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Evidence shows human transmission in deadly outbreak of mysterious disease in Bolivia

At TropMed2020, scientists describe rush to gauge risks of Chapare virus, an emerging hemorrhagic fever seen previously in only one patient

Arlington, Va. - Researchers have discovered that a deadly virus found in Bolivia can spread from person to person in healthcare settings, raising potential concerns of additional outbreaks in the future, according to new findings presented today at the annual meeting of the American Society of Tropical Medicine and Hygiene (ASTMH). The research also provides preliminary evidence regarding the species of rodent that carries the virus and may spread it to people or to other animals that can infect humans.

Researchers from the U.S. Centers for Disease Control and Prevention (CDC) laid out new clues to the many mysteries surrounding the Chapare virus, which caused at least five infections near Bolivia's capital city, La Paz, in 2019--three of them fatal. Prior to that, the only record of the disease was a small cluster and a single confirmed case in 2004 in Bolivia's Chapare Province, about 370 miles east of La Paz. The recent outbreak surprised health authorities, since initially all they knew was that it was a hemorrhagic fever that produced symptoms similar to diseases such as Ebola. It sparked a rapid mobilization of infectious disease experts from Bolivia's Ministry of Health, the CDC and the Pan-American Health Organization (PAHO) to explore the origins of the disease, including securing samples from patients and developing a new diagnostic test.

"Our work confirmed that a young medical resident, an ambulance medic and a gastroenterologist all contracted the virus after encounters with infected patients--and two of these healthcare workers later died," said Caitlin Cossaboom, DVM, PhD, MPH, an epidemiologist with the CDC's Division of High-Consequence Pathogens and Pathology. "We now believe many bodily fluids can potentially carry the virus."

Cossaboom said the confirmation of human-to-human transmission shows healthcare providers and anyone else dealing with suspected cases must take extreme care to avoid contact with items that may be contaminated with blood, urine, saliva or semen. For example, there is evidence that the medical resident who died from the disease may have been infected while suctioning saliva from a patient. The ambulance medic who was infected, but survived, was likely infected when he resuscitated the same medical resident as she was being transported to the hospital after she fell ill. Researchers also detected viral RNA in the semen of one survivor 168 days after infection, which also raises the possibility of sexual transmission. Further investigation is necessary to learn about other potential routes of transmission.

Chapare belongs to a group of viruses called arenaviruses. They include dangerous pathogens such as Lassa virus, which causes thousands of deaths annually in West Africa, and Machupo virus, which has caused deadly outbreaks in Bolivia. Like those pathogens, Chapare virus can cause hemorrhagic fevers--a condition also seen in Ebola patients that can produce severe problems across multiple organs, leaving patients struggling to survive. Cossaboom noted that patients in the 2019 Chapare outbreak suffered fevers, abdominal pain, vomiting, bleeding gums, skin rash and pain behind the eyes. There is no specific treatment, so patients are treated mainly with intravenous fluids and other supportive care.

There is still much that remains unknown about Chapare virus, chiefly where it originated, how it infects humans, and the likelihood of larger outbreaks in Bolivia and elsewhere in South America. Cossaboom presented new evidence of Chapare viral RNA detected in rodents collected from an area around the home

and nearby farmlands of the first patient identified in the 2019 outbreak--an agriculture worker who also died. She cautioned that the evidence stops well short of proving the rodents were the source of his infection--viral RNA is not proof that the rodents were infectious--though it offers an important clue.

"The genome sequence of the RNA we isolated in rodent specimens matches quite well with what we have seen in human cases," she said.

The rodent species that tested positive for viral RNA, commonly known as the pigmy rice rat and the small-eared pigmy rice rat, are found across Bolivia and several neighboring countries. Rodents are a key source or reservoir of similar viruses, including Lassa virus.

Scientists believe the Chapare virus could have been circulating in Bolivia for several years, but infected patients may have been wrongly diagnosed as suffering from dengue, a disease that is common in the region and can produce similar symptoms.

All-Hands on Deck to Solve a Deadly Mystery

Cossaboom's colleague at the CDC, Maria Morales-Betoulle, PhD, described an intensive effort involving Bolivian health officials in La Paz, scientists from the Bolivian Center for Tropical Diseases (CENETROP) in Santa Cruz de la Sierra, colleagues at PAHO and infectious disease experts at CDC headquarters in Atlanta to get a handle on the 2019 outbreak. She said that when it became clear the illness was not caused by dengue, patient samples collected by Bolivian authorities were quickly dispatched to a highly secure biosafety level 4 (BSL-4) CDC laboratory. Once there, they were subjected to analysis with advanced next generation genome sequencing technology. CDC experts were able to identify the virus as Chapare because it matched sequence data derived from the patient involved in the original 2004 infection.

"We isolated the virus, and we were expecting to find a more common disease, but the sequence data pointed to Chapare virus," Morales-Betoulle said. "We were really surprised because the 2019 outbreak in La Paz occurred long after the first case was identified in 2004."

Morales-Betoulle said that the availability of new sequencing tools allowed CDC experts to rapidly develop an RT-PCR test for detecting Chapare--the same type of test often used to diagnose COVID-19, which is considered the gold standard for diagnostics.

The investigation then moved back to CENETROP in Santa Cruz de la Sierra, where there is a BSL-3 lab and team capable of securing and analyzing patient samples.

She said several collaborators on the team involved in the Chapare response already were in South America investigating other viral hemorrhagic fevers when the 2019 outbreak occurred.

"That allowed us to mobilize and move really quickly," she said.

Morales-Betoulle and Cossaboom said future work will focus on using the diagnostic tests to conduct surveillance to identify additional human infections and field work to determine whether rodents are involved in spreading the disease. Since the outbreak, CENETROP identified three additional suspected cases, including one involving a child. All are believed to have survived. Additional testing at CDC is anticipated.

"While there is still much that remains unknown about Chapare virus, it's commendable how quickly this team was able to develop a diagnostic test, confirm human-to-human transmission and uncover preliminary evidence of the virus in rodents," said ASTMH President Joel Breman, MD, DTPH, FASTMH. "It's a valuable lesson that international scientific teams, equipped with the latest tools and freely sharing their insights, are our best front-line defense against the disruptive threats of deadly infectious diseases."

https://bit.ly/36VumvZ

Actively speaking two languages protects against cognitive decline

Researchers conclude that regularly speaking two languages contributes to cognitive reserve and delays the onset of the symptoms associated with cognitive decline and dementia.

In addition to enabling us to communicate with others, languages are our instrument for conveying our thoughts, identity, knowledge, and how we see and understand the world. Having a command of more than one enriches us and offers a doorway to other cultures, as discovered by a team of researchers led by scientists at the Open University of Catalonia (UOC) and Pompeu Fabra University (UPF). Using languages actively provides neurological benefits and protects us against cognitive decline associated with ageing.

In a study published in the journal *Neuropsychologia*, the researchers conclude that regularly speaking two languages -and having done so throughout one's life- contributes to cognitive reserve and delays the onset of the symptoms associated with cognitive decline and dementia.

"We have seen that the prevalence of dementia in countries where more than one language is spoken is 50% lower than in regions where the population uses only language to communicate", asserts researcher Marco Calabria, a member of the Speech Production and Bilingualism research group at UPF and of the Cognitive NeuroLab at the UOC, and professor of Health Sciences Studies, also at the UOC.

Previous work had already found that the use of two or more languages throughout life could be a key factor in increasing cognitive reserve and delaying the onset of dementia; also, that it entailed advantages of memory and executive functions.

"We wanted to find out about the mechanism whereby bilingualism contributes to cognitive reserve with regard to mild cognitive impairment and Alzheimer's, and if there were differences regarding the benefit it confers between the varying degrees of bilingualism, not only between monolingual and bilingual speakers", points out Calabria, who led the study.

Thus, and unlike other studies, the researchers defined a scale of bilingualism: from people who speak one language but are exposed, passively, to another, to individuals who have an excellent command of both and use them interchangeably in their daily lives.

To construct this scale, they took several variables into account such as the age of acquisition of the second language, the use made of each, or whether they were used alternatively in the same context, among others.

The researchers focused on the population of Barcelona, where there is strong variability in the use of Catalan and Spanish, with some districts that are predominantly Catalan-speaking and others where Spanish is mainly spoken. "We wanted to make use of this variability and, instead of comparing monolingual and bilingual speakers, we looked at whether within Barcelona, where everyone is bilingual to varying degrees, there was a degree of bilingualism that presented neuroprotective benefits", Calabria explains.

Bilingualism and Alzheimer's

At four hospitals in the Barcelona and metropolitan area, they recruited 63 healthy individuals, 135 patients with mild cognitive impairment, such as memory loss, and 68 people with Alzheimer's, the most prevalent form of dementia. They recorded their proficiency in Catalan and Spanish using a questionnaire and established the degree of bilingualism of each subject. They then correlated this degree with the age at which the subjects' neurological diagnosis was made and the onset of symptoms.

To better understand the origin of the cognitive advantage, they asked the participants to perform various cognitive tasks, focusing primarily on the executive control system, since the previous

studies had suggested that this was the source of the advantage. In all, participants performed five tasks over two sessions, including memory and cognitive control tests.

"We saw that people with a higher degree of bilingualism were given a diagnosis of mild cognitive impairment later than people who were passively bilingual", states Calabria, for whom, probably, speaking two languages and often changing from one to the other is life-long brain training. According to the researcher, this linguistic gymnastics is related to other cognitive functions such as executive control, which is triggered when we perform several actions simultaneously, such as when driving, to help filter relevant information.

The brain's executive control system is related with the control system of the two languages: it must alternate them, make the brain focus on one and then on the other so as not to cause one language to intrude in the other when speaking.

"This system, in the context of neurodegenerative diseases, might offset the symptoms. So, when something does not work properly as a result of the disease, the brain has efficient alternative systems to solve it thanks to being bilingual", Calabria states, who then continues: "we have seen that the more you use two languages and the better language skills you have, the greater the neuroprotective advantage. Active bilingualism is, in fact, an important predictor of the delay in the onset of the symptoms of mild cognitive impairment, a preclinical phase of Alzheimer's disease, because it contributes to cognitive reserve".

Now, the researchers wish to verify whether bilingualism is also beneficial for other diseases, such as Parkinson's or Huntington's disease.

Reference work:

Marco Calabria, Mireia Hernández, Gabriele Cattaneo, Anna Suades, Mariona Serra, Montserrat Juncadella, Ramón Reñé, Isabel Sala, Alberto Lleó, Jordi Ortiz-Gil, Lidia Ugas, Asunción Ávila, Isabel Gómez Ruiz, César Ávila, Albert Costa (2020) "Active bilingualism delays the onset of mild cognitive impairment", Neuropsychologia, Vol. 146, 107528, ISSN 0028-3932, https://doi.org/10.1016/j.neuropsychologia.2020.107528

https://bit.ly/3nICG97

When temperatures rise, dog ticks more likely to choose humans over canines

New study presented at TropMed20 shows how climate change could expand and intensify the risk of disease that kills one in five if not treated early

Arlington, Va.- A variety of ticks that carry the bacteria causing the deadly disease Rocky Mountain spotted fever (RMSF) are more than twice as likely to shift their feeding preference from dogs to humans when temperatures rise, a sign that climate change could expand and intensify human disease risks, according to a new study presented today at the Annual Meeting of the American Society of Tropical Medicine and Hygiene (ASTMH).

"Our work indicates that when the weather gets hot, we should be much more vigilant for infections of RMSF in humans," said Laura Backus, MPH, DVM, who led the study at the University of California, Davis School of Veterinary Medicine (UC-Davis). "We found that when temperatures rose from about 74 to 100 degrees Fahrenheit, brown dog ticks that carry the disease were 2.5 times more likely to prefer humans over dogs."

Cases of RMSF and related diseases, collectively known as spotted fever rickettsiosis, have risen dramatically over the last 20 years. The disease is treatable with antibiotics if detected in the first week of infection, but once an infection takes hold, the fatality rate for RMSF victims can exceed 20%. Complications can include damaged blood vessels; inflammation of the heart, lungs or brain; and kidney failure. Over the last 10 years, public health authorities have been particularly alarmed by a rash of deadly RMSF outbreaks among indigenous communities in Arizona and northern Mexico.

Backus said there have been indications from earlier work that

brown dog ticks, which are found throughout the continental United States, may be more aggressive toward humans in hot weather. And scientists warn that climate change is greatly expanding areas of the country experiencing multiple days when temperatures top 100 degrees Fahrenheit, or about 38 degrees Celsius. Backus and her colleagues at UC-Davis wanted to gain more definitive insights into how rising temperatures might elevate the risk of RMSF infections.

For their experiment, they constructed two large wooden boxes measuring about 3 feet tall and 2 feet wide, which were then connected to each other by a clear plastic tube. They conducted a series of tests that involved putting a human in one box, a dog in the other and ticks in the clear plastic tube between them. The researchers then observed, over 20-minute intervals, whether the ticks, which seek out hosts to feed on based on smell, preferred dogs or humans--first at temperatures of around 74 degrees Fahrenheit (23.3 degrees Celsius) and then at 100 degrees Fahrenheit (37.8 degrees Celsius).

Backus said that at the higher temperature, one type of brown dog tick, known as the tropical lineage tick, was especially decisive in shifting its preferences from dogs to humans. Currently, tropical lineage brown dog ticks are found across the southern regions of the United States, in places like Arizona, Florida, southern California and southern Georgia. However, Backus said that their range is expected to move northward as climate change causes average temperatures to rise.

Brown dog ticks belonging to another lineage, the temperate lineage, are found throughout the lower 48 states and may also carry RMSF. Backus said that while the temperate ticks showed only a slight increase in preference for humans over dogs in the higher temperature test, they exhibited a pronounced decrease in their preference for dogs. Many ticks simply shifted from clearly pro-dog to neutral--they did not move toward either subject.

"We believe that this decreased preference for dogs--combined with a slight increase in preference for humans--suggests that hot temperatures may also elevate risks of RMSF in areas where the temperate ticks are more common," Backus said.

She added that it's important to identify conditions that can increase infection risks--and put health officials on higher alert--because symptoms in the crucial early phase of RMSF, when it's relatively easy to treat, can be mistaken for a number of more common ailments. They include headache, fever and muscle aches. Backus said there is also a need for better diagnostic tests since the existing test is time-consuming and may produce false negatives.

"The findings from the use of this simple but effective laboratory experiment to gauge how rising temperatures might lead to more human infections with a very dangerous tick-borne pathogen adds to the growing evidence of the increasing connection between climate change and its impact on health," said ASTMH President Joel Breman, MD, DTPH, FASTM. "Climate change is moving so quickly that it is critical to keep pace with the many ways it may alter and intensify the risk of a wide range of infectious diseases so we are better prepared to diagnose, treat and prevent them."

https://bit.ly/3fkrKLU

Scientists Failed to Use Common Sense Early in the Pandemic

The WHO's initial advice not to wear masks in the fight to contain COVID sowed dangerous confusion

By Naomi Oreskes

As a scientist and historian of science, I get asked a lot by friends and family to comment on scientific questions. Are vaccines safe? Is red meat bad for you? How much time do we have left to fix climate change?

Many of these matters are not nearly as complicated as they have sometimes been made out to be. Vaccination is broadly safe for

most people; eating large amounts of red meat is associated with higher rates of death from a number of cancers; and scientists think we have about a decade left to get greenhouse gas emissions under control and avoid the worst consequences.

Lately nearly all the questions involve COVID-19—particularly the matter of masks. The argument for wearing them is pretty straightforward: viruses are spread in droplets, which are expelled when an infected person talks, shouts, sings or just breathes. A properly constructed and fitted mask can prevent the spread of those droplets and therefore the spread of the virus. That is why surgeons have been routinely wearing medical-grade masks since the 1960s (and many doctors and nurses wore cloth masks long before then). It is also why in many parts of Asia, people routinely wear masks in public.

A flimsy or poorly fitting face covering may not be much use, but—barring the risk of generating a false sense of security—it is unlikely to do harm.

So it stands to reason that, when in public, most people should wear masks. The U.S. Centers for Disease Control and Prevention summarizes: "Masks are recommended as a simple barrier to help prevent respiratory droplets from traveling into the air.... This is called source control."

So why are people confused?

One reason is that we have been getting conflicting messages. In April the World Health Organization told the general public not to mask, while the CDC told us we should. In June the WHO adjusted its guidance to say that the general public should wear nonmedical masks where there was widespread community transmission and physical distancing was difficult. Meanwhile CDC director Robert R. Redfield declared that "cloth face coverings are one of the most powerful weapons we have to slow and stop the spread of the virus—particularly when used universally." Today government guidance around the globe varies from masks only for sick people to masks mandatory for all.

Why the contradictory messaging? In particular, why did the WHO say in April not to wear masks? At the time, there was a severe shortage of personal protective equipment; the WHO evidently feared that ordinary people would rush out to buy masks, denying them to medical personnel. According to one report, officials were also concerned that widespread masking would lead to a false sense of security, leading people to ignore other safety measures, such as handwashing and self-isolation.

If the WHO had simply said this, there would have been a lot less confusion. But apparently there was another problem. At the time, no direct evidence existed regarding community spread of this particular virus, and most previous studies were done in clinical settings. The WHO put it this way: "There is currently no evidence that wearing a mask (whether medical or other types) by healthy persons in the wider community setting, including universal community masking, can prevent them from infection with respiratory viruses, including COVID-19."

This is a common pattern in science: conflating the absence of evidence with evidence of absence. It arises from the scientific norm of assuming a default hypothesis of no effect and placing burden of proof of those asserting an affirmative claim. Usually this makes sense: we do not want to overturn established science on the basis of an assertion or speculation. But when public health and safety are at stake, this standard becomes priggish. ***If we have evidence that something may help—and is unlikely to do harm—there is little excuse for not recommending it.*** And when there is a mechanistic reason to think it might help, the lack of clinical trials should not be a barrier to acting on mechanistic knowledge.

One epidemiologist offered some common sense: "Randomized

trials don't support a big effect of face masks, but there is the mechanistic plausibility for face masks to work.... So why not consider it?"

In nearly all areas of science, our evidence is imperfect or incomplete, but this is no excuse not to act on what we know.

https://go.nature.com/3fiZycm

For better health, don't sleep your age

Older people with 'young' sleep patterns have more robust cognition than those whose rest is typical for their age.

Older people with sleep patterns like those of younger people tend to be in better physical and cognitive health than those with disrupted sleep.

Shaun Purcell at Harvard Medical School in Boston, Massachusetts, and his colleagues tracked the sleep of 3,819 people between 54 and 96 years old by recording their brain waves through electroencephalogram sensors that the participants wore throughout the night.

The researchers then scored each person's sleep for more than 150 sleep characteristics and brain-activity patterns. These included factors such as sleep disturbance, the length of the sleep cycles in which dreams occur and preference for mornings or evenings.

The team found that older people with 'young' sleep patterns tend to have stronger cognitive abilities and a lower incidence of some health problems than do older people whose sleep patterns more closely reflect their age.

Although it is unclear whether the better sleep improves health or vice versa, the researchers say that techniques such as electrical stimulation of the brain might modify sleep patterns in older people and improve their health.

Nature Hum. Behav. (2020)

https://bit.ly/3nF7lEq

Microscopic worms pee milk on their children as their bodies decompose

C. elegans turn their aging bodies into food for their children

Brittney G. Borowiec

In a new preprint on *bioRxiv*, researchers based in the U.K. report that nematodes (*Caenorhabditis elegans*) give their offspring a head start in life by peeing milk on them.

It's actually not milk in the strictest *sense* of the world – milk comes for the mammary glands of mammals — but the worms are passing a nutritious, liquid food from parent to baby.

But how does a 1 mm long worm with less than 1000 cells make a nutritional supplement for its young?

Adult *C. elegans* live a short life. Within a few days of reaching sexual maturity, their bodies break down and stop functioning, a process called senescence. Their intestine atrophies into a fatty, yolk-like material and their muscles fragment into pieces. Researchers used to chalk up the appearance of the yolk mass as just a weird thing that happened as the worm aged, like how you pull muscles from standing up wrong. Old nematode bodies hold together enough to make yolk, but degeneration of other parts of the reproductive system eventually inhibit successful egg-laying. (Interestingly, if a fertilized egg is not laid within about 12.5 hours, it hatches inside the worms body, where it then eats and kills its parent.)

The decomposing goo isn't wet garbage after all: it's worm milk. Post-reproductive mother worms vent the yolk through their vulva and on to their offspring, providing them with a boost of nutrients to support their growth.

What's more is the worm's lactation and senescence processes involve some of the same biological machinery (through the insulin/IGF-1 signaling pathway). This suggests that these two

processes are closely related — nematodes don't just happen to make yolk as they get old; self-decomposition linked with yolk production evolved to as a way of passing on as much of their energy as possible to their offspring.

https://bit.ly/36YiMQO

Teaching and complex tools 'evolved together'

The human ability to teach and our use of complex tools may have evolved together, according to new research.

The improvement of technologies across generations, known as "cumulative cultural evolution", is central to our success as a species—but its origins are a mystery.

The new study, led by the University of Exeter, tested the power of teaching on the development of simple and more complex tools—and found teaching stands out when tackling complicated problems. This suggests that, as early humans developed more complex tools, natural selection began to favour those who could teach.

"Humans have an unrivalled ability to pass knowledge down the generations," said senior author Dr. Alex Thornton, of the Centre for Ecology and Conservation on Exeter's Penryn Campus in Cornwall.

"Traditional theories assumed that cumulative cultural evolution requires specialised processes, like teaching, to transmit information accurately, but this cannot explain why these processes evolved in the first place.

"Our aim in this study was to test the hypothesis that these processes gradually 'co-evolved' with an increasing reliance on complex tools."

More than 600 people took part in the study, forming "chains" to develop a simple tool (a boat made of waterproof paper) or a more complex tool (a basket made of pipe cleaners).

All tools were used to carry marbles, with success measured by number of marbles carried.

The development chain involved ten "generations"—ten versions of the tool being made.

Each participant either saw the tool made by the previous person in the chain, watched the previous person make the tool (and could thus imitate and learn from them) or spoke to the previous participant—allowing teaching to take place.

"Simple and complex tools generally improved down the 'generations', and for simple tools this improvement was about the same in all three study conditions," said Dr. Amanda Lucas, of the University of Exeter.

Ten versions of tools developing (left to right) in the different study conditions. **Credit: University of Exeter**

"With complex tools, teaching consistently led to more improvement compared to other conditions.

"Teaching seemed to be particularly useful in allowing new, high-performing designs to be transmitted."

Dr. Lucas added: "We are incredibly grateful to local community groups across Cornwall who took part in the research, including Women's Institutes, sports clubs, craft societies, museums, theatres, galleries, libraries and community gardeners.

"This meant that our study represented a diversity of ages, backgrounds and skills, which is important as many of these types of experiments, that intend to investigate something essential about being human, recruit a narrower sample of university students only."

Dr. Alex Thornton continued: "The effects we found were gradual—but the idea here was to look at the origins of cumulative cultural evolution, and over many generations these gradual improvements would add up.

"Our findings point to an evolutionary feedback loop between tool-making and teaching.

"This suggests that our ancestors could have started to make modest cumulative improvements to simple tools without the need for teaching, but as tools became more complex, teaching started to become advantageous.

"The evolution of improved teaching skills would in turn allow the production of even more complex and effective tools."

The study also found that simple tools tended to "converge" towards a common design, while complex tools remained diverse and different—reflecting the diversity of technologies across human societies today.

The paper, published in the journal *Proceedings of the Royal Society B*, is entitled: "The value of teaching increases with tool complexity in cumulative cultural evolution."

More information: *The value of teaching increases with tool complexity in cumulative cultural evolution, Proceedings of the Royal Society B (2020). rspb.royalsocietypublishing.or … .1098/rspb.2020.1885*

https://go.nature.com/3kR8Eyq

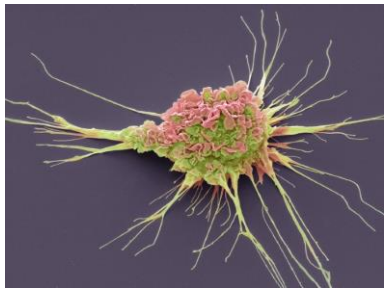
How the microbiome rouses the body's virus-fighting powers

A molecule on the surface of a common gut microbe helps to activate genes involved in the immune response.

Bacteria that thrive in the guts of humans and other mammals make a molecule that goads crucial immune cells into action, thus helping to repel invasive viruses.

The mammalian gut is occupied by trillions of harmless bacteria, including the abundant species *Bacteroides fragilis*.

To investigate the microbiome–host relationship, Dennis Kasper at Harvard Medical School in Boston, Massachusetts, and his colleagues analysed how a molecule in *B. fragilis*'s outer membrane affects the immune system of mice. The team looked in particular at the rodents' dendritic cells, which act as the scouts of the immune system.



A dendritic cell (pictured; artificially coloured). Bacteria abundant in the gut wield molecules that activate these cells, which help the body to resist viruses.

Credit: Steve Gschmeissner/SPL

The researchers found that when dendritic cells were exposed to the membrane molecule, they secreted a powerful signalling chemical called interferon-β. That chemical in turn switched on a battery of genes that affect the immune response.

Dendritic cells that were combined with the bacterial molecule in a laboratory dish largely fended off infection by influenza A virus, but almost half of the cells in a control group became infected.

Many relatives of *B. fragilis* have membrane molecules that stir a similar response, the authors say.

Cell (2020)

https://bit.ly/2KmkKmo

Strange Case Sees Kids Develop Coronavirus Antibodies Without Ever Testing Positive

Unusual case may provide unique insight into the mystery of why children seemed to be less susceptible to developing COVID-19

Peter Dockrill

From the early days of the coronavirus pandemic, scientists observed that children seemed to be less susceptible to developing COVID-19, although the exact reasons why remain unclear.

Now, an unusual case in Australia may provide unique insight into the mystery, thanks to the experience of a young family from Melbourne.

In this family of five, the two parents became sick with COVID-19 after attending an interstate wedding without their children. However, the symptoms didn't show until days after they had returned from the trip.

Nonetheless, completely unbeknownst to them, they had brought SARS-CoV-2 into their home, and exposed their children to it.

Once both the parents developed symptoms – including cough, congested nose, fever and headache – the entire family was tested for the virus.

The parents' tests came back positive. The children's tests came back negative.

"It was jaw-droppingly amazing because they'd spent a week and a half with us while we were COVID-positive," the mother, Leila Sawenko, told ABC News.

Nonetheless, the really surprising part was still to come.

Healthcare workers asked the family to repeat the tests, but again the children's tests came back negative for SARS-CoV-2, even though two of the boys in the family (aged 9 and 7) had mild symptoms.

The youngest child, a 5-year-old daughter, remained asymptomatic throughout the entire episode, even though she was frequently sleeping in the same bed as the parents during their sickness (physical distancing precautions not feasible in the household during their quarantine).

Intrigued by the children's negative results while living in such close proximity to their infected parents, researchers asked the family to take part in a study, analysing samples of their blood, saliva, stools, and urine, and taking nose and throat swabs every two to three days.

Strangely enough, despite repeated polymerase chain reaction (PCR) tests showing the children were consistently SARS-CoV-2 PCR negative, the researchers found SARS-CoV-2 specific antibodies in saliva of all the family members, and in detailed serology testing.

In other words, the children never tested positive for the virus, but some level of exposure to the virus had nonetheless triggered an immune response inside them, and one seemingly capable of countering the infection.

"The youngest child, who showed no symptoms at all, had the strongest antibody response," says immunologist Melanie Neeland from Murdoch Children's Research Institute (MCRI).

"Despite the active immune cell response in all children, levels of cytokines, molecular messengers in the blood that can trigger an inflammatory reaction, remained low. This was consistent with their mild or no symptoms."

Fortunately, all the family members who got sick recovered and did not require medical care.

The mechanisms behind the children's immune response is not yet fully understood, but figuring out how and why their immune responses were activated (in the absence of any confirmed cases of the virus) could shed a lot of light on children's susceptibility to COVID-19 more broadly.

"This study is kind of our first step to look really in-depth at the immune system of children and to see what components may be responding to the virus," first author of the study, paediatrician Shidan Tosif from the University of Melbourne, told *The Age*.

"The fact these children were able to shut down the virus and without even showing a positive test result suggests they have some level of their immune system which is able to respond and deal effectively with the virus, without them ever becoming very unwell."

In effect, the researchers think that the children did actually become infected by the virus, but their immune systems were somehow able to mount an anti-virus response that was highly effective in restricting virus replication, unlike their parents.

That immune response was so effective, it could have brought the viral load so low, that it went under the sensitivity of the PCR testing, which is another issue that bears further examination, the team thinks.

"The discordance between the virological PCR results and clinical serological testing, despite an evident immune response, highlights limitations to the sensitivity of nasopharyngeal PCR and current diagnostic serology in children," the researchers write.

For Leila Sawenko and her family, they're just happy to have all the swabs and tests behind them, and thrilled to contribute in their own way to our better understanding of this pervasive virus, and what it arouses inside us.

"It was a 'wow' moment that despite the fact the kids had tested negative, they had developed antibodies," Sawenko told *ABC News*.

"You could just see the look on the faces of the doctors. They were completely astounded and really excited to think that there was this discovery."

The findings are reported in *Nature Communications*.

https://bit.ly/2UPDWem

The Lancet Microbe: Infectiousness peaks early in COVID-19 patients, emphasising the need to rapidly isolate cases

Systematic review and meta-analysis of three human coronaviruses suggests that people infected with SARS-CoV-2 are most likely to be highly infectious in the first week after symptom onset, highlighting the need to identify and isolate cases early.

Peer-reviewed / Systematic review and meta-analysis / People

- ***Systematic review and meta-analysis of three human coronaviruses suggests that people infected with SARS-CoV-2 are most likely to be highly infectious in the first week after symptom onset, highlighting the need to identify and isolate cases early.***
- ***SARS-CoV-2 viral load appears to peak in the upper respiratory tract (which is thought to be the main source of transmission [1]) early in the disease course (from symptom onset to day five) while SARS-CoV and MERS-CoV viral load peak later, providing the likely explanation for why the COVID-19 pandemic spreads more rapidly in the community.***
- ***The evidence so far on SARS-CoV-2 points to a pattern of a nine-day period of infectiousness. As the study only looks at confirmed cases and not those who may have been exposed, it is unable to provide insight into the recommended duration of quarantine.***
- ***Although viral loads appear to be similar between people infected with SARS-CoV-2 who develop symptoms and those who do not, most studies indicate that asymptomatic individuals may clear the virus faster from their body and might be infectious for a shorter amount of time.***

Although SARS-CoV-2 genetic material may still be detected in respiratory or stool samples for several weeks, no live virus (that can cause infection) was found in any type of sample collected beyond nine days of symptoms starting and people with SARS-CoV-2 are mostly likely to be highly infectious from symptom onset and the following five days, according to a systematic review

and meta-analysis of three human coronaviruses published in *The Lancet Microbe* journal.

"This is the first systematic review and meta-analysis that has comprehensively examined and compared viral load and shedding for these three human coronaviruses. It provides a clear explanation for why SARS-CoV-2 spreads more efficiently than SARS-CoV and MERS-CoV and is so much more difficult to contain," says lead author Dr Muge Cevik of the University of St Andrews, UK.

"Our findings are in line with contact tracing studies which suggest the majority of viral transmission events occur very early, and especially within the first 5 days after symptom onset, indicating the importance of self-isolation immediately after symptoms start. We also need to raise public awareness about the range of symptoms linked with the disease, including mild symptoms that may occur earlier on in the course of the infection than those that are more prominent like cough or fever." [2]

This study specifically looked at people infected with SARS-CoV-2 and mainly those who were hospitalised, so the results are only relevant for the period of self-isolation for people with confirmed COVID-19, and do not apply to people quarantining who may or may not have been exposed after contact with someone infected. Many countries currently recommend that people with a SARS-CoV-2 infection should self-isolate for 10 days, which the authors say is in line with their findings, cautiously covering the period of infectiousness.

Understanding when patients are most likely to be infectious is of critical importance for informing effective public health measures to control the spread of SARS-CoV-2. This study looked at key factors involved in this: viral load (how the amount of the virus in the body changes throughout infection), viral RNA shedding (the length of time someone sheds viral genetic material (RNA), which does not necessarily indicate a person is infectious, as this is not necessarily able to replicate), and isolation of the live virus (a stronger indicator of a person's infectiousness, as the live virus is isolated and tested to see if it can successfully replicate in the laboratory).

The researchers included 98 studies that had five or more participants, cohort studies and randomised controlled trials; 79 focussed on SARS-CoV-2, 73 of which included hospitalised patients only; eight on SARS-CoV; and 11 on MERS-CoV infection. From these studies, the authors calculated the average length of viral RNA shedding and examined the changes in viral load and the success of isolating the live virus from different samples collected throughout an infection.

Analysing the results from the SARS-CoV-2 studies showed that the average length of time of viral RNA shedding into the upper respiratory tract, lower respiratory tract, stool and serum were 17 days, 14.6 days, 17.2 days and 16.6 days, respectively. The longest length of time that RNA shedding lasted was 83, 59, 35 and 60 days, respectively.

Of the eleven studies that attempted to isolate the live virus, all eight studies included that used respiratory samples successfully managed to culture viable virus within the first week of illness. Of the studies that also measured RNA viral load, these demonstrated a link between the success of isolating the live virus with viral load levels. No study included in this systematic review managed to successfully isolate live virus beyond day nine of symptoms in any type of sample, despite persistently high viral RNA loads. So far, only a few studies successfully isolated the live virus from stool samples despite prolonged RNA shedding, and the role of oral-faecal transmission for SARS-CoV-2 remains unclear.

"These findings suggest that in clinical practice, repeat PCR testing may not be needed to deem that a patient is no longer infectious, as this could remain positive for much longer and does not necessarily

indicate they could pass on the virus to others. In patients with non-severe symptoms, their period of infectiousness could instead be counted as 10 days from symptom onset," says Dr Cevik. [2]

The highest viral load of SARS-CoV-2 RNA were detected early in the course of the disease - at the time symptoms begin, or before day five of symptoms. In contrast, the viral loads 8 and MERS-CoV peaked at 10-14 days and 7-10 days after symptom onset, respectively - explaining why transmission of these viruses can be effectively reduced by immediate identification, isolation and quarantine of people who show symptoms of the disease.

Only twelve studies reported on asymptomatic individuals infected with SARS-CoV-2 and of those, six also looked at how quickly people cleared the viral material out of their body.

"Although viral RNA loads appear to be largely similar between those with and without symptoms, a few studies suggest that asymptomatic individuals might clear the viral material from their bodies faster," says Dr Cevik. "Several studies have found that individuals with asymptomatic infection may clear the virus faster, suggesting that those without symptoms may be as infectious as those with symptoms at the beginning of infection, but may be infectious for a shorter period. However, at this stage, there are limited data available on the shedding of infectious virus in asymptomatic individuals to inform any policy change on quarantine duration in the absence of testing." [2]

This is the most comprehensive study of these three respiratory coronaviruses to date and is larger than the previous one meta-analysis on SARS-CoV-2, but the authors note some limitations. Many of the patients across the different studies included in the systematic review and meta-analysis were hospitalised and received a range of treatments that may affect the course of their infection, the studies included different populations who were followed up and managed differently, and in the interpretation of statistics used to measure the length of viral shedding. The period of infectiousness may also not exactly align with the successful culturing of the live virus from samples, although these are likely to broadly overlap.

"The majority of studies included in our review were performed in patients who were admitted to hospital. Therefore, our findings may not apply to people with milder infection although these results suggest those with milder cases may clear the virus faster from their body. Additionally, the increasing deployment of treatments, such as dexamethasone, remdesivir as well as other antivirals and immunomodulators in clinical trials are likely to influence viral shedding in hospitalised patients. Further studies on viral shedding in this context are needed" says senior author, Dr Antonia Ho of MRC-University of Glasgow Centre for Virus Research, UK. [2]

[1] https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations

[2] *Quote direct from author and cannot be found in the text of the Article*

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More people are getting COVID-19 twice, suggesting immunity wanes quickly in some

Reinfections hint that immunity against COVID-19 may be fragile and wane relatively quickly

By Jop de Vrieze

In late June, Sanne de Jong developed nausea, shortness of breath, sore muscles, and a runny nose. At first, she thought it might be lingering effects from her COVID-19 infection in the spring. De Jong, 22, had tested positive on 17 April and suffered mild symptoms for about 2 weeks. She tested negative on 2 May—just in time to say farewell to her dying grandmother—and returned to work as a nursing intern in a hospital in Rotterdam, the Netherlands. But when her symptoms re-emerged, her doctor suggested she get tested again. “A reinfection this soon would be peculiar, but not

impossible," she told De Jong, who by then had again lost her sense of smell and had abdominal pains and diarrhea.

The call from her municipal health service came on 3 July. De Jong had tested positive again. "You're kidding me!" she recalls saying.

Scientists are keenly interested in cases like hers, which are still rare but on the rise. Reinfections hint that immunity against COVID-19 may be fragile and wane relatively quickly, with implications not just for the risks facing recovered patients, but also for how long future vaccines might protect people. "The question everybody wants to answer is: Is that second one going to be less severe most of the time or not?" says Derek Cummings, who studies infectious disease dynamics at the University of Florida. "And what do reinfections teach us about SARS-CoV-2 immunity in general?"

South Korean scientists reported the first suspected reinfections in April, but it took until 24 August before a case was officially confirmed: a 33-year-old man who was treated at a Hong Kong hospital for a mild case in March and who tested positive again at the Hong Kong airport on 15 August after returning from a trip to Spain. Since then, at least 24 other reinfections have been officially confirmed—but scientists say that is definitely an underestimate.

To count as a case of reinfection, a patient must have had a positive polymerase chain reaction (PCR) test twice with at least one symptom-free month in between. But virologist Chantal Reusken of the Dutch National Institute for Public Health and the Environment (RIVM) explains that a second test can also be positive because the patient has a residue of nonreplicating viral RNA from their original infection in their respiratory tract, because of an infection with two viruses at the same time or because they had suppressed but never fully cleared the virus. So most journals want to see two full virus sequences, from the first and second illnesses, that are sufficiently different, says Paul Moss, a hematologist at the University of Birmingham. "The bar is very high," Moss says. "In many cases, the genetic material just isn't there."

Even if it is, many labs don't have the time or money to clinch the case. As a result, the number of genetically proven reinfections is orders of magnitude lower than that of suspected reinfections. The Netherlands alone has 50 such cases, Brazil 95, Sweden 150, Mexico 285, and Qatar at least 243.

The Hong Kong patient's second infection was milder than the first, which is what immunologists would expect, because the first infection typically generates some immunity. That may explain why reinfections are still relatively rare, says Maria Elena Bottazzi, a molecular virologist at Baylor College of Medicine and Texas Children's Hospital.

They could become more common over the next couple of months if early cases begin to lose their immunity. Reinfections with the four coronaviruses that cause the common cold occur after an average of 12 months, a team led by virologist Lia van der Hoek at Amsterdam University Medical Center recently showed. Van der Hoek thinks COVID-19 may follow that pattern: "I think we'd better prepare for a wave of reinfections over the coming months." That's "bad news for those who still believe in herd immunity through natural infections," she adds, and a worrisome sign for vaccines.

Others are less pessimistic. Although antibodies can wane substantially within months—particularly in patients with less severe disease—they sometimes persist, even in mild cases. Neutralizing antibodies, the most important kind, as well as memory B cells and T cells seem to be relatively stable over at least 6 months, a preprint posted on 16 November shows, which "would likely prevent the vast majority of people from getting hospitalized disease, severe disease, for many years," lead author Shane Crotty of the La Jolla Institute for Immunology told *The New York Times*.

And there are hints that people who have serious COVID-19 mount the strongest responses, just as in the two other serious human diseases caused by coronaviruses, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome. Both trigger high antibody levels that last up to 2 years, and T cell responses to SARS can be detected even longer. Because of these persistent immune defenses, "I expect that most reinfections will be asymptomatic," says Antonio Bertoletti, an infectious disease specialist at the National University of Singapore. He says being reinfected might even be a good thing, "since you will continue to boost and train your immune system."

Not all reinfections seen so far are milder. "We see all different combinations," Reusken says. The second time Luciana Ribeiro, a surgeon in Rio de Janeiro, got sick, it was much worse. She was first infected by a colleague in March, developed mild symptoms, and tested negative afterward. Three months later, Ribeiro had symptoms again—she could no longer smell her breakfast, she says—but she didn't immediately get a test because she thought she was immune. When she grew more and more tired, she requested a computerized tomography scan. "It showed that half of my lungs were affected," Ribeiro says. "'This clearly is COVID,' the radiologist told me. I didn't believe it, but I tested positive."

Ribeiro thinks she was reinfected by a patient in the intensive care unit where she works, and that her second episode may have been worse because virus-laden aerosols produced during a medical procedure entered her lungs. But she has another theory as well: "It could be that the virus has become more virulent in the meantime."

So far, no proof exists of mutations that would make the virus more pathogenic or that might help the virus evade immunity. But a recent preprint by a team at the Swedish Medical Center in Seattle suggests one may exist. The team describes a person who was infected in March and reinfected 4 months later. The second virus had a mutation common in Europe that causes a slight change in the virus' spike protein, which helps it break into human cells. Although symptoms were milder the second time, neutralization experiments showed antibodies elicited by the first virus did not work well against the second, the authors note, "which could have important implications for the success of vaccine programs."

And some scientists worry about another scenario that could make the second episode worse: enhanced disease, in which a misfiring immune response to the first infection exacerbates the second one. In dengue fever, for example, antibodies to an initial infection can actually help dengue viruses of another serotype enter cells, leading to a more severe and sometimes fatal second infection. In some other diseases, the first infection triggers ineffective, nonneutralizing antibodies and T cells, hampering a more effective response the second time around.

A recent preprint published by Chinese researchers suggested patients whose first COVID-19 infection is very severe may have ineffective antibodies, which might make them more prone to severe reinfections. But so far there's no evidence from reinfected patients to suggest enhanced disease is at work in COVID-19—although scientists haven't ruled it out either. Vaccination against some diseases can also trigger enhancement later—a known or suspected complication of vaccines against dengue and respiratory syncytial virus in humans and a coronavirus disease in cats. But there is no evidence that candidate COVID-19 vaccines do so, Cummings says. "Having worked with dengue I can say the empirical basis for enhanced disease is just not there, while it was very strong in dengue."

De Jong's virus samples were both sequenced in Reusken's lab, with a surprising outcome: The sequences were not identical, but showed so much similarity that RIVM virologist Harry Vennema says she probably did not clear the virus in April and that it started

to replicate again in June. "I did have a lot of stress after that first episode because my grandmother died," De Jong says. "Maybe that had an impact on my immune system."

That makes her case different from a true reinfection—although Vennema says perhaps they should be considered similar, because in both cases the immune system failed to mount a protective response. His lab has found at least one similar case, he says, suggesting some unconfirmed reinfections might actually be a resurgence of the original virus.

Other coronaviruses can also cause persistent infections, says Stanley Perlman of the University of Iowa. In 2009, his team showed that an encephalitis-causing mouse coronavirus can linger in the body and continuously trigger immune responses, even if it doesn't replicate. And in a preprint posted on 5 November, a team of U.S. scientists shows SARS-CoV-2 can persist for months inside the gut. Persistent infections, they suggest, may help explain the extraordinarily long-lasting symptoms that afflict some COVID-19 survivors.

De Jong is experiencing some of those symptoms. Although she tested negative in September and has high levels of neutralizing antibodies, suggesting she is protected for at least a couple of months, she still suffers from gastrointestinal complaints, fatigue, and cognitive impairment. De Jong says her story is a warning to people who had the virus and think they're now invulnerable: "Please be cautious. You can get it again."

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'Exceptional' cancer patients yield clues to better drug treatments

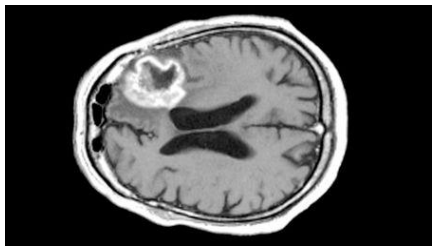
An effort to systematically study "exceptional responders" is yielding data that could help improve cancer treatments.

By Jocelyn Kaiser

Although even the best cancer drugs don't buy much time for most people whose cancer has spread, there are rare exceptions: the patients whose multiple tumors melt away and who remain healthy years later. Researchers have long dismissed these "exceptional responders" as unexplainable outliers. Now, an effort to systematically study them is yielding data that could help improve cancer treatments.

The project, led by the U.S. National Cancer Institute (NCI), examined the DNA of tumors and immune cells found around or within those cancers in 111 exceptional responders. In 26 of the patients, scientists found genomic changes to the tumors or immune clues that may explain why a drug that didn't work for most people shrank the responders' tumors for months or years. Some cases suggest combining certain drugs could yield better outcomes.

The findings show that examining these fortunate few is worthwhile, says Dale Garsed of the Peter MacCallum Cancer Centre in Australia. The study "opens new avenues for treating comparable cancers in the wider population," he says.



A scan of a patient with glioblastoma, a type of brain cancer. In rare cases, patients receiving chemotherapy for this cancer have been tumor-free for years. **Living Art Enterprises, LLC/Science Source**

The former NCI director who launched the initiative in 2014 is equally excited. "It is gratifying to see so much novel information from this initial survey of cancer patients who have done unexpectedly well with existing therapies," says cancer biologist Harold Varmus of Weill Cornell Medicine, who did not work on the study itself. The results are "complex," he notes, but they "promote unique hypotheses" and underscore the value of conducting genomic tests of patients' tumors in order to customize treatments.

Varmus was inspired in part by a bladder cancer patient who responded to a generally lackluster drug because of certain mutations in her tumor.

From more than 500 cases submitted by clinical researchers, NCI selected those that fit specific criteria: The patient's tumors shrank or disappeared in response to a drug that worked for less than 10% of patients overall in a clinical trial. Or the patient had a response that lasted at least three times longer than it had for a typical patient. A team led by NCI's Louis Staudt and Percy Ivy pared the patient list further to those who had enough medical data and tumor samples with intact DNA. Their team ran these 111 cases through a battery of genomic analyses and tests for immune cells in and near the tumors.

In 26 cases, the data appeared to explain the patient's exceptional response. For example, a patient with brain cancer who was still alive after more than 10 years had received a chemotherapy drug called temozolomide that kills tumor cells by damaging their DNA. The patient's tumor had genomic changes that crippled two DNA repair pathways that cells use to counter the drug's assault, the NCI team reports today in *Cancer Cell*. A colon cancer patient in remission for nearly 4 years after temozolomide treatment had two changes that crippled DNA repair pathways and had received a second experimental drug that blocked a third one.

"Every backup system that would have reversed the damage was inactivated" in this person, Staudt says. These results suggest treating some patients with a cocktail of drugs, each blocking different DNA repair pathways, could be useful, Ivy says.

Two patients who had received chemotherapy for rectal cancer and bile duct cancer had unexpected tumor mutations—they were in the *BRCA* genes, best known for causing breast cancer.

BRCA mutations also weaken DNA repair, which made the tumors vulnerable to chemotherapy.

In other cases, tumors shrank after the patients had received a drug that blocks a protein that drives cell growth.

The tumors had DNA changes that spurred high activity of the protein's gene, which made the tumor cells highly dependent on the growth signal; as a result, the drug worked unusually well.

In other exceptional responders, their tumors were infiltrated with unusually high levels of certain immune cells. This suggests their immune systems were primed to swoop in and destroy tumors once a cancer drug started to kill some cells, Staudt says.

The findings suggest more patients should have their tumors analyzed with genomic tests so doctors can select appropriately matching drugs. But results may still be hard to interpret—many tumors had combinations of mutations and immune cell changes, the NCI authors found.

As for the 85 cases the NCI team could not solve, Staudt says the molecular evidence wasn't strong enough to draw any conclusions. His team is putting data for all 111 patients online in an NCI database so that other researchers can study it and look for similar cases. "Maybe we missed something," he says.

Researchers in North America, Europe, and Australia have launched similar exceptional responder projects, and NCI researchers hope some of these efforts can pool their data. Staudt would like to see a study of at least 1000 patients. "These are puzzles to be solved," he says. "I do think they teach us something."

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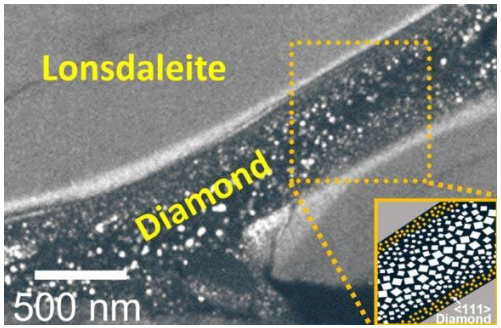
Researchers Create Two Types of Diamond at Room Temperature

Created in minutes in a laboratory at room temperature

A team of scientists from Australia and the United States has created two types of diamond — regular diamond and a diamond-like phase called lonsdaleite, which is found in nature at the sites of

meteorite impacts — in minutes in a laboratory at room temperature, a process that normally takes billions of years, huge amounts of pressure and super-hot temperatures.

Diamond is an attractive material due to its extreme hardness, high thermal conductivity, quantum optical, and biomedical applications.



McCulloch et al. created 'rivers' of regular diamond and lonsdaleite, named after the crystallographer Dame Kathleen Lonsdale, the first woman elected as a Fellow to the Royal Society. Lonsdaleite has a different crystal structure to regular diamond, and is predicted to be 58% harder. **Image credit: McCulloch et al., doi: 10.1002/smll.202004695.**

There is still much that is not understood about how diamonds form, particularly at room temperature and without catalysts.

"Natural diamonds are usually formed over billions of years, about 150 km deep in the Earth where there are high pressures and temperatures above 1,000 degrees Celsius," said senior author Professor Jodie Bradby, a researcher in the Research School of Physics at the Australian National University.

In the new study, Professor Bradby, RMIT Professor Dougal McCulloch and their colleagues used advanced electron microscopy techniques to capture solid and intact slices from the experimental samples to create snapshots of how nanocrystalline diamond and lonsdaleite formed.

"Our pictures showed that the regular diamonds only form in the middle of lonsdaleite veins under this new method developed by our team," Professor McCulloch said.

"Seeing these little 'rivers' of lonsdaleite and regular diamond for the first time was just amazing and really helps us understand how they might form."

The team previously created lonsdaleite, also called hexagonal diamond, in the lab only at high temperatures.

But their new results show both lonsdaleite and regular diamond can also form at normal room temperatures by just applying high pressures of 100 GPa.

"The twist in the story is how we apply the pressure," Professor Bradby said.

"As well as very high pressures, we allow the carbon to also experience something called 'shear' — which is like a twisting or sliding force."

"We think this allows the carbon atoms to move into place and form lonsdaleite and regular diamond."

"Lonsdaleite has the potential to be used for cutting through ultra-solid materials on mining sites," she said.

"Creating more of this rare but super useful diamond is the long-term aim of this work."

"Being able to make two types of diamonds at room temperature was exciting to achieve for the first time in our lab," said co-author Xingshuo Huang, a PhD student in the Research School of Physics at the Australian National University.

The research is described in a paper in the journal *Small*.

Dougal G. McCulloch et al. Investigation of Room Temperature Formation of the Ultra-Hard Nanocarbons Diamond and Lonsdaleite. Small, published online November 4, 2020; doi: 10.1002/smll.202004695

https://bit.ly/3nM91Ml

In a Wild Twist, Asymptomatic Children Can Spread Malaria to Mosquitoes

Children infected with malaria can become 'superspreaders' and pass the parasite to droves of local mosquitoes, even if the kids never develop symptoms of the disease, a new study suggests.

Nicoletta Lanese

Since this disease is passed from humans to mosquitoes and then

back again, rather than from person to person, this finding is worrisome.

If malaria goes untreated in these asymptomatic children, the parasites will continue to circulate among mosquitoes, even in places that employ intensive malaria controls like insecticides, bednets, and free diagnostic tests and treatments.

According to new research, presented Wednesday (Nov. 18) at the annual meeting of the American Society of Tropical Medicine and Hygiene (ASTMH), even a small number of infected children can transmit malaria parasites to a mob of mosquitoes, which can then go on to infect more humans.

From their new research in Uganda, the researchers concluded that asymptomatic children between ages 5 and 15 are the main source of infection for local mosquitoes in the region they studied.

Some of these children were so-called superspreaders, meaning they infected a much larger number of mosquitoes than others; in experiments where mosquitoes were fed blood samples from infected people, more than 60 percent of the resulting mosquito infections could be traced back to just four asymptomatic children, two of whom were school-age. The other two superspreaders were ages 3 and 4.

Despite some children becoming infected with multiple malaria clones during the study, these kids never fell ill and continued to lead a "normal life … somehow living with all these parasites," said lead author Chiara Andolina, a graduate student and malaria expert at Radboud University Medical Center in the Netherlands.

Malaria is well controlled in the region the team studied, but should control efforts ever falter or cease, these children could potentially fuel a resurgence of disease in the area.

To prevent malaria cases from rebounding, control efforts could specifically target school-age children, senior author Teun Bousema, a malaria epidemiologist at Radboud, told Live Science.

For example, regular malaria screenings and treatment campaigns in schools could have a "very meaningful impact" on depleting reservoirs of malaria, and ultimately, driving the case count down to zero, he said.

Spotting superspreaders

Asymptomatic malaria infections make up 80 percent or more of the cases detected through comprehensive screenings in areas where the disease regularly circulates, Bousema said. Studies suggest that these asymptomatic infections crop up most often in school-age children.

While scientists agree that mosquitoes pick up malaria from both symptomatic and asymptomatic people, there's a question as to whether one kind of infection is more or less infectious than the other. In search of the answer, the study authors travelled to the Tororo district of Uganda.

Malaria was once incredibly common in Tororo; as recently as 2011, each resident was bitten about 310 times per year by malaria-infected mosquitoes, Andolina said in her ASTMH presentation. Now, after years of intensive malaria control, infection rates have plummeted. In 2018, exposure to infectious mosquitoes fell to only 0.43 bites per person, per year.

"It's sort of a blueprint for what you can expect - if you really invest very heavily in malaria control, you can bring malaria burden down," Bousema said. But to completely eliminate malaria, scientists have to find and purge any remaining hideouts of the parasite, he added.

To do so in Tororo, the team recruited 531 adults and children from 80 households and monitored them for malaria for two years. Each month they conducted diagnostic tests and collected blood samples from the participants; the blood was screened for malaria parasites and then used in mosquito-feeding experiments.

To pass from humans to mosquitoes, malaria parasites must first

mature into gametocytes; once being ingested by the blood-sucking insects, the gametocytes divide into sex cells, fertilize each other and multiply.

With this in mind, the team also analysed the density of gametocytes in the human blood samples, as the number can hint at how infectious that blood might be to mosquitoes.

Over the course of the study, the team detected 148 episodes of malaria - 38 symptomatic and 110 asymptomatic. They conducted nearly 540 mosquito-feeding experiments with blood from 107 of the infected people, using an apparatus that keeps the blood warm with circulating water.

In each experiment, dozens of mosquitoes got released into a container with the apparatus, where they could access the blood through a membrane that mimicked human skin.

The team later dissected the fed mosquitos to see how many became infected, and the vast majority of infections were linked to blood from asymptomatic people.

In all, blood from symptomatic people only infected 0.6 percent of the total infected mosquitoes.

Targeting hidden reservoirs

This trend is likely due, in part, to symptomatic people having easy access to malaria treatment, the authors said.

"In our study, children and adults if they fell sick .. often they went to the clinic before they developed these transmissible gametocytes," Bousema said. Gametocytes take nine to 12 days to reach maturity, during which time most symptomatic people had already gotten treatment. "It actually demonstrates that if your access to care is very good, you can prevent symptomatic individuals from transmitting."

The challenge then becomes identifying infected people without symptoms, so that their chains of transmission can also be broken, he said.

Notably, some asymptomatic people in the study remained infectious for months, though their gametocyte levels fluctuated over time. For example, two children remained infectious for six months without ever developing symptoms of malaria.

"Asymptomatic infections really dominated in children .. and schoolchildren somehow have longer duration infections, higher gametocyte densities, and thus were really the important source for mosquitoes to become infected," Bousema said.

Overall, the researchers estimated that children ages 5 to 15 represent nearly 57 percent of the infectious reservoir, meaning they carry most of the parasites that could infect mosquitoes with malaria. Following school-age children, children younger than 5 represent 27.5 percent of the reservoir, while those age 16 and older represent the remaining 15.7 percent.

Malaria control measures, such as insecticide-treated nets to cover people's beds, are often prioritized for young children under age 5 and pregnant women, but school-age children might get overlooked, the authors noted.

Beyond nets, test-and-treat campaigns at schools could help snuff out new cases of malaria before they get passed to local mosquitoes, they said, and preventative medications, many of which can also be used to treat malaria, could help kids avoid picking up the parasites in the first place.

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Plant evolves to become less visible to humans

A plant used in traditional Chinese medicine has evolved to become less visible to humans, new research shows.

Scientists found that Fritillaria delavayi (*梭砂贝母 suo sha bei mu*) plants, which live on rocky slopes of China's Hengduan mountains, match their backgrounds most closely in areas where they are heavily harvested. This suggests humans are "driving" evolution of

this species into new colour forms because better-camouflaged plants have a higher chance of survival.

The study was carried out by the Kunming Institute of Botany (Chinese Academy of Sciences) and the University of Exeter.

"It's remarkable to see how humans can have such a direct and dramatic impact on the colouration of wild organisms, not just on their survival but on their evolution itself," said Professor Martin Stevens, of the Centre for Ecology and Conservation on Exeter's Penryn Campus in Cornwall

Fritillaria delavayi in a population with high harvest pressure. **Yang Niu**

"Many plants seem to use camouflage to hide from herbivores that may eat them—but here we see camouflage evolving in response to human collectors. "It's possible that humans have driven evolution of defensive strategies in other plant species, but surprisingly little research has examined this."

In the new study, the researchers measured how closely plants from different populations matched their mountain environment and how easy they were to collect, and spoke to local people to estimate how much harvesting took place in each location.

They found that the level of camouflage in the plants was correlated with harvesting levels. In a computer experiment, more-camouflaged plants also took longer to be detected by people.

Fritillaria delavayi in a population with low harvest pressure. **Yang Niu**

Fritillaria delavayi is a perennial herb that has leaves—varying in colour from grey to brown to green—at a young age, and produces a single flower per year after the fifth year. The bulb of the fritillary species has been used in Chinese medicine for more than 2,000 years, and high prices in recent years have led to increased harvesting.

"Like other camouflaged plants we have studied, we thought the evolution of camouflage of this fritillary had been driven by herbivores, but we didn't find such animals," said Dr. Yang Niu, of the Kunming Institute of Botany. "Then we realised humans could be the reason."

Professor Hang Sun, of the Kunming Institute of Botany, added: "Commercial harvesting is a much stronger selection pressure than many pressures in nature. "The current biodiversity status on the earth is shaped by both nature and by ourselves." The paper, published in the journal *Current Biology*, is entitled: "Commercial harvesting has driven the evolution of camouflage in an alpine plant."

https://bit.ly/33bPI7w

Field geology at Mars' equator points to ancient megaflood

Floods once washed through Gale Crater around 4 billion years ago - hints at possibility that life may have existed there

by Blaine Friedlander

Floods of unimaginable magnitude once washed through Gale Crater on Mars' equator around 4 billion years ago—a finding that hints at the possibility that life may have existed there, according to data collected by NASA's Curiosity rover and analyzed in joint project by scientists from Jackson State University, Cornell University, the Jet Propulsion Laboratory and the University of Hawaii. The research, "Deposits from Giant Floods in Gale Crater and Their Implications for the Climate of Early Mars," was published Nov. 5 in *Scientific Reports*.

The raging megaflood—likely touched off by the heat of a meteoritic impact, which unleashed ice stored on the Martian surface—set up gigantic ripples that are tell-tale geologic structures

familiar to scientists on Earth.

"We identified megafloods for the first time using detailed sedimentological data observed by the rover Curiosity," said co-author Alberto G. Fairén, a visiting astrobiologist in the College of Arts and Sciences. "Deposits left behind by megafloods had not been previously identified with orbiter data."

As is the case on Earth, geological features including the work of water and wind have been frozen in time on Mars for about 4 billion years. These features convey processes that shaped the surface of both planets in the past.

This case includes the occurrence of giant wave-shaped features in sedimentary layers of Gale crater, often called "megaripples" or antidunes that are about 30-feet high and spaced about 450 feet apart, according to lead author Ezat Heydari, a professor of physics at Jackson State University.

The antidunes are indicative of flowing megafloods at the bottom of Mars' Gale Crater about 4 billion years ago, which are identical to the features formed by melting ice on Earth about 2 million years ago, Heydari said.

The most likely cause of the Mars flooding was the melting of ice from heat generated by a large impact, which released carbon dioxide and methane from the planet's frozen reservoirs. The water vapor and release of gases combined to produce a short period of warm and wet conditions on the red planet.

Condensation formed water vapor clouds, which in turn created torrential rain, possibly planetwide. That water entered Gale Crater, then combined with water coming down from Mount Sharp (in Gale Crater) to produce gigantic flash floods that deposited the gravel ridges in the Hummocky Plains Unit and the ridge-and-trough band formations in the Striated Unit.

The Curiosity rover science team has already established that Gale Crater once had persistent lakes and streams in the ancient past. These long-lived bodies of water are good indicators that the crater, as well as Mount Sharp within it, were capable of supporting microbial life.

"Early Mars was an extremely active planet from a geological point of view," Fairén said. "The planet had the conditions needed to support the presence of liquid water on the surface—and on Earth, where there's water, there's life. "So early Mars was a habitable planet," he said. "Was it inhabited? That's a question that the next rover Perseverance ... will help to answer."

Perseverance, which launched from Cape Canaveral on July 30, is scheduled to reach Mars on Feb. 18, 2021.

More information: *E. Heydari et al, Deposits from giant floods in Gale crater and their implications for the climate of early Mars, Scientific Reports (2020). DOI: 10.1038/s41598-020-75665-7*

https://wb.md/3kWs590

Add Delirium to Checklist of COVID-19 Symptoms in Seniors

Delirium should be included on checklists of the presenting signs and symptoms of COVID-19, particularly in elderly adults, according to a multicenter study of seniors visiting emergency departments.

Diana Swift

Overall, 28% of the 817 older adults who presented to the emergency department and were diagnosed with COVID-19 had delirium, according to a study published online November 19 in *JAMA Network Open*. Morevoer, 16% of these patients had delirium that was not accompanied by typical symptoms or signs of SARS-CoV-2 infection.

Among patients with delirium, there was a greater probability of admission to the intensive care unit compared with patients who presented without delirium (adjusted relative risk [aRR], 1.67; 95% CI, 1.30 – 2.15), as well as a greater probability of death (aRR,

1.24; 95% CI, 1.00 – 1.55).

"These findings suggest the clinical importance of including delirium on checklists of presenting signs and symptoms of COVID-19 that guide screening, testing, and evaluation," write Maura Kennedy, MD, MPH, and colleagues.

"I was absolutely seeing cases of delirium where there were no other symptoms of COVID-19, but we didn't have lot of data on the frequency of this," explained Kennedy, an emergency department physician at Massachusetts General Hospital and an assistant professor of emergency medicine at Harvard Medical School, Boston.

"And the rate was somewhat surprising compared with that seen in non-COVID studies of delirium, but then our study population was more at risk, coming from long-term care facilities and having prior stroke or dementia," she said.

The most common form of delirium was hypoactive sleepiness and nonresponsiveness, although hyperactivity and agitation were also seen.

Kennedy thinks the addition of delirium as a common presenting symptom to diagnostic checklists would prevent some cases from being missed and allow earlier identification and management of COVID-19 patients at high risk for poor outcomes.

"We certainly don't want to send them back undiagnosed to a long-term care facility or promote transmission within the hospital," she told *Medscape Medical News*.

That step has already been implemented in some US centers. "Delirium is something we've been looking at since the early summer," said geriatrician Angela Catic, MD, an assistant professor at Baylor College of Medicine's Huffington Center on Aging and the Michael E. DeBakey VA Medical Center, Houston, Texas.

"If we see delirium, we're looking for COVID-19," said Catic, who was not involved in the study.

In Catic's experience, it is "not at all atypical" to see patients whose only symptom of COVID-19 is delirium. As with other infections and diseases, "the aging brain is incredibly vulnerable," she said.

According to William W. Hung, MD, MPH, an assistant professor of geriatrics and palliative medicine at the Icahn School of Medicine at Mount Sinai, New York City, delirium is "generally a common sign of something seriously wrong" in older adults. "In the case of COVID-19, low oxygenation caused by the infection may play a role," he told *Medscape Medical News*.

Although he agreed that delirium should be included in the differential diagnosis of COVID-19, how frequently it is the only symptom at presentation would need to be determined in a considerably larger population, he said.

Joining the company of those observing this COVID-19 manifestation is Christopher R. Carpenter, MD, a professor of emergency medicine at Washington University in St. Louis, St. Louis, Missouri. He was not a participant in the current study.

"I have absolutely seen and documented delirium as the presenting complaint in older adult patients who were ultimately diagnosed with SARS-CoV-2, and since March, I contemplate SARS-CoV-2 each time I identify delirium," Carpenter told *Medscape Medical News*.

"Honestly, I — and most of my colleagues — are considering SARS-CoV-2 for a range of symptoms and complaints these days, because of the odd presentations we've all encountered."

Study Details

For the study, Kennedy and colleagues enrolled consecutive adults aged 65 years and older who were diagnosed with active COVID-19 and who presented to emergency departments at seven centers in Massachusetts, Maine, Connecticut, Michigan, and North Carolina on or after March 13, 2020.

Active infection with SARS-CoV-2 was determined on the basis of

results of nasal swab polymerase chain reaction tests (99% of cases) or the appearance and distribution of ground-glass opacities on chest radiography or CT (1%).

Of the 817 patients enrolled, 386 (47%) were men, 493 (62%) were White, 215 (27%) were Black, and 54 (7%) were Hispanic or Latinx. The mean age of patients was 77.7 years (standard deviation, 8.2). Their age placed them at risk for chronic comorbidities and cognitive problems; indeed, 15% had at least four chronic conditions, and 30% had existing cognitive impairment.

The authors note that among the 226 patients (28%) who had delirium at presentation, 60 (27%) had experienced delirium for a duration of 2 to 7 days.

Additionally, of the 226 patients who exhibited delirium as a primary symptom, 84 (37%) showed no typical COVID-19 symptoms or signs, such as cough, fever, or shortness of breath.

The presence of delirium did not correlate with any of the typical COVID-19 symptoms in particular; Kennedy noted that only 56% of patients in the cohort had a fever at presentation.

Delirium at presentation was significantly associated with a median hospital stay of more than 8 days (aRR, 1.14; 95% CI, .97 – 1.35) and a greater risk for discharge to a rehabilitation facility (aRR, 1.55; 95% CI, 1.07 – 2.26). Factors associated with delirium included age older than 75 years, residence in a nursing home or assisted-living facility, previous use of psychoactive medications, vision impairment, hearing impairment, stroke, and Parkinson's disease.

Kennedy noted that the rate of delirium observed in this study is much higher than that generally reported in emergency department studies conducted before the COVID-19 pandemic. In those studies, the delirium rate ranged from 7% to 20%. The associated risk factors, however, are comparable.

"Mounting evidence supports the high occurrence of delirium and other neuropsychiatric manifestations with COVID-19, with previously reported rates of 22% to 33% among hospitalized patients," Kennedy and associates write.

In Carpenter's opinion, the development of incident delirium while receiving care in the emergency department, as opposed to delirium at the time of presentation, has been exacerbated by the no-visitor policies mandated by the pandemic, which have prevented visits even from personal caregivers of patients with moderate to severe dementia.

"Although healthcare systems need to be cognizant of the risk of spread to uninfected caregivers, there's a risk-benefit balance that must be found, because having one caregiver at the bedside can prevent delirium in cognitively impaired patients," said Carpenter, who was not involved in the current study.

Among the barriers to improving the situation, Carpenter cited the lack of routine delirium screening and the absence of high-quality evidence to support emergency department interventions to mitigate delirium.

"Layer those challenges on top of COVID-19's rapidly evolving diagnostic landscape, frequent atypical presentations, and asymptomatic carriers across all age groups and the negative impact of delirium is magnified," Carpenter said.

Once elderly patients are hospitalized, Kennedy recommends the nonpharmacologic guidelines of the Hospital Eelder Help Program for reducing delirium risk. Recommendations include the providing of adequate sleep, hydration, and nutrition, as well as function restoration, precipitant avoidance, and reorientation.

The study was supported in part by the National Institute on Aging and the Massachusetts Medical School. The authors, Carpenter, Hung, and Catic have disclosed no relevant financial relaitonships. JAMA Netw Open. Published online November 19, 2020. Full text

https://bit.ly/35Spbhg

Superspreader Events Played a Key Role in Igniting The Current Pandemic Globally

Large clusters are more than just extreme outliers, but rather the pandemic's likely main engine of transmission.

Kelly Macnamara, AFP

At churches, on cruise ships, and even in the White House, superspreading events that can sicken dozens, even hundreds, of people have illustrated the potential for the coronavirus to infect in dramatic bursts.

Experts say these large clusters are more than just extreme outliers, but rather the pandemic's likely main engine of transmission.

And understanding where, when, and why they happen could help us tame the spread of the virus in the period before a vaccine may be widely available.

Research increasingly suggests that the coronavirus SARS-CoV-2 does not fan out evenly across the population, but spreads at the extremes in an almost "all or nothing" pattern.

Many studies now suggest the majority of people with COVID-19 barely pass it on to anyone else, but when infections happen, they can be explosive and supercharge an outbreak. Then the virus can infect "10, 20, 50, or even more people", said Benjamin Althouse, research scientist at the Institute for Disease Modeling.

This corresponds to the "80/20 rule" of epidemiology, where 80 percent of cases come from only 20 percent of those infected, but Althouse said this coronavirus may be even more extreme, with 90 percent of cases coming from potentially just 10 percent of carriers.

This transmission pattern is like "throwing matches on a pile of kindling", he told AFP.

"You throw one match, it doesn't ignite. You throw another match, it doesn't ignite. You throw yet another match, and this time you see flames blaze up," he said.

"For SARS-CoV-2, this means that while it is difficult to establish in new places, once established, it can spread rapidly and far."

Virus 'hallmark'

Superspreading events have grabbed headlines, looming large in the narrative of the unfolding pandemic.

In February, the Diamond Princess and its 4,000 passengers spent weeks in quarantine at port in Japan as the number of infections on board climbed, reaching 700.

The same month a 61-year-old woman, known as "Patient 31", attended several church services of the Shincheonji Church of Jesus in the South Korean city of Daegu.

The Korea Centers for Disease Control and Prevention has since linked more than 5,000 infections to Shincheonji.

More recently the virus managed to infiltrate the White House despite a host of measures to keep it out.

Political gatherings, business conferences, and sports tournaments have all acted as infection incubators, but these high profile events could just be the tip of the iceberg.

A study by US researchers, based on one of the world's largest contact tracing operations and published in *Science* in September, found that "superspreading predominated" in transmission.

Analysing data from the first four months of the pandemic in the states of Tamil Nadu and Andhra Pradesh in India, the authors found that just eight percent of infected individuals accounted for 60 percent of new cases, while 71 percent of people with the virus did not pass it on to any of their contacts.

Perhaps this should not be a surprise.

Maria Van Kerkhove, an infectious disease epidemiologist at the heart of the World Health Organization's pandemic response, tweeted in October that "superspreading is a hallmark" of coronaviruses. Indeed, it has been observed in many infectious diseases.

One of the most famous superspreaders was Mary Mallon, a cook working in New York in the early 1900s who was the first documented healthy carrier of typhoid bacteria in the US.

Blamed for giving the illness to dozens of people, she was given the unsympathetic label "Typhoid Mary" and forcibly confined for years. Measles, smallpox and Ebola also see clustering patterns, as did the other coronaviruses, SARS and MERS.

K factor

Early in the pandemic, much attention was focused on the basic reproduction number (R0) of SARS-CoV-2.

This helps calculate the speed a disease can spread by looking at the average number of others a person with the virus infects.

But looking at transmission through this metric alone often "fails to tell the whole story", said Althouse, who co-authored a paper on the limitations of R0 in the Journal of the Royal Society Interface this month. For instance, he said Ebola, SARS-CoV-2, and influenza, all have an R0 value of around two to three.

But while people with the flu tend to infect two or three others "consistently", the transmission pattern for those with Ebola and SARS-CoV-2 is overdispersed, meaning most will hardly spread it and some will give rise to tens of other cases.

A different metric – "k" – is used to capture this clustering behaviour, although it usually requires "more detailed data and methodology", said Akira Endo, a research student at the London School of Hygiene and Tropical Medicine.

His modelling from the early international spread of the virus, published in Wellcome Open Research, suggested SARS-CoV-2 could be highly overdispersed.

A telltale clue, he said, was that some countries reported numerous imported cases but no signs of sustained transmission – like the match analogy – while others reported large local outbreaks with only a few imported cases.

But even k may not give the full picture, said Felix Wong, a postdoctoral fellow at the Massachusetts Institute of Technology.

His research analysing known COVID-19 superspreading events, published this month in the journal *PNAS*, found that they were happening even more frequently than predicted by traditional epidemiological models.

They are "extreme, yet probable occurrences", Wong told AFP.

Biology vs opportunity

So why does superspreading occur?

We don't know definitively whether biological factors, such as viral load, play much of a role. But what we do know is people can spread SARS-CoV-2 without symptoms and given a poorly-ventilated, crowded space – particularly where people talk, shout, or sing – the virus can run rampant. This could be why a study in *Nature* this month found that restaurants, gyms, and cafes account for most COVID-19 infections in the United States. Using the mobile phone data of 98 million people, researchers found about 10 percent of venues accounted for over 80 percent of cases.

Given this, experts say the focus should be on these types of spaces – and reducing opportunities for the virus to access large numbers of people. Wong said his modelling showed that if each individual was limited to ten transmissible contacts, "viral transmission would quickly die down".

Tracking back

Overdispersed spread also means that most people testing positive for the virus are likely to be part of a cluster.

This opens up another way to trace infections: backwards.

"The idea being that it could be more efficient to trace back, and isolate, superspreaders than it is to trace downstream and isolate individuals who, even if they were infected, might transmit the virus to very few people," said Wong.

Both Japan and South Korea have used backwards contact tracing,

which has been credited with helping them curb their epidemics, along with other control measures.

Masks, social distancing and reducing contacts are all ways to limit transmission opportunities, Althouse said, adding that even characterising people as "superspreaders" is misleading.

"There are vast differences in biology between individuals – I may have a million times more virus in my nose than you – but if I am a recluse, I can infect no one," he said.

https://go.nature.com/3fr3ibZ

Coronaviruses closely related to the pandemic virus discovered in Japan and Cambodia

The viruses, both found in bats stored in laboratory freezers, are the first SARS-CoV-2 relatives to be found outside China.

Smriti Mallapaty

Two lab freezers in Asia have yielded surprising discoveries. Researchers have told *Nature* they have found a coronavirus that is closely related to SARS-CoV-2, the virus responsible for the pandemic, in horseshoe bats stored in a freezer in Cambodia. Meanwhile, a team in Japan has reported the discovery of another closely related coronavirus — also found in frozen bat droppings.

The viruses are the first known relatives of SARS-CoV-2 to be found outside China, which supports the World Health Organization's search across Asia for the pandemic's animal origin. Strong evidence suggests that SARS-CoV-2 originated in horseshoe bats, but whether it passed directly from bats to people, or through an intermediate host, remains a mystery.

The virus in Cambodia was found in two Shamel's horseshoe bats (*Rhinolophus shameli*) captured in the country's north in 2010. The virus's genome has not yet been fully sequenced — nor its discovery published — making its full significance to the pandemic hard to ascertain.

If the virus is very closely related to — or even an ancestor of — the pandemic virus, it could provide crucial information about how SARS-CoV-2 passed from bats to people, and inform the search for the pandemic's origin, says Veasna Duong, a virologist at Institute Pasteur in Phnom Penh, who led the search of the old samples in Cambodia and alerted *Nature* to their discovery in early November.

To provide such insights, the virus would have to share more than 97% of its genome with SARS-CoV-2, which is more than its closest known relative, say researchers.

But the new virus might be more distantly related, in which case, studying it will help scientists to learn more about the diversity in this virus family, says Etienne Simon-Loriere, a virologist at the Pasteur Institute in Paris, who plans to sequence the virus, after which it will be shared publicly.

A coronavirus related to SARS-CoV-2 has been found in Shamel's horseshoe bats captured in Cambodia in 2010. **Merlin D. Tuttle/SPL**

That is the case with the other virus, called Rc-o319, identified in a little Japanese horseshoe bat (*Rhinolophus cornutus*) captured in 2013. That virus shares 81% of its genome with SARS-CoV-2, according to a paper[1] published on 2 November — which makes it too distant to provide insights into the pandemic's origin, says Edward Holmes, a virologist at the University of Sydney in Australia.

No matter what the Cambodian team find, both discoveries are exciting because they confirm that viruses closely related to SARS-CoV-2 are relatively common in *Rhinolophus* bats, and even in bats found outside of China, says Alice Latinne, an evolutionary biologist at the Wildlife Conservation Society Vietnam in Hanoi, who has seen some of the Cambodian team's analysis but was not involved in the investigation.

"This is what we were looking for, and we found it," says Duong. "It was exciting and surprising at the same time."

Pandemic origins

The findings also suggest that other as yet undiscovered SARS-CoV-2 relatives could be stored in lab freezers, says Aaron Irving, an infectious-diseases researcher at Zhejiang University in Hangzhou, China, who also plans to test stored samples of bats and other mammals for antibodies against SARS-CoV-2.

"I did not expect to find a relative of SARS-CoV-2," says virologist Shin Murakami at the University of Tokyo, who was part of the team that decided to retest frozen animal samples for viruses in the wake of the pandemic.

Only a handful of known coronaviruses are closely related to SARS-CoV-2, including its closest known relative RaTG13. It was discovered in intermediate horseshoe bats (*Rhinolophus affinis*) in the Chinese province of Yunnan in 2013, and was published[2] only earlier this year. There are also several other coronaviruses, found in other *Rhinolophus* bats and pangolins captured between 2015 and 2019, which scientists now know to be closely related to SARS-CoV-2.

"SARS-CoV-2 probably wasn't a brand new virus that popped up all of a sudden. Viruses in this group existed before we became aware of them in 2019," says Tracey Goldstein, associate director of the One Health Institute at the University of California, Davis, who is involved with the Cambodian team.

Latinne says the discoveries confirm that *Rhinolophus* bats are the reservoir of these viruses.

Virus in Cambodia

Duong's team captured the Shamel's horseshoe bats in Cambodia as part of the US-government-funded PREDICT project, which surveyed wildlife worldwide for viruses with pandemic potential for decades and ended earlier this year. In April, the US Agency for International Development gave the programme an additional US$3 million and a 6-month extension to look for evidence of SARS-CoV-2 in animal samples — mostly bats, as well as pangolins and other animals — that were sitting in laboratory freezers in Laos, Malaysia, Nepal, Thailand, Vietnam, and Cambodia. A full report of these investigations is expected in the coming weeks.

Duong says preliminary genome sequencing of a short fragment of the new bat virus — 324 base pairs long — showed that it was similar to the same region in SARS-CoV-2 and RaTG-13, suggesting that the three are closely related. That region is highly conserved in coronaviruses, says Latinne, and is often used to quickly identify whether a virus is new or known. But it's not yet clear whether RaTG-13 or the new virus is more closely related to SARS-CoV-2.

It is difficult to say with such a small fragment, says Vibol Hul, a virologist also at the Institute Pasteur in Cambodia, who trapped the Shamel's horseshoe bats at the entrance to a cave in 2010. The genomes of most known coronaviruses contain about 30,000 base pairs.

In a separate analysis, the Cambodia team sequenced some 70% of the new virus's genome using the technology available locally, says Erik Karlsson, a virologist at the Institute Pasteur in Cambodia, who helped to analyse the bats. Missing from that sequence were the instructions for crucial parts of the virus, such as the genes that encode the spike protein that coronaviruses typically use to enter cells. Sequencing that section will indicate whether this virus can infect human cells, says Duong.

The new virus would have to be at least 99% similar to SARS-CoV-2 to be an immediate ancestor of the current pandemic virus, says Irving. The genomes of RaTG13 and SARS-CoV-2 differ by only 4%, but that divergence represents between 40 and 70 years of evolution since they shared a common ancestor. Although decades

apart, the viruses are similar enough to use the same receptor to enter cells. Cell studies suggest that RaTG13 could infect people.

Another close relative

Of the known coronaviruses related to SARS-CoV-2, the newly discovered Rc-o319 seems to be the most distantly related, says Duong.

In cell studies, the Japan team found that the virus can not bind to the receptor that SARS-CoV-2 uses to enter human cells, suggesting that it could not easily infect people.

Shin says his colleagues captured more bats in Japan earlier this year, and plan to test them for coronaviruses. And in October, Hul returned to the cave in northern Cambodia to catch more bats.

More SARS-CoV-2-related coronaviruses probably exist in *Rhinolophus* bat populations, which live across the region, says Holmes. “Hopefully, one or more of these will be so closely related to SARS-CoV-2 that we can regard it as the true ancestor.”

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