/2ElZb2C

New Study Says Honey Is Better For Colds Than Drugs. Here's What You Need to Know

It is also cheap, easy to access and has limited harms.

David Nield

Honey appears to be a preferable treatment for cough or cold symptoms rather than antibiotics and over-the-counter medicines, according to a new systematic review that's looked at the results from 14 previous studies - but the conclusions may not be quite so clear-cut as they appear at first.

"Honey is a frequently used lay remedy that is well known to patients," write the researchers from the University of Oxford in the UK. "It is also cheap, easy to access and has limited harms."

One particular area of interest is the comparison of honey to antibiotics. With antibiotics often causing side effects and antibiotic resistance on the rise, there are multiple advantages to using honey as an alternative remedy, the authors of the review point out.

"Since the majority of upper respiratory tract infections (URTIs) are viral, antibiotic prescription is both ineffective and inappropriate," write the researchers. "However, a lack of effective alternatives, as well as a desire to preserve the patient-doctor relationship, both contribute to antibiotic over-prescription."

People have been using honey to help deal with coughs and colds for a long, long time - but research on its efficacy has been rather patchy, leaving room for doubt on how much it actually alleviates cold symptoms across diverse age groups, compared with other options.

The team's review is based on 1,761 individuals across 14 studies and concludes that honey is effective at treating the symptoms of URTIs – including sore throats, blocked noses, coughs and general congestion. However, while the conclusion seems promising, the studies included appear to be emblematic of the issues affecting such research.

"With meta-analyses, it's all about the included studies. If the literature you're relying on is bad, you can't really say much about the subject except that you need more research," says Gideon Meyerowitz-Katz, an epidemiologist from the University of Wollongong in Australia, who was not involved in the research.

"In this review, most of the included research seems to have worrying inconsistencies and some outright mistakes, which means we have to be really careful about reading too much into the results."

As anyone who's experienced a common cold will know, existing treatments and therapies often make a small difference in the overall course of the ailment; honey can feel like it's doing *something* – and the researchers say it's worth following up with large, high-quality, placebo-controlled trials.

"The meta-analysis itself was done well, but the quality of the studies on honey for URTI/cough seems to just be really low. That means that we can only really say that we aren't sure yet if honey helps, because we haven't properly answered the question," Meyerowitz-Katz told ScienceAlert.

In the meantime, work continues to look at how beneficial honey might be in terms of its antibacterial properties, and how it might be helpful for treating other ailments besides coughs and colds. Sometimes the best treatments are the ones nature has already provided for us - but more research is definitely needed.

The research has been published in *BMJ Evidence-Based Medicine*.

https://bit.ly/3aNDVyA

Massive, well-preserved reptile found in the belly of a prehistoric marine carnivore

When paleontologists uncovered an ichthyosaur, they didn't expect to find another fossil in its stomach

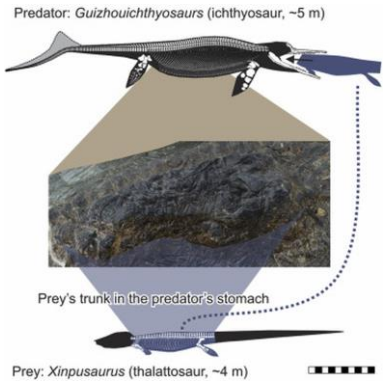
When paleontologists digging in a quarry in southwestern China uncovered the nearly complete skeleton of a giant, dolphin-like marine reptile known as an ichthyosaur, they didn't expect to find another fossil in its stomach. This second skeleton belonged to a four-meter-long, lizard-like aquatic reptile known as a thalattosaur and is one of the longest fossils ever found in the stomach of a prehistoric marine reptile. While the researchers can't say for sure whether the thalattosaur was scavenged or preyed upon, their work could be the oldest direct evidence that Triassic marine reptiles like ichthyosaurs--previously thought to be cephalopod feeders--were apex megapredators. The findings appear August 20th in the journal *iScience*.

"If you look across all the similar marine reptiles that lived in the age of dinosaurs, we've actually never found something articulated like this in the stomach," says co-author Ryosuke Motani, a professor of paleobiology at the University of California, Davis.

"Our ichthyosaur's stomach contents weren't etched by stomach acid, so it must have died quite soon after ingesting this food item. At first, we just didn't believe it, but after spending several years visiting the dig site and looking at the same specimens, we finally were able to swallow what we were seeing."

This image shows the ichthyosaur specimen with its stomach contents visible as a block that extrudes from its body. **Ryosuke Motani**

Because stomach contents are rarely found in marine fossils, researchers rely on tooth and jaw shapes to learn what prehistoric species may have eaten. While prehistoric apex predators are typically thought to have large teeth with sharp cutting edges, some modern predatory species like crocodiles use blunt teeth to consume large prey items with grasping force instead of cutting. Ichthyosaurs share these blunter teeth, but with no direct evidence of large prey consumption in these prehistoric marine reptiles, scientists believed that they fed on small prey like cephalopods.



However, the discovery of the giant thalattosaur in the stomach of the ichthyosaur found by Motani, Da-Yong Jiang, a paleontologist at Peking University in China, and their team suggests that this was not the case.

"Now, we can seriously consider that they were eating big animals, even when they had grasping teeth," says Motani. "It's been suggested before that maybe a cutting edge was not crucial, and our

discovery really supports that. It's pretty clear that this animal could process this large food item using blunt teeth."

While the researchers now know that the ichthyosaur could eat animals as large as the thalattosaur, they don't know if it killed this individual, or simply scavenged it. "Nobody was there filming it," says Motani. However, there is reason to believe this was not a case of scavenging: modern marine decomposition studies suggest that if left to decay, the thalattosaur's limbs would disintegrate and detach before the tail.

Instead, the researchers found the opposite in these fossils. The thalattosaur's limbs were at least partially attached to its body in the stomach, while a disconnected tail was found many yards away, leading the researchers to believe it was ripped off and left behind by a predator like the ichthyosaur.

Whether or not the ichthyosaur killed its last meal, the fossil provides the oldest direct evidence that these giant marine reptiles consumed animals larger than humans. "We now have a really solid articulated fossil in the stomach of a marine reptile for the first time," Motani says. "Before, we guessed that they must have eaten these big things, but now, we can say for sure that they did eat large animals. This also suggests that megapredation was probably more common than we previously thought."

The team is still excavating the site where the pair of fossils were found, which has now been turned into a museum. "We've been digging in that particular quarry for more than ten years now, and still, new things are coming out," says Motani. "At this point, it's beyond our initial expectations, and we'll just have to see what we'll discover next."

This work was supported by the National Natural Science Foundation of China, the Ministry of Science and Technology, and the National Geographic Society Committee for Research and Exploration.

iScience, Jiang et al.: "Evidence supporting predation of 4-meter marine reptile by Triassic megapredator." https://www.cell.com/iscience/fulltext/S2589-0042(20)30534-4

https://bit.ly/3qjIVw5

Immune Biomarkers Tied to Severe COVID-19: Study

Increases in the levels of three cytokines are among the features linked to poor outcomes.

Ruth Williams

A study of COVID-19 patients at two London hospitals has identified blood-based immunological changes that are linked to the disease and, in some cases, to symptom severity. The results, reported in *Nature Medicine* on Monday (August 17) join a growing body of data on how the human immune system responds to SARS-CoV-2 that will hopefully lead to prognostic tools and potential treatments.

“The study is a nice comprehensive characterization of the different trajectories of host response against SARS-CoV-2 [and] technically well performed,” Antonio Bertoletti an emerging infectious disease researcher at Duke-National University of Singapore who was not involved in the research, writes in an email to *The Scientist*. It provides “some specific findings, like the severe drop of dendritic cells and the inflammatory cytokine profile,” he adds, “[that] might predict the worsening of the disease.”

Microbiologist and immunologist Stanley Perlman of the University of Iowa who also was not a part of the research team is less optimistic about the potential for prediction. “They came up with parameters that seem to define the different [severity] groups,” he says, “but for an individual [patient] it’s very hard” to make a prediction because “there is so much overlap” between the groups.

He nonetheless praises the efforts of the authors of the paper and similar endeavors, saying such studies provide “a sense for what seems to be happening in people who do worse, which in itself is useful, if not for prognosis . . . it can help you in management [of the disease].”

Since late 2019, the novel coronavirus SARS-CoV-2 has been relentlessly and rampantly spreading from person to person across the globe. While in many people the virus causes no ill effects, in others it ravages the lungs, leaving them hospitalized for weeks, and in some the infection is fatal. More than 780,000 people have died from the disease worldwide to date.

For a disease with such diversity of symptoms and outcomes, and in patients of different ages and sexes with different underlying conditions, finding a common immune signature for COVID-19—a set of immune proteins and cells that define the disease—may seem like an impossibility, but immunologist Adrian Hayday of King's College London and the Francis Crick Institute was not discouraged by the odds.

Despite "extraordinary heterogeneity" within patient populations, he says, "immune responses against potentially lethal pathogens can have very dominant effects that rise above the background and therefore provide you with an immune signature."

Discovering such a signature would be of great value, he explains. For one thing, "you might find things that are unique to COVID-19 and that might give you some very important things to target therapeutically," he says. And, it might identify "changes that actually could give the doctors a very early indication of which way a patient was going to go."

For Hayday and his colleagues' study, the team collected blood samples from 63 patients with mild, moderate, and severe COVID-19 who were admitted to Guys and St. Thomas's hospitals in London from March to May this year, and from 55 control individuals, including healthy people who had previously tested positive for coronavirus (and had had no or mild symptoms), people with other respiratory tract infections, and healthy individuals with no recent respiratory infections.

The researchers performed flow cytometry experiments and protein assays on the blood samples to analyze the presence and characteristics of various immune cell types and to measure antibodies and other immune factors. IP-10 levels in a patient's first blood sample could even predict the length of hospital stay

Among the results, the team found that almost all COVID-19 patients had robust production of anti–SARS-CoV-2 antibodies—which raises questions about the general usefulness of convalescent plasma treatment, which supplies antibodies from recovered donors, says clinician scientist Manu Shankar-Hari of King's College London who coauthored the study. Indeed, the FDA's plan to approve the treatment is now on hold due to lack of evidence of efficacy. A report in *Immunity*, however, suggests antibody quality, not quantity, is linked to outcome and therefore that plasma from survivors might be qualitatively better than that of very sick patients. There were also three patients in Haday and Shankar-Hari's study in whom no antibodies were detected and all three died, suggesting select individuals may benefit.

As a whole, patient samples were also enriched for plasmablasts (antibody secreting cells), markers of T cell exhaustion, and the cytokines IL-8, IL-6, IL-10, and IP-10, while lacking in basophils and certain subpopulations of dendritic cells and monocytes compared with healthy controls.

Some of these immune features were also seen in patients with other respiratory tract infections. Others, such as low basophils and dendritic cells and high IP-10, were particular to COVID-19.

Some features correlated with the severity of disease. Through a longitudinal study of individual patients—taking blood samples on different days during the hospital stay—the team showed that those patients who had high levels of IL-6, IL-10, and especially IP-10 when their first blood sample was taken were more likely to have a

poorer outcome than patients in whom these cytokine levels were lower.

The trio of cytokines was "quite an extraordinary predictor that could discern whether a patient at admission with respiratory difficulties would actually improve or worsen," says Hayday. IP-10 levels in a patient's first blood sample could even predict the length of hospital stay, he adds.

"It's a great paper," says Michael Betts of the University of Pennsylvania who was not involved in the work, and "it certainly agrees with a lot of the literature that has accumulated already." He notes that while some differences exist between the new results and other COVID-19 signature studies, for the most part they are similar. Hayday's group has made the raw data available here.

It remains to be seen—in longitudinal validation studies with a larger cohort of patients—whether the trio of cytokines will be reliable predictors of severity, says Shankar-Hari, and whether they might be worthy targets for therapy.

For now, "we still know little about why different infected individuals [have] such diversity of symptoms and outcomes," writes Bertoletti, "but at least we start to understand what is occurring in such different manifestations and this is important to clinical management."

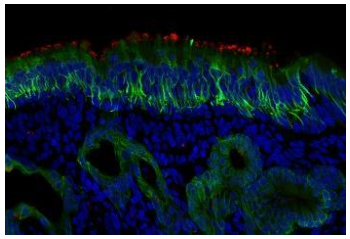
A.G. Laing et al., "A dynamic COVID-19 immune signature includes associations with poor prognosis," Nat Med, doi:10.1038/s41591-020-1038-6, 2020.

https://bit.ly/3j5lHeR

Study adds to evidence that cells in the nose are key entry point for SARS CoV-2

"Hook" of cells used by SARS-CoV-2 to latch onto and infect cells up to 700 times more prevalent in olfactory supporting cells lining the inside of the upper part of the nose

Scientists at Johns Hopkins Medicine, experimenting with a small number of human cell samples, report that the "hook" of cells used by SARS-CoV-2 to latch onto and infect cells is up to 700 times more prevalent in the olfactory supporting cells lining the inside of the upper part of the nose than in the lining cells of the rest of the nose and windpipe that leads to the lungs. These supporting cells are necessary for the function/development of odor-sensing cells.



Red stain is ACE2. The green probe is staining CK18, which is found in supporting cells and mucus glands. **Photo by Mengfei Chen**

The findings, from a preliminary study of cells lining both the nose and trachea, could advance the search for the best target for topical or local antiviral drugs to treat COVID-19, and offers further clues into why people with the virus sometimes lose their sense of smell.

A summary of the findings appears in a letter published Aug. 19 in the *European Respiratory Journal*.

"Loss of the sense of smell is associated with COVID-19, generally in the absence of other nasal symptoms, and our research may advance the search for a definitive reason for how and why that happens, and where we might best direct some treatments," says Andrew Lane, M.D., professor of otolaryngology-head and neck surgery, and director of the Division of Rhinology and Skull Base Surgery at the Johns Hopkins University School of Medicine.

Lane's medical practice focuses on people with nasal and sinus problems, who oftentimes, he says, lose their sense of smell -- a condition called anosmia.

Scientists have known that SARS-CoV-2 latches on to a biological hook on the surface of many types of human cells, called an angiotensin-converting enzyme 2 receptor (ACE2). The receptor reels in essential molecules.

In a bid to explore the ACE2 link to COVID-19 in more detail, Lane, Mengfei Chen, Ph.D., a research associate in Lane's lab at the Johns Hopkins University School of Medicine, and others on his

team took a close look at ACE2 levels in nasal tissue specimens from 19 adult men and women with chronic rhinosinusitis (inflammation of nasal tissue) and in tissues from a control group of four people who had nasal surgeries for issues other than sinusitis.

The researchers also studied tissue samples of the trachea from seven people who underwent surgery for abnormal narrowing of the trachea.

Cells from children were not examined for this study, in part because they tend to have low ACE2 levels in the cells lining the nose, which may contribute to generally less severe illness among children infected with the SARS-CoV-2 virus. None of the study participants had been diagnosed with COVID-19.

The scientists used a high-resolution imaging technique called confocal microscopy to produce very sharp images of cells lining the nasal and tracheal airways. They used fluorescent stains to identify ACE2 receptors.

They found high levels of ACE2 among nasal cells that give structural support called sustentacular cells. These cells are located in an area called the olfactory neuroepithelium, where odor-sensing neurons are found.

The researchers say this area of the nose may be particularly vulnerable to infection and might be the only infected site even when there are no symptoms. Because of this, they urge people to wear masks and wear them correctly.

For the study, depending on the biopsy sample, cells in the olfactory neuroepithelium had a 200-fold to 700-fold increase in ACE 2 proteins compared with other samples from the nose and trachea. Because the cells with high levels of ACE2 are associated with odor sensing, the researchers suggest that infection of these cells may be the reason some people with COVID-19 experience loss of smell.

Two of seven trachea specimens had low levels of ACE2 receptors, and the amount of those receptors was similar between study participants with and without chronic rhinosinusitus.

Because the cells lining the nose may prove to be a key entry point for SARS-CoV-2, Lane says there may be ways to target those particular cells with topical antiviral drugs or other therapies directly to that area.

The researchers plan to advance this research by investigating COVID-19-infected tissue from the noses of humans to confirm if the SARS-CoV-2 virus does indeed target support cells in the nose.

Funding for the study was provided by the National Institutes of Health's National Institute of Allergy and Infectious Diseases and National Institute on Deafness and other Communication Disorders (R01 AI132590, R01 DC016106.

Other scientists who contributed to the research include Wenjuan Shen, Nicholas Rowan, Heather Kulaga, Alexander Hillel and Murugappan Ramanathan Jr., of Johns Hopkins.

https://bbc.in/2ElU96r

Breast cancer: One-dose radiotherapy 'as effective as full course'

A single targeted dose of radiotherapy could be as effective at treating breast cancer as a full course, a long-term study suggests.

By Rachel Schraer Health reporter

Researchers said people who received the shorter treatment were also less likely to die of other cancers and heart disease in the following five years. But cancer specialists have raised concerns about the study's methodology.

A fifth of patients in the study received extra doses of radiotherapy.

The study's lead author, Prof Jayant Vaidya, said he had expected a proportion of the women to need extra radiotherapy, since post-op tests could reveal tumours were bigger or more aggressive than expected. This still left 80% of women benefiting from a shorter course of treatment with fewer side-effects, he said.

Targeted Intraoperative Radiotherapy (TARGIT-IORT) involves a single, targeted dose of radiation inside the breast, immediately

after the tumour is removed. This type of radiotherapy, developed by doctors at University College London (UCL), is delivered using a small device placed inside the breast, directly on the site of the cancer.

It means patients can receive radiation treatment at the same time as their operation to have their cancer removed. And they shouldn't have to return for any further treatments, which can involve 15 to 30 hospital visits for people having a standard course of radiotherapy. This treatment is already available on the NHS in a small number of clinics that have the right equipment.

During the pandemic, NHS England has reduced the number of visits people need to make for standard radiotherapy after surgery to about five.

The TARGIT-A trial involved 2,298 women with breast cancer in 10 countries being given either targeted therapy during surgery or a standard course of radiotherapy between 2000 and 2012.

The study reported at the 10-year mark that a single dose of radiation during surgery was as effective as a prolonged course.

This latest study, which followed women up for five years after their treatment, confirmed that conclusion, the researchers said.

And it found fewer in the group receiving the single-dose treatment had died from other causes, including heart disease, lung problems and other cancers. UCL said previous studies had shown the treatment also had fewer radiation-related side-effects, including pain and changes to the breast's appearance.

'Cancer-free'

Writer Marcelle Bernstein received the one-off treatment eight years ago, and has had the all-clear ever since.

"Within two months of diagnosis I was cancer-free," she said.

And, having seen her mother die of breast cancer 25 years earlier, she felt it was important she "wouldn't be a cancer sufferer longer than necessary".

"I just liked the idea of something treating just the tiny area affected and not touching the rest of the body," she said.

However, 20% of the women in the study given a single dose of radiation did go on to have further radiotherapy treatments, when tests discovered "unsuspected higher-risk factors".

Concerns

Joanne Haviland at the Institute of Cancer Research raised concerns about some of the definitions the researchers used in their study.

"Conventional radiotherapy has evolved considerably since the design of the TARGIT-A trial, including shorter treatment schedules and smaller volumes of breast treated, with greatly improved patient experience and extremely high levels of clinical cure at very low cost to the NHS."

Martin Ledwick of Cancer Research UK said: "As the women taking part in the study received radiotherapy at the same time as having a lumpectomy, doctors weren't able to analyse their tumours in advance to see if they would need a longer course of radiotherapy until after their operation.

"While 20% of the women in this study did then need additional treatment, 80% of patients were spared this."

https://bit.ly/2QiGyz3

Some 'Healthy' Kids Can Carry as Much COVID-19 Virus as Severely Sick Adults

Just because kids often don't show symptoms, doesn't mean they don't carry any traces of the virus

Carly Cassella

Summer in the Northern Hemisphere is coming to an end, and if we're not super careful about reopening our schools and daycare centres, experts warn children could soon play a much bigger role in the pandemic.

Just because kids often don't show symptoms, doesn't mean they don't carry any traces of the virus, new research has shown.

While children might contract COVID-19 at lower rates to adults and show milder or no symptoms, once they do catch the virus, scientists say they may carry unusually high loads of it.

This means even without any obvious symptoms, kids with COVID-19 are potentially contagious, carrying a high number of viral particles from school to home and back again.

"During this COVID-19 pandemic, we have mainly screened symptomatic subjects, so we have reached the erroneous conclusion that the vast majority of people infected are adults," says pediatric gastroenterologist Alessio Fasano who works at MassGeneral Hospital for Children in Boston.

"However, our results show that kids are not protected against this virus. We should not discount children as potential spreaders for this virus."

The study, which was conducted at two hospitals in Boston during the peak of an outbreak, is said to be the most comprehensive analysis of pediatric COVID-19 patients to date.

Among 192 children and young people between the ages of 0 and 22, the authors found 49 kids who were carrying SARS-CoV-2 (the coronavirus that causes COVID-19) and 18 kids who had multisystem inflammatory syndrome in children (MIS-C) - an ailment related to COVID-19.

Compared to adults hospitalised for COVID-19, these children had surprisingly higher levels of coronavirus in their airways, especially in the first two days of contracting it.

"I was not expecting the viral load to be so high," admits pediatric pulmonologist Lael Yonker from Massachusetts General Hospital.

"You think of a hospital, and of all of the precautions taken to treat severely ill adults, but the viral loads of these hospitalised patients are significantly lower than a 'healthy child' who is walking around with a high SARS-CoV-2 viral load."

That's a disturbing result, because having a higher viral load could potentially mean more shedding of the virus and, therefore, a greater risk of contagion. While this study did not examine transmissibility of the virus directly, the findings do suggest children may be a hidden source of spread.

While other studies have found kids show fewer immune receptors for SARS-CoV-2 than adults, the new research suggests this has little impact on the actual presence of the virus.

Instead, it seems even when children show mild or no symptoms, they are, in fact, carrying high doses of the virus, enough to hospitalise an adult.

"Pediatric patients displayed no apparent difference in viral load compared with adults requiring intubation for severe SARS-CoV-2 infection when stratified by time. Viral load in children in the symptomatic/early infection phase was significantly higher than in hospitalised adults with severe disease with over 7 days of symptoms," the team writes in the study.

Some initial research on adults suggests higher viral loads are linked to more severe outcomes, but for some reason, this doesn't appear to be the case in children.

In the end, the authors say this could make infection-control strategies much harder to implement, especially since mild symptoms of COVID-19 appear so similar to other common illnesses.

"Identifying SARS-CoV-2 infection in children will become even more challenging during pollen allergy season and influenza season this fall," the authors write.

While fever is usually the first symptom of COVID-19, the study found only half the children with acute SARS-CoV-2 infections presented with a high body temperature.

This suggests temperature screening may not be an effective tool in reopening schools and daycare centres. Instead, the authors suggest

focusing on strategies like social distancing, mask use, viral screening, and/or remote learning.

"Without infection control measures such as these," the authors conclude, "there is significant risk that the pandemic will persist, and children could carry the virus into the home, exposing adults who are at higher risk of developing severe disease."

In communities of lower income, where multiple generations often live under the same roof, this could very well be deadly.

In the study, nearly 20 percent of acute SARS-CoV-2 infections and those with MIS-C did not have a known household exposure to the virus.

It's not clear how this infection spreads through a house or a school, but recent research suggests it might have to do with the age of the child. Children under 10, for instance, do not seem to spread the virus as far as their older counterparts.

"This study provides much-needed facts for policymakers to make the best decisions possible for schools, daycare centers and other institutions that serve children," Fasano says.

"Kids are a possible source of spreading this virus, and this should be taken into account in the planning stages for reopening schools." Fasano is worried about what will happen if schools reopen fully.

The study was published in the *Journal of Pediatrics*.

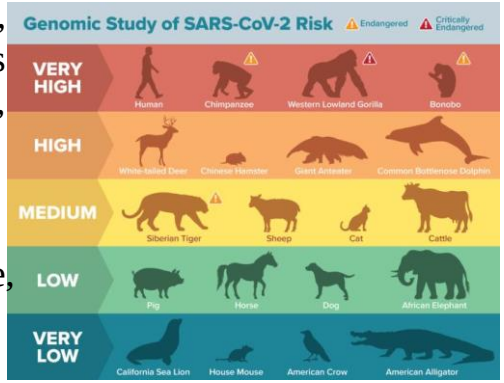
https://bit.ly/3qmas06

Genomic analysis reveals many animal species may be vulnerable to SARS-CoV-2 infection

Humans are not the only species facing a potential threat from SARS-CoV-2

Humans are not the only species facing a potential threat from SARS-CoV-2, the novel coronavirus that causes COVID-19, according to a new study from the University of California, Davis.

An international team of scientists used genomic analysis to compare the main cellular receptor for the virus in humans -- angiotensin converting enzyme-2, or ACE2 -- in 410 different species of vertebrates, including birds, fish, amphibians, reptiles and mammals.



ACE2 is normally found on many different types of cells and tissues, including epithelial cells in the nose, mouth and lungs. In humans, 25 amino acids of the ACE2 protein are important for the virus to bind and gain entry into cells.

A new genomic study ranks the potential of the SARS-CoV-2 spike protein to bind to the ACE2 receptor site in 410 vertebrate animals. Old World primates and great apes, which have identical amino acids at the binding site as humans, are predicted to have a very high propensity for binding ACE2 and are likely susceptible to SARS-CoV-2 infection. **Matt Verdolivo/UC Davis**

The researchers used these 25 amino acid sequences of the ACE2 protein, and modeling of its predicted protein structure together with the SARS-CoV-2 spike protein, to evaluate how many of these amino acids are found in the ACE2 protein of the different species.

"Animals with all 25 amino acid residues matching the human protein are predicted to be at the highest risk for contracting SARS-CoV-2 via ACE2," said Joana Damas, first author for the paper and a postdoctoral research associate at UC Davis. "The risk is predicted to decrease the more the species' ACE2 binding residues differ from humans."

About 40 percent of the species potentially susceptible to SARS-CoV-2 are classified as "threatened" by the International Union for Conservation of Nature and may be especially vulnerable to human-to-animal transmission. The study was published Aug. 21 in the *Proceedings of the National Academy of Sciences*.

"The data provide an important starting point for identifying vulnerable and threatened animal populations at risk of SARS-CoV-2 infection," said Harris Lewin, lead author for the study and a

distinguished professor of evolution and ecology at UC Davis. "We hope it inspires practices that protect both animal and human health during the pandemic."

Endangered species predicted to be at risk

Several critically endangered primate species, such as the Western lowland gorilla, Sumatran orangutan and Northern white-cheeked gibbon, are predicted to be at very high risk of infection by SARS-CoV-2 via their ACE2 receptor.

Other animals flagged as high risk include marine mammals such as gray whales and bottlenose dolphins, as well as Chinese hamsters.

Domestic animals such as cats, cattle and sheep were found to have a medium risk, and dogs, horses and pigs were found to have low risk for ACE2 binding. How this relates to infection and disease risk needs to be determined by future studies, but for those species that have known infectivity data, the correlation is high.

In documented cases of SARS-COV-2 infection in mink, cats, dogs, hamsters, lions and tigers, the virus may be using ACE2 receptors or they may use receptors other than ACE2 to gain access to host cells. Lower propensity for binding could translate to lower propensity for infection, or lower ability for the infection to spread in an animal or between animals once established.

Because of the potential for animals to contract the novel coronavirus from humans, and vice versa, institutions including the National Zoo and the San Diego Zoo, which both contributed genomic material to the study, have strengthened programs to protect both animals and humans.

"Zoonotic diseases and how to prevent human to animal transmission is not a new challenge to zoos and animal care professionals," said co-author Klaus-Peter Koepfli, senior research scientist at Smithsonian-Mason School of Conservation and former conservation biologist with the Smithsonian Conservation Biology Institute's Center for Species Survival and Center for Conservation Genomics.

"This new information allows us to focus our efforts and plan accordingly to keep animals and humans safe."

The authors urge caution against overinterpreting the predicted animal risks based on the computational results, noting the actual risks can only be confirmed with additional experimental data. The list of animals can be found here.

Research has shown that the immediate ancestor of SARS-CoV-2 likely originated in a species of bat. Bats were found to be at very low risk of contracting the novel coronavirus via their ACE2 receptor, which is consistent with actual experimental data.

Whether bats directly transmitted the novel coronavirus directly to humans, or whether it went through an intermediate host, is not yet known, but the study supports the idea that one or more intermediate hosts was involved. The data allow researchers to zero in on which species might have served as an intermediate host in the wild, assisting efforts to control a future outbreak of SARS-CoV-2 infection in human and animal populations.

Additional authors on the study include: Marco Corbo, UC Davis Genome Center; Graham M. Hughes and Emma C. Teeling, University College Dublin, Ireland; Kathleen C. Keough and Katherine S. Pollard, UC San Francisco; Corrie A. Painter, Nicole S. Persky, Diane P. Genereux, Ross Swofford, Kerstin Lindblad-Toh and Elinor K. Karlsson, Broad Institute of MIT and Harvard, Cambridge, Massachussetts; Michael Hiller, Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany; Andreas R. Pfenning, Carnegie Mellon University, Pittsburgh; Huabin Zhao, Wuhan University, Wuhan, China; Oliver A. Ryder, San Diego Zoo Institute for Conservation Research, Escondido, and UC San Diego; Martin T. Nweeia, Harvard School of Dental Medicine, Boston, and Smithsonian Institution, Washington D.C.

The research in this study was coordinated as part of the Genome 10K Organization, which includes the Bat1K, Zoonomia, the Vertebrate Genomes Project and the Earth BioGenome Project. Genomic information for the study was also provided the National Center for Biotechnology Information's GenBank, the San Diego Zoo's Frozen Zoo and the Smithsonian's Global Genome Initiative. This work was supported by the Robert and Rosabel Osborne Endowment.

https://bit.ly/2QkoUv0

Researchers validate rapid tests to detect dengue, Zika, yellow fever and other viruses

The method identifies and distinguishes between flaviviruses that cause many diseases in humans and animals in Brazil.

There are more than 70 species of flavivirus, and many cause diseases in humans and animals, including dengue, Zika and yellow fever viruses. A novel flavivirus identification test that is both fast and sensitive has been validated in Brazil by Mariana Sequetin Cunha and collaborators at the Adolfo Lutz Institute, a leading epidemiological surveillance laboratory that reports to the São Paulo state government.

An article on the topic has been published in Archives of Virology.

The research was supported by São Paulo Research Foundation - FAPESP via a Thematic Project, for which the principal investigator (PI) was Maurício Lacerda Nogueira, and a Regular Research Grant for which the PI was Paulo Cesar Maiorka.

"We set out to improve the monitoring of flaviviruses in Brazil by means of a reliable method. To this end, we used the RT-qPCR assay technique," Sequetin told. RT-qPCR stands for reverse transcription quantitative polymerase chain reaction. The laboratory technique combines reverse transcription of RNA into DNA and amplification of specific DNA targets using polymerase chain reaction. It is considered the gold standard for rapid identification of viruses and is recommended by the World Health Organization for diagnosing infection by SARS-CoV-2.

"Until recently, the main method used in Brazil to identify flaviviruses required inoculating the brains of newborn mice with suspected material sampled from human patients or animals," Sequetin said. "When I joined the Adolfo Lutz Institute as a researcher in 2012, I decided to establish an alternative method that would not require the mice but would submit the patient's blood, serum or viscera sample directly to RT-qPCR."

The key question was whether RT-qPCR would be sensitive enough to detect small amounts of viruses in the samples analyzed. Sequetin recalled that the Adolfo Lutz Institute maintained a large number of deep-frozen mice that had been inoculated in the 1990s and stored at -80 °C. "I extracted genetic material from their brains and sought the threshold for detection of different flaviviruses by preparing increasingly dilute solutions," she said.

The protocol established was shown to be highly sensitive and specific. It can be used to detect the different flaviviruses that occur in Brazil and for viral monitoring in sentinel animals and vectors.

"We're going to test it on new samples that we're receiving. I expect to find flaviviruses not described in the literature, especially in mosquitos," Sequetin said.

https://bit.ly/34qjxTh

A 70 degree shift on Jupiter's icy moon Europa was the last event to fracture its surface

Europa's outer icy shell has completely reoriented itself in one of the last geologic events recorded on its young surface.

Europa's poles are not where they used to be. Cracks in the surface of Jupiter's icy moon indicate its shell of ice rotated by 70 degrees sometime in the last several million years. In addition to supporting prior evidence for the existence of a subsurface ocean, it also means that the geologic history of Europa's surface must be reexamined.

New research, led by Universities Space Research Association's Senior Staff Scientist Dr. Paul Schenk at the Lunar and Planetary Institute (LPI), confirms that Europa's large global scale circular patterns formed during a large reorientation of the its icy outer shell with respect to its spin axis, a process known as true polar wander. This can only happen if the icy shell is uncoupled, or floating free, separated from the rocky core of the planet by a liquid water ocean.

The findings were published July 29, 2020 in *Geophysical Research Letters*.

"Our key finding is that the fractures associated with true polar wander on Europa cross-cut all terrains. This means that the true polar wander event is very young and that the ice shell and all features formed on it have moved more than 70° of latitude from where they first formed," reports Dr. Schenk. "If true, then the entire recorded history of tectonics on Europa should be reevaluated."

Using a combination of global maps from Galileo and Voyager data with improved precision, and detailed topographic data derived from them, a team of scientists from the LPI in Houston, the University of California at Santa Cruz, and the University of Arizona in Tucson have correlated large fractures on the surface of Europa with previously identified concentric circular depressions on the surface.

NASA's Galileo spacecraft orbited Jupiter from 1995 to 2003 and returned hundreds of images of Europa's surface. Reconstruction of the global map of Europa at 200-meter resolution in color in preparation for a return to Europa revealed that these mysterious fracture systems were part of the circular true polar wander patterns identified previously. Topographic mapping in the highest resolution images of the fractures at 40 meters per pixel show that the fractures are more than 200 meters deep. The fractures cut through all known terrains and thus show that the deformation related to the global reorientation (or true polar wander) event was one of the last events to occur on Europa. These features also imply that the floating ice shell on Europa may have thickened over time.

"Another important aspect of this work is that it makes predictions for additional features and ice shell properties which can be tested when the planned Europa Clipper spacecraft starts observing Europa," says coinvestigator Francis Nimmo at the University of California at Santa Cruz.

"In addition to generating global-scale tectonic features, true polar wander also produces global-scale gravity and shape perturbations, which affects gravity and shape constraints on the interior structure," says coinvestigator Isamu Matsuyama at the University of Arizona.

These too can be searched for and tested when Europa Clipper arrives later this decade. Europa Clipper will complete the map of Europa, including high-resolution images and soundings of these features. These maps will help determine the absolute age of these fractures and depressions and other consequences of the polar wander event that created them.

Paul Schenk et al. A Very Young Age for True Polar Wander on Europa from Related Fracturing, Geophysical Research Letters (2020). DOI: 10.1029/2020GL088364

https://bit.ly/32mD0BB

Scientists Just Discovered Another Trick Bacteria Use to Avoid The Immune System

Bacteria release toxins to disarm the mitochondria in immune cells, which triggers apoptosis

David Nield

For their own self-preservation, infectious bacteria often try their best to stay out of the way of the immune system in our bodies – and scientists have found a surreptitious and previously undiscovered way that they do this.

What happens is that the bacteria release toxins to disarm the mitochondria in immune cells, those tiny organelles that act as the engine rooms of cells. Once the immune cells sense that their mitochondria are inactive, they trigger apoptosis or programmed cell death.

The findings could give us new ways of tackling infectious bacteria, particularly those that have grown resistant to antibiotics – although

up to this point, experiments have only been carried out on mice in the laboratory.

"Ironically, it is the activation of host cell death factors that deliver the final blow to mitochondria which induces apoptosis, not the bacterial toxins themselves," says molecular biologist Pankaj Deo from the Monash Biomedicine Discovery Institute (MBDI) in Australia.

In other words, the bacteria toxins aren't directly killing immune cells, but rather setting in motion a chain of events that causes our body's emergency responders to kill themselves. Our immune cells are using mitochondria as infection sensors.

That was the case in tests on mice described in this study: by targeting genetic controls for apoptosis in the rodents, the scientists were able to reduce inflammation in the animals and lower the risk of infection.

The bacterial pathogens *Neisseria gonorrhoeae*, uropathogenic *Escherichia coli*, and *Pseudomonas aeruginosa* were the ones tested – all of which are commonly found in hospitals and can develop resistance to drugs – but the team says the findings would also apply to other species of bacteria.

"We've shown in this paper that we can accelerate the immune response," says molecular biologist Thomas Naderer from MBDI.

"The other side is that if that response persists and we get constant inflammation – which is usually associated with bacterial infection and which causes a lot of tissue damage – we have a new way to shut down that tissue-damaging inflammation."

Previously, attention had been focussed on bacterial toxins that created a different type of automatic cell death, called pyroptosis. Here, the researchers have spotted other mitochondria-targeting toxins wrapped up in structures called outer membrane vesicles.

Now that we know more about how the mitochondria are being targeted, scientists might be able to stop it. Further trials will be needed on humans to work out exactly what's going on at the microorganism level, but it's possible that existing drugs could be reengineered and new drugs could be developed to fight off infection.

With pathogens becoming smarter and smarter when it comes to dodging the drugs we send in to beat them – as well as evading the body's own defences – any new innovations in treatment could make a significant difference.

"There's been a lot of effort trying to block endotoxins that kill immune cells, but this study really shifts the focus onto different toxins that might be more important," says Naderer. "It gives us a few good leads that we can look at as a next step."

The research has been published in *Nature Microbiology*.

https://bit.ly/2Exea9D

Blood pressure medication improves COVID-19 survival rates

Researchers studying 28,000 patients taking antihypertensives find medication for high blood pressure could improve Covid-19 survival rates and reduce the severity of infection

Peer reviewed - meta-analysis - humans

Medication for high blood pressure could improve Covid-19 survival rates and reduce the severity of infection - according to new research from the University of East Anglia. Researchers studied 28,000 patients taking antihypertensives - a class of drugs that are used to treat hypertension (high blood pressure).

They found that the risk of severe Covid-19 illness and death was reduced for patients with high blood pressure who were taking Angiotensin-Converting Enzyme inhibitors (ACEi) or Angiotensin Receptor Blockers (ARB).

Lead researcher Dr Vassilios Vassiliou, from UEA's Norwich Medical School, said: "We know that patients with cardiovascular diseases are at particular risk of severe Covid-19 infection. But at

the start of the pandemic, there was concern that specific medications for high blood pressure could be linked with worse outcomes for Covid-19 patients.

"We wanted to find out what the impact of these medications is for people with Covid-19. "We therefore studied the outcomes for patients taking antihypertensives - looking particularly at what we call 'critical' outcomes such as being admitted to intensive care or being put on a ventilator, and death."

The research was led by UEA in collaboration with the Norfolk and Norwich University Hospital. The team analysed data from 19 studies related to Covid-19 and ACEi and ARB medications. The meta-analysis involved more than 28,000 patients and is the largest and most detailed such study to date.

They compared data from Covid-19 patients who were taking ACEi or ARB medications with those who were not - focusing on whether they experienced 'critical' events (admission to intensive care and invasive or non-invasive ventilation) and death.

Dr Vassiliou said: "We found that a third of Covid-19 patients with high blood pressure and a quarter of patients overall were taking an ACEi/ARBs. This is likely due to the increasing risk of infection in patients with co-morbidities such as cardiovascular diseases, hypertension and diabetes.

"But the really important thing that we showed was that there is no evidence that these medications might increase the severity of Covid-19 or risk of death.

"On the contrary, we found that there was a significantly lower risk of death and critical outcomes, so they might in fact have a protective role - particularly in patients with hypertension.

"Covid-19 patients with high blood pressure who were taking ACEi/ARB medications were 0.67 times less likely to have a critical or fatal outcome than those not taking these medications.

"As the world braces itself for a potential second wave of the infection, it is particularly important that we understand the impact that these medications have in Covid-19 patients.

"Our research provides substantial evidence to recommend continued use of these medications if the patients were taking them already.

"However, we are not able to address whether starting such tablets acutely in patients with Covid-19 might improve their prognosis, as the mechanism of action might be different," he added.

'Effect of Renin-Angiotensin-Aldosterone System inhibitors in patients with COVID-19: a systematic review and meta-analysis of 28,872 patients' is published in the journal Current Atherosclerosis Reports on August 24, 2020.

https://bit.ly/2Eq51zQ

Fewer fungi types in lungs linked to worse disease in acute respiratory distress syndrome

Having fewer different types of fungi in the lungs is linked to increased severity of disease in ARDS patients.

Many COVID-19 patients develop acute respiratory distress syndrome (ARDS), a life-threatening condition where the lungs cannot provide the body's vital organs with enough oxygen. Patients with ARDS are usually placed on ventilators to help get enough oxygen into their bodies. Now, new research presented at the 'virtual' European Respiratory Society International Congress [1] has found that having fewer different types of fungi in the lungs is linked to increased severity of disease in ARDS patients.

The human microbiome [2] is made up of tiny organisms such as bacteria, viruses and fungi. Presenting her research to the meeting, Ms Noel Britton, a PhD candidate at the University of Pittsburgh, USA, said that up to now researchers had tended to concentrate on studying the effects of bacteria on human health, partly because the microbiome is primarily composed of bacteria and there are technical difficulties in extracting enough fungi to study.

"In terms of numbers of cells, fungi are outnumbered by bacteria by several orders of magnitude," she said. "Additionally, while it is now well established that the lungs play host to a distinct and dynamic microbiome, they don't represent a rich environment for microbes to thrive, and they generally have many fewer microbes than the gut--the body site where scientists have focused the most microbiome research. It can be difficult to pick up a signal from such a low mass of fungi and to be sure that the sequences identified are not due to contamination in the laboratory.

"We wanted to carry out this research as acute respiratory distress syndrome is characterised by a hyper-inflammatory over-reaction of the immune system and we know that fungi can be involved in activating and regulating the human immune system. There are no known therapies for the successful treatment of ARDS and very little is known about why some patients have a hyper-inflammatory response. The diversity of the microbiome, and specifically of fungi, may play an important role in understanding why some patients develop ARDS and some do not."

Ms Britton and her colleagues enrolled 202 mechanically-ventilated patients in the study between October 2011 and September 2019. As far as they know, none of these patients had COVID-19 but they are continuing to enrol patients through the pandemic and a future analysis will look at those with confirmed COVID-19.

Of the 202 patients in this analysis, 21% had a diagnosis of ARDs, the average age was 50 years old and 61% were women. The researchers collected mucus-based secretions from the trachea (the main airway leading down to the lungs) and extracted DNA to analyse in the laboratory using a technique called next generation sequencing.

Ms Britton said: "We identified about 100 different types of fungi in the lungs of mechanically-ventilated, critically ill patients. The diversity was quite low in all of the samples, but in samples in which a single species dominated, the diversity was very low. A large number of patients had samples that were dominated by a single fungal species from the Candida type; this made up more than 50% of the fungi present in these samples and it is known to be involved in causing disease in humans."

Fungal diversity was lower in ARDS patients than in those without the disease. In ARDS patients, shock, sepsis and organ failure were associated with lower diversity. Decreased diversity was linked with worse injury to the lungs, more intensive treatment and elevated levels of a protein called pentraxin-3, which is an indicator of inflammation and disease severity.

"The association of lower fungal diversity with clinical markers of disease severity is an important finding because it provides evidence for a relationship between the lung microbiome and clinical outcomes in critical illness," said Ms Britton. "We will continue to investigate this further because there is much that is not understood about the development and treatment of ARDS and this study may point us towards an important diagnostic or treatment-based discovery."

It is not known how fungal (or other microorganism) diversity develops, but fungi are most likely to enter the lungs through inhaling tiny amounts of saliva into the lungs.

"As the human body's second-largest mucosal surface area, roughly the same size as a tennis court, human lungs are constantly exposed to fungi through inhalation," said Ms Britton. "Airborne fungi are especially prevalent, comprising up to 50,000 spores per cubic metre of air, and so the respiratory tract is exposed to a wide variety. Inhaled fungi can be extremely diverse and include species known to be disease-causing as well as those believed to be harmless in humans."

Tobias Welte, who was not involved in the research, is the European Respiratory Society Past President, Professor of

Pulmonary Medicine and Director of the Department of Pulmonary and Infectious Diseases at Hannover University School of Medicine, Germany. He said: "In the last few years much attention has focused on the microbiome, particularly in the gut, and its relationship to a variety of health problems. Fungi are harder to study than other components of the lung microbiota, such as bacteria and viruses, but we're starting to see more evidence that they also have a role in chronic lung disease.

"The finding from this study, that less diversity in the mycobiome is linked to worse outcomes for patients with acute respiratory distress syndrome, is fascinating. It's too early to know what this might mean for patients and their doctors, but it has the potential to lead to new diagnostic tests and better treatments."

[1] Abstract no: 3044, "Diversity of the lung microbiome is associated with severity of disease in acute respiratory distress syndrome", by Noel Britton et al; Online from Monday 24 August and presented in the "New insights into mechanical ventilation in the intensive care unit" session at 09.30 hrs CEST on Monday 7 September: https://k4.ersnet.org/prod/v2/Front/Program/Session?e=259&session=12387

[2] The human microbiome is the collective genetic material of the community of micro-organisms (such as bacteria, viruses and fungi) that live in and on our bodies. The term "microbiota" usually refers to the bacteria, fungi and viruses themselves, while the term "microbiome" usually refers to the genetic material.